DRUGDEX® Evaluations

PALIPERIDONE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Antipsychotic
  Benzisoxazole

2) Dosing Information
- **a)** Adult
  - **1)** Schizophrenia
    - **a)** extended-release tablets, initial 6 mg/day ORALLY; may increase by 3 mg/day increments at intervals of r maximum of 12 mg/day (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

3) Contraindications
- **a)** hypersensitivity to paliperidone, risperidone, or to any product component (Prod Info INVEGA(R) extended-release

4) Serious Adverse Effects
- **a)** Death
- **b)** Ischemia
- **c)** Tachyarrhythmia

5) Clinical Applications
- **a)** FDA Approved Indications
  - **1)** Schizophrenia

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In

B) Synonyms
Paliperidone

C) Physicochemical Properties
- **1)** Molecular Weight
  - **a)** 426.49 (Prod Info INVEGA(TM) extended-release oral tablets, 2006)
- **2)** Solubility
  - **a)** Paliperidone is practically insoluble in water, 0.1N sodium hydroxide solution, and hexane; slightly soluble dimethylformamide; and sparingly soluble in 0.1N hydrochloric acid and methylene chloride (Prod Info INVEG release oral tablets, 2006).

1.2 Storage and Stability

A) Preparation
- **1)** Oral route
  - **a)** ADMINISTRATION
    - **1)** Paliperidone may be taken without regard to meals (Prod Info INVEGA(TM) extended-release oral tal
    - **2)** Extended-release tablets must be swallowed whole with liquid, do not chew, divide, or crush (Prod In extended-release oral tablets, 2006)

B) Oral route
- **1)** Tablet, Extended Release
  - **a)** Store paliperidone extended-release tablets at 25 degrees Celsius (77 degrees Fahrenheit), with excursio 30 degrees Celsius (59 to 86 degrees Fahrenheit). Protect from moisture (Prod Info INVEGA(TM) extended-r 2006).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

1.3.1 Normal Dosage

1.3.1.A Oral route

1.3.1.A.1 Schizophrenia

a) The recommended dose of extended-release oral tablets is 6 milligrams/day (mg/day) with increases intervals of at least 5 days, to a maximum of 12 mg/day. In some patients, a lower starting dose of 3 mg/ Dose increases above 6 mg/day should only be made after clinical reassessment (Prod Info INVEGA(TM oral tablets, 2006).

1.3.2 Dosage in Renal Failure

A) In mild renal impairment (creatinine clearance 50 to less than 80 milliliters/minute (mL/minute)), the maximum 6 mg once daily. In moderate to severe renal impairment (creatinine clearance 10 to less than 50 mL/minute), the recommended dose is 3 mg once daily (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

2.0 Pharmacokinetics

Drug Concentration Levels

ADME

2.2 Drug Concentration Levels

A) Peak Concentration

1) 8.85 ng/mL (single-dose, oral solution) (Vermeir et al, 2008)

a) The mean Cmax (standard deviation) was 8.85 ng/mL (+/- 1.31 ng/mL) after a single, 1-mg dose of palipe administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacokinetic stu were 40 to 63 years of age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (mean, 73.38 kg) with a mean 25.5 kg/m(2) (range, 24 to 28 kg/m(2)). There was no difference in the Cmax between the 2 poor and 3 exten metabolizers. Nor was there a difference in Cmax and the genotypic expression of UGT1A1 and UGT1A6 me (Vermeir et al, 2008).

B) Time to Peak Concentration

1) 24 hours (extended-release tablets) (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

a) After a single dose of paliperidone, plasma concentration reaches its peak in approximately 24 hours (Pro extended-release oral tablets, 2006).

b) The median Tmax was 1.5 hr (range, 1 to 1.5 hr) after a single, 1-mg dose of paliperidone solution admini caucasian, male volunteers in the fasted state, in an open-label pharmacokinetic study (n=5). The males wer age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (mean, 73.38 kg) with a mean body mass index of 25 to 28 kg/m(2) (Vermeir et al, 2008).

C) Steady State

1) 4 to 5 days (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

a) Paliperidone reaches steady-state concentration within 4 to 5 days after initiation of therapy. The steady-s ratio for a 9-mg dose was 1.7 (range, 1.2 to 3.1) (Prod Info INVEGA(TM) extended-release oral tablets, 2006

D) Area Under the Curve

1) 187 ng x hr/mL (Vermeir et al, 2008)

a) The mean AUC (0 to infinity) was 187 ng x hr/mL (standard deviation of +/- 29.3 ng x hr/mL) after a single paliperidone solution administered to healthy, caucasian, male volunteers in the fasted state, in an open-labe study (n=5). The males were 40 to 63 years of age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (mean mean body mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m(2)). There was no difference in the AUC (0 to in 24 hr) between the 2 poor and 3 extensive CYP2D6 metabolizers. Nor was there a difference in AUC and the of UGT1A1 and UGT1A6 metabolizing enzymes (Vermeir et al, 2008).

b) The area under the curve concentration (AUC) of paliperidone was not reported in patients with normal re the average AUC was increased among patients with renal impairment due to reduced clearance. Following a milligram dose of paliperidone extended-release, there was a 1.5-fold increase in drug exposure among patie impairment (creatinine clearance (CrCl) 50 to less than 80 milliliters/minute (mL/min)); a 2.6-fold increase am moderate renal impairment (CrCl 30 to less than 50 mL/min); and a 4.8-fold increase among those with severe (CrCl 10 to less than 30 mL./min) (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) 28% (extended-release tablet) (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

a) The absolute oral bioavailability of paliperidone extended-release tablet is 28% (Prod Info INVEGA(T oral tablets, 2006).

B) Effects of Food

1) Increase peak concentration (Cmax) by 60% and mean area under the curve (AUC) by 54% (Prod Info IN release oral tablets, 2006)

a) After administration of paliperidone extended-release 12 milligrams to healthy ambulatory individuals, calorie meal increased mean peak concentration (Cmax) and mean area under the curve concentration (by 60% and 54%, respectively, compared with administration under fasting states (Prod Info INVEGA(TM oral tablets, 2006).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) 74% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

1) The plasma protein binding of paliperidone is 74% (Prod Info INVEGA(TM) extended-release ora

B) Distribution Kinetics

1) Volume of Distribution

a) 487 L (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

1) Paliperidone has a volume of distribution (Vd) of 487 liters (L) (Prod Info INVEGA(TM) extended- 2006).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver: limited (Vermeir et al, 2008; Prod Info INVEGA(TM) extended-release oral tablets, 2006)

a) While in vitro data indicated that paliperidone was metabolized by cytochrome P450 2D6 (CYP2D6) a isozymes, these isozymes played a limited role in the overall elimination of paliperidone based on in vivo was found between extensive and poor metabolizers of CYP2D6 substrates in the clearance or exposure Info INVEGA(TM) extended-release oral tablets, 2006).

b) There were 4 primary metabolic pathways identified in vivo, each accounting for no more than 10% o dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission (Vermeir et al, 2008).

c) Metabolism was limited after a single, 1-mg dose of paliperidone solution administered to healthy, cau volunteers in the fasted state, in an open-label pharmacokinetic study (n=5). On average the 4 identified accounted for approximately 3% to 5% of the dose. The males were 40 to 63 years of age (mean, 51.2 y 68.7 kg to 78.6 kg (mean, 73.38 kg) with a mean body mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m 2008).

B) Metabolites

1) M1 (Vermeir et al, 2008)

a) The pathway for paliperidone to M1 formation was oxidative N-dealkylation, after a single, 1-mg dose solution administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharma The males were 40 to 63 years of age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (mean, 73.38 mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m(2)). A mean of 4.55% (standard deviation, +/-1.42%) o excreted in the urine as M1 metabolite (Vermeir et al, 2008).

2) M9 (Vermeir et al, 2008)

a) The pathway for paliperidone to M9 formation was monohydroxylation, after a single, 1-mg dose of pa administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacokineti males were 40 to 63 years of age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (mean, 73.38 kg) w mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m(2)). A mean of 3.75% (standard deviation, +/-1.42%) o excreted in the urine as M1 metabolite. The detection of M9 was in the urine of extensive metabolizers b metabolizers (Vermeir et al, 2008).

3) M10 (Vermeir et al, 2008)

a) The pathway for paliperidone to M10 formation was benzisoxazole scission and hydroxylation, after a paliperidone solution administered to healthy, caucasian, male volunteers in the fasted state, in an open- study (n=5). The males were 40 to 63 years of age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (m mean body mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m(2)). M10 was excreted in the feces (Verme

4) M11 (Vermeir et al, 2008)

a) The pathway for paliperidone to M11 formation was benzisoxazole scission, after a single, 1-mg dose

solution administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharma
The males were 40 to 63 years of age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (mean, 73.38
mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m(2)). M11 was excreted in the feces (Vermeir et al, 200

5) M12 (Vermeir et al, 2008)

a) The pathways for paliperidone to M12 formation was alcohol dehydrogenation and also nonenzymati
mg dose of paliperidone solution administered to healthy, caucasian, male volunteers in the fasted state,
pharmacokinetic study (n=5). The males were 40 to 63 years of age (mean, 51.2 years) and weighed 68
(mean, 73.38 kg) with a mean body mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m(2)). A mean of 2.7
deviation, +/-1.66%) of the dose was excreted in the urine as M12 metabolite (Vermeir et al, 2008).

6) M16 (Vermeir et al, 2008)

a) The pathway for paliperidone to M16 formation was glucuronidation, after a single, 1-mg dose of palip
administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacokineti
males were 40 to 63 years of age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (mean, 73.38 kg) v
mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m(2)). A mean of 4.06% (standard deviation, +/-1.03%) c
excreted in the urine as M16 metabolite (Vermeir et al, 2008).

2.3.4 Excretion

A) Kidney

1) Renal Clearance (rate)

a) 53.1 +/- 9.47 mL/min (Vermeir et al, 2008)

1) The mean renal clearance was 53.1 +/- 9.47 mL/min after a single, 1-mg dose of paliperidone so
healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacokinetic study (n=5
to 63 years of age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (mean, 73.38 kg) with a mean
25.5 kg/m(2) (range, 24 to 28 kg/m(2)). The mean clearances (standard deviation) were as follow: cr
113 +/- 10.3 mL/min, glomerular filtration rate, 25.9 +/- 2.36 mL/min; and active renal clearance, 27.
(Vermeir et al, 2008).

2) Renal Excretion (%)

a) 59% (range, 51% to 67%) unchanged (Vermeir et al, 2008; Prod Info INVEGA(TM) extended-release

1) One week following administration of a single oral dose of immediate-release radioactive-paliperi
in 5 healthy volunteers, 59% (range, 51% to 67%) of the dose was excreted into the urine unchange
26% to 41%) was recovered as metabolites, 6% to 12% of the dose was not recovered (Prod Info IN
release oral tablets, 2006).

2) The mean total dose excreted in the urine was 59.4% (standard deviation +/- 7.12%) after a sing
paliperidone solution administered to healthy, caucasian, male volunteers in the fasted state, in an o
pharmacokinetic study (n=5). About half of the renal excretion occurred by active secretion. The M1
metabolites were detected in the urine. The males were 40 to 63 years of age (mean, 51.2 years) ar
78.6 kg (mean, 73.38 kg) with a mean body mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m(2)) (V

B) Feces

1) Not detected (Vermeir et al, 2008)

a) No unchanged drug was recovered in the feces. Fecal excretion did not differ between poor and exte
metabolizers. The M10 and M11 metabolites were detected in the feces (Vermeir et al, 2008).

C) Total Body Clearance

1) Not reported (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

a) Clearance of paliperidone was not reported in patients with normal renal function. However, total clea
was reduced with decreasing estimated creatinine clearance (CrCl). Following administration of a 3-milli
paliperidone extended release, there was a 32% reduction in patients with mild renal impairment (CrCl 5
milliliters/minute (mL/min)); a 64% reduction in patients with moderate renal impairment (CrCl 30 to less
a 71% reduction in patients with severe renal impairment (CrCl 10 to less than 30 mL./min) (Prod Info IN
release oral tablets, 2006).

b) The mean total plasma clearance was 91 +/- 15 mL/min after a single, 1-mg dose of paliperidone solu
healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacokinetic study (n=5). Th
63 years of age (mean, 51.2 years) and weighed 68.7 kg to 78.6 kg (mean, 73.38 kg) with a mean body
kg/m(2) (range, 24 to 28 kg/m(2)) (Vermeir et al, 2008).

2.3.5 Elimination Half-life

A) Parent Compound

1) approximately 23 hours (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

a) The terminal elimination half-life of paliperidone is approximately 23 hours (Prod Info INVEGA(TM) ex
tablets, 2006).

2) renal impairment, 24 hours to 51 hours

a) The mean terminal elimination half-lives of paliperidone following administration of a 3-milligram dose
extended-release were increased to 24 hours, 40 hours, and 51 hours among individuals with mild (creat
50 to less than 80 milliliters/minute (mL/min)), moderate renal impairment (CrCl 30 to less than 50 mL/mi
10 to less than 30 mL./min) renal impairment, respectively. The elimination half-life was 23 hours among
renal function (CrCl at or above 80 mL/min) (Prod Info INVEGA(TM) extended-release oral tablets, 2006

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Oral (Tablet, Extended Release)

a) Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-relate with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duratior in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1 death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-tr about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, m appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Ob suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as characteristic(s) of the patients is not clear. Paliperidone is not approved for the treatment of patients with dement (Prod Info INVEGA(R) extended-release oral tablets, 2008).

3.1 Contraindications

A) hypersensitivity to paliperidone, risperidone, or to any product component (Prod Info INVEGA(R) extended-release

3.2 Precautions

A) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attri cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia) (Prod Info INVEGA(R) extende 2008)

B) bradycardia; increased risk of torsade de pointes and/or sudden death (Prod Info INVEGA(R) extended-release ora

C) cardiac arrhythmias; use should be avoided due to risk of prolonged QT interval (Prod Info INVEGA(R) extended-r 2008)

D) cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (eg, dehydration, antihypertensive medications); increased risk of orthostatic hypotension and syncope (Prod Info INVEGA(R) extended 2008)

E) concomitant use of other drugs known to prolong the QTc interval, such as Class IA (eg, quinidine, procainamide) amiodarone, sotalol) antiarrhythmics, antibiotics (eg, gatifloxacin, moxifloxacin), and antipsychotics (eg, chlorpromazin should be avoided (Prod Info INVEGA(R) extended-release oral tablets, 2008)

F) conditions that may contribute to elevated body temperature (eg, strenuous exercise, extreme heat exposure, dehy anticholinergic use); may disrupt body temperature regulation (Prod Info INVEGA(R) extended-release oral tablets, 20

G) congenital long QT syndrome; increased risk of torsade de pointes and/or sudden death (Prod Info INVEGA(R) ex tablets, 2008)

H) diabetes mellitus or risk factors for diabetes mellitus; increased risk of severe hyperglycemia; monitor blood glucos (R) extended-release oral tablets, 2008)

I) elderly patients, especially elderly women are at increased risk of tardive dyskinesia (Prod Info INVEGA(R) extende 2008)

J) esophageal dysmotility and aspiration may occur; use cautiously in patients at risk for aspiration pneumonia (Prod extended-release oral tablets, 2008)

K) gastrointestinal narrowing, severe (eg, esophageal motility disorders, small bowel inflammatory disease, short gut adhesions or decreased transit time, peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverti swallow a tablet whole; ingestion of drugs in nondeformable controlled-release formulations may cause obstructive sy INVEGA(R) extended-release oral tablets, 2008)

L) hyperglycemia (some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death) is a risk (Pro extended-release oral tablets, 2008)

M) hypokalemia or hypomagnesemia; increased risk of torsade de pointes and/or sudden death (Prod Info INVEGA(R oral tablets, 2008)

N) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info INVE release oral tablets, 2008)

O) neuroleptic malignant syndrome, potentially fatal, has been reported in association with antipsychotic drugs; imme drug (Prod Info INVEGA(R) extended-release oral tablets, 2008)

P) Parkinson's disease or dementia with Lewy bodies; increased sensitivity to antipsychotic medications (Prod Info IN release oral tablets, 2008)

Q) seizure disorder, history, or conditions that lower the seizure threshold (Prod Info INVEGA(R) extended-release or

R) suicide risk (Prod Info INVEGA(R) extended-release oral tablets, 2008)

S) tardive dyskinesia, potentially irreversible, may occur (Prod Info INVEGA(R) extended-release oral tablets, 2008)

3.3 Adverse Reactions

Cardiovascular Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Immunologic Effects

Neurologic Effects

Other

3.3.1 Cardiovascular Effects

Bradyarrhythmia

Hypotension

Ischemia

Orthostatic hypotension

Prolonged QT interval

Tachyarrhythmia

Tachycardia

3.3.1.A Bradyarrhythmia

1) During the pre-marketing phase, bradycardia was reported infrequently (1 in 100 to 1 in 1000) in patients t paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=2,720); however, causal relationship to p been determined (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3.3.1.B Hypotension

1) Incidence: 5% geriatric (Tzimos et al, 2008)

2) Geriatric

a) During the double-blind phase of a safety trial in 114 geriatric patients, the incidence of hypotension v patients receiving paliperidone extended-release (ER), compared with 0% (0/38) in patients receiving pla prospective, 6-week, double-blind, randomized, placebo-controlled, optional 24-week open-label extensi the open-label phase, the incidence of hypotension was 0% (0/30) of patients switched to paliperidone E was 2% (1/58) in patients continuing with paliperidone ER treatment from the double-blind phase. In gen was well tolerated in the geriatric population compared with placebo. The study included 114 patients (m with 99% having moderate to severe schizophrenia, receiving either placebo or median mean dose of pa milligrams/day (mg/day) during the double-blind phase and median mean doses of 7.4 mg and 8.5 mg in placebo/paliperidone ER and paliperidone ER/paliperidone ER groups, respectively, during the open-lab 2008).

3.3.1.C Ischemia

1) Incidence: rare (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) During the pre-marketing phase, ischemia was reported rarely (less than 1 in 1000) in patients treated wit ranging from 3 mg to 12 mg orally once daily (n=2,720); however, causal relationship to paliperidone has not (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3.3.1.D Orthostatic hypotension

1) Incidence: 1% to 4% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, orthostatic hypotension occurred in 1% to 4 with paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 1% in placebo-tre The incidence of orthostatic hypotension increased with the dose, occurring particularly at the 9-mg and 12-m INVEGA(TM) extended-release oral tablets, 2006).

3) Geriatric

a) During the double-blind phase of a safety trial in 114 geriatric patients, the incidence of orthostatic hy (3/76) in patients receiving paliperidone extended-release (ER), compared with 0% (0/38) in patients rec according to a prospective, 6-week, double-blind, randomized, placebo-controlled, optional 24-week ope safety trial. In general, paliperidone ER was well tolerated in the geriatric population compared with place included 114 patients (mean age of 70 years), with 99% having moderate to severe schizophrenia, recei median mean dose of paliperidone ER 8.4 milligrams/day (mg/day) during the double-blind phase and m 7.4 mg and 8.5 mg in the placebo/paliperidone ER and paliperidone ER/paliperidone ER groups, respect label phase (Tzimos et al, 2008).

3.3.1.E Prolonged QT interval

1) Incidence: 3% to 7% (Tzimos et al, 2008; Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, prolongation of QTc interval occurred in 3% treated with paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 3% in plac (n=355). Among ECG measurements taken during these trials, a change in QTc interval exceeding 60 millise occurred only in 1 subject in the 12-mg group. Overall, none of the subjects had a QTc interval exceeding 50 time point (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3) Geriatric

a) During the double-blind phase of a safety trial in 114 geriatric patients, the incidence of electrocardiog prolongation was 7% (5/76) in patients receiving paliperidone extended-release (ER), compared with 3% receiving placebo according to a prospective, 6-week, double-blind, randomized, placebo-controlled, opt label extension safety trial. During the open-label phase, the incidence of QTc interval prolongation was switched to paliperidone ER from placebo, and 3% (2/58) in patients continuing with paliperidone ER trea double-blind phase. Prolonged QTcB prolongation of 500 milliseconds or greater led to discontinuation o patients assigned to paliperidone ER. In general, paliperidone ER was well tolerated in the geriatric popu placebo. The study included 114 patients (mean age of 70 years), with 99% having moderate to severe s receiving either placebo or median mean dose of paliperidone ER 8.4 milligrams/day (mg/day) during the and median mean doses of 7.4 mg and 8.5 mg in the placebo/paliperidone ER and paliperidone ER/palip respectively, during the open-label phase (Tzimos et al, 2008).

3.3.1.F Tachyarrhythmia

1) Incidence: 12% to 14% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, tachyarrhythmia occurred in 12% to 14% of paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 7% in placebo-treated Additional cardiac disorders occurring at a higher incidence than placebo included first-degree atrioventricula block, and sinus arrhythmia (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3.3.1.G Tachycardia

1) Incidence: 16% geriatric (Tzimos et al, 2008)

2) Geriatric

a) During the double-blind phase of a safety trial in 114 geriatric patients, the incidence of tachycardia w patients receiving paliperidone extended-release (ER), compared with 0% (0/38) in patients receiving pla prospective, 6-week, double-blind, randomized, placebo-controlled, optional 24-week open-label extensi the open-label phase, the incidence of tachycardia was 13% (4/30) of patients switched to paliperidone E was 10% (6/58) in patients continuing with paliperidone ER treatment from the double-blind phase. Hear beats/minute or greater occurred in 25% in the paliperidone ER group compared with 5% in placebo duri phase. During the open-label phase, the incidence of heart rates of 100 beats/minute or greater was 20% to paliperidone ER from placebo, and was 16% in patients continuing with paliperidone ER treatment fro phase. Pulse rate increases were more prominent in patients aged 70 to 75 years compared with age 64 general, paliperidone ER was well tolerated in the geriatric population compared with placebo. The study (mean age of 70 years), with 99% having moderate to severe schizophrenia, receiving either placebo or paliperidone ER 8.4 milligrams/day (mg/day) during the double-blind phase and median mean doses of 7 the placebo/paliperidone ER and paliperidone ER/paliperidone ER groups, respectively, during the open et al, 2008).

3.3.3 Endocrine/Metabolic Effects

Hyperprolactinemia

Metabolic syndrome

Weight gain

3.3.3.A Hyperprolactinemia

1) Incidence: geriatric, 45% to 49% (Tzimos et al, 2008)

2) Antipsychotic-induced hyperprolactinemia was reported in 65.6%, 45.1%, and 42.4% of women of childbe postmenopausal women, and men, respectively, in an open-label, clinical trial of patients treated with first-ge or risperidone at average doses of 4.2 to 5.2 mg/day. Compared to baseline, prolactin levels were significantl 0.05) following use of first-generation antipsychotics (ie, chlorpromazine, droperidol, flupenthixol, fluphenazin paliperidone, perazine, perphenazine, pimozide, trifluoperazine, and zuclopenthixol) or risperidone in several patients with schizophrenia. Younger patients and women of childbearing potential have a greater risk for hyp following treatment with higher doses of these antipsychotics. Hyperprolactinemia may potentially result in m sexual dysfunction, bone mineral density (ie, osteopenia and osteoporosis), and breast and pituitary tumors (

3) Geriatric

a) During the double-blind phase of a safety trial in 114 geriatric patients, the incidence of increased pro male patients and 49% in female patients receiving paliperidone extended-release (ER), according to a p double-blind, randomized, placebo-controlled, optional 24-week open-label extension safety trial. The ma was 75.3 +/- 10.8 nanograms/mL in females and 27.2 +/- 8.7 nanograms/mL in males. During the open-l levels increased in patients switched to paliperidone ER from placebo, and was stable for patients contin ER treatment from the double-blind phase. In general, paliperidone ER was well tolerated in the geriatric with placebo. The study included 114 patients (mean age of 70 years), with 99% having moderate to sev receiving either placebo or median mean dose of paliperidone ER 8.4 mg/day during the double-blind ph doses of 7.4 mg and 8.5 mg in the placebo/paliperidone ER and paliperidone ER/paliperidone ER group the open-label phase (Tzimos et al, 2008).

4) Management

a) Appropriate drug selection, monitoring and management are all important when prescribing antipsych potential for inducing hyperprolactinemia. Prior to treatment with an antipsychotic, question patients rega or galactorrhea. Female patients should be assessed for menstrual abnormalities and male patients, for dysfunction. In the event that any of these symptoms are present, consider obtaining baseline prolactin l be informed of the potential for sexual dysfunction with antipsychotic use. Several weeks after an antipsy obtain a prolactin level measurement. In cases where the patient experiences troublesome adverse effe prolactin levels and discontinuing the antipsychotic is not an option, treatment with a dopamine agonist (cabergoline) should be considered (Bostwick et al, 2009).

3.3.3.B Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.C Weight gain

1) Incidence: 6% to 9% (Prod Info INVEGA(R) extended-release oral tablets, 2008a)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, weight gain of at least 7% of body weight w 9% of patients treated with paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compare treated patients (n=355). The incidence of weight gain increased with the dose, particularly at the 9-mg and 1 INVEGA(R) extended-release oral tablets, 2008a).

3.3.4 Gastrointestinal Effects

Abdominal pain

Xerostomia

3.3.4.A Abdominal pain

1) Incidence: 1% to 3% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, upper abdominal pain occurred in 1% to 3% with paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 1% in placebo-tre (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3.3.4.B Xerostomia

1) Incidence: 1% to 3% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, dry mouth occurred in 1% to 3% of patients paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 1% in placebo-treated (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3.3.5 Hematologic Effects

3.3.5.A Thrombocytopenia

1) Incidence: rare (Prod Info INVEGA(TM) extended-release oral tablets, 2006)
2) During the pre-marketing phase, thrombocytopenia was reported rarely (less than 1 in 1000) in patients tr paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=2,720); however, causal relationship to p been determined (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3.3.7 Immunologic Effects

3.3.7.A Anaphylaxis

1) Incidence: rare (Prod Info INVEGA(TM) extended-release oral tablets, 2006)
2) During the pre-marketing phase, anaphylactic shock occurred rarely (less than 1 in 1000) in patients treat doses ranging from 3 mg to 12 mg orally once daily (n=2,720); however, causal relationship to paliperidone h determined (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3.3.9 Neurologic Effects

Akathisia

Dizziness

Dystonia

Extrapyramidal disease

Headache

Somnolence

Tremor

3.3.9.A Akathisia

1) Incidence: 3% to 10% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)
2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, akathisia occurred in 3% to 10% of patients paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 4% in placebo-treated incidence of akathisia increased with the dose, occurring particularly at the 9-mg and 12-mg doses (Prod Info extended-release oral tablets, 2006).

3.3.9.B Dizziness

1) Incidence: 7% geriatric (Tzimos et al, 2008)
2) Geriatric
a) During the double-blind phase of a safety trial in 114 geriatric patients, the incidence of dizziness was receiving paliperidone extended-release (ER), compared with 0% (0/38) in patients receiving placebo ac prospective, 6-week, double-blind, randomized, placebo-controlled, optional 24-week open-label extensi the open-label phase, the incidence of dizziness was 3% (1/30) of patients switched to paliperidone ER f 10% (6/58) in patients continuing with paliperidone ER treatment from the double-blind phase. In genera well tolerated in the geriatric population compared with placebo. The study included 114 patients (mean 99% having moderate to severe schizophrenia, receiving either placebo or median mean dose of paliper milligrams/day (mg/day) during the double-blind phase and median mean doses of 7.4 mg and 8.5 mg in placebo/paliperidone ER and paliperidone ER/paliperidone ER groups, respectively, during the open-lab 2008).

3.3.9.C Dystonia

1) Incidence: 1% to 5% (Prod Info INVEGA(R) extended-release oral tablets, 2008b)
2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, dystonia occurred in 1% to 5% of patients t paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared with 1% in placebo-treate Dystonic reactions included muscle spasms, oculogyration, and trismus. The incidence of dystonia increased occurring particularly at the 9-mg and 12-mg doses (Prod Info INVEGA(R) extended-release oral tablets, 200
3) During the first few days after initiating treatment with an antipsychotic medication, symptoms of dystonia susceptible individuals. Symptoms may include spasm of neck muscles, which may progress to tightening of difficulty, breathing difficulty, and/or protrusion of the tongue. These symptoms can occur at low doses but m occur with a greater severity) with high potency and at higher doses of first generation antipsychotic medicati younger age groups appear to be at greater risk for developing acute dystonia (Prod Info INVEGA(R) extend 2008b).

3.3.9.D Extrapyramidal disease

1) Incidence: 2% to 7% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, extrapyramidal disorders occurred in 2% to with paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 2% in placebo-tre Extrapyramidal symptoms (EPS) included akathisia, dyskinesia, dystonia, hyperkinesia, and tremor, and Parl involved bradykinesia, cogwheel rigidity, drooling, hypertonia, hypokinesia, muscle rigidity, and musculoskele incidence of EPS increased with the dose, occurring particularly at the 9-mg and 12-mg doses (Prod Info INV release oral tablets, 2006).

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.E Headache

1) Incidence: 11% to 14% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, headache occurred in 11% to 14% of patier paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 12% in placebo-treate (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3.3.9.F Somnolence

1) Incidence: 6% to 11% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, somnolence occurred in 6% to 11% of patie paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 7% in placebo-treated incidence of somnolence increased with the dose, particularly at the 9-mg and 12-mg doses (Prod Info INVE release oral tablets, 2006).

3) Geriatric

a) During the double-blind phase of a safety trial in 114 geriatric patients, the incidence of somnolence v patients receiving paliperidone extended-release (ER), compared with 5% (2/38) in patients receiving pla prospective, 6-week, double-blind, randomized, placebo-controlled, optional 24-week open-label extensi the open-label phase, the incidence of somnolence was 7% (2/30) of patients switched to paliperidone E was 0% (0/58) in patients continuing with paliperidone ER treatment from the double-blind phase. During phase, an age-related increase in the incidence of somnolence was seen in patients receiving paliperido to 69 years, 11% in age 70 to 75 years, and 14% in age greater than 75 years. In general, paliperidone E in the geriatric population compared with placebo. The study included 114 patients (mean age of 70 yea moderate to severe schizophrenia, receiving either placebo or median mean dose of paliperidone ER 8.4 (mg/day) during the double-blind phase and median mean doses of 7.4 mg and 8.5 mg in the placebo/pa paliperidone ER/paliperidone ER groups, respectively, during the open-label phase (Tzimos et al, 2008).

3.3.9.G Tremor

1) Incidence: 3% to 4% (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) In 3 short-term (6-week), fixed-dose, placebo-controlled trials, tremor occurred in 3% to 4% of patients tre doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 3% in placebo-treated patients (n=3 INVEGA(TM) extended-release oral tablets, 2006).

3.3.16 Other

Death

Extrapyramidal disease

3.3.16.A Death

1) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antip associated with an even greater risk for death than atypical antipsychotics when administered to elderly patie and older) with dementia. Atypical versus no antipsychotic use and conventional versus atypical antipsychoti comparisons were made. A total of 27,259 matched pairs were identified and the dementia cohort was stratifi residence (community versus long-term care facilities). In order to adjust for difference in baseline health stat matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evalua 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant incr death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in bot dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk di percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 2.07); absolute risk differen points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. Th associated with conventional antipsychotics was even greater than the risk identified with atypical antipsycho adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.5 care cohort (adjusted risk difference for both was 1.1 percentage points). The risk appeared to persist to 180 Some important limitations to the study include unknown or unmeasured confounders may influence the resu could not be examined (Gill et al, 2007).

2) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater ris

with the use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared wit
antipsychotic medications. The analysis excluded patients with cancer and included only new users of antips
The primary study outcome was 180-day all-cause mortality. A set of potential confounders was measured ba
utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patien
and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in th
group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortali
confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which controlled for potential confounders
mortality ratio for the risk of death within 180 days for conventional versus atypical drug therapy was 1.32 (95
When the most frequently prescribed conventional antipsychotic drugs were compared with risperidone, the r
associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine was 1.29 (95% CI, 1.19 to 1.40), wh
difference associated with olanzapine. The increased mortality risk for conventional versus atypical drug thera
when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also durin
therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regre
score, and instrumental variable estimation confirmed the results of the study (Schneeweiss et al, 2007).

3.3.16.B Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info INVEGA(TM) extended-relea
(All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other)
controlled studies in women or studies in women and animals are not available. Drugs should be given only if
justifies the potential risk to the fetus.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown

3) Clinical Management

a) Adequate and well controlled studies with paliperidone have not been conducted in pregnant women. Whi
generation antipsychotic drugs during the last trimester of pregnancy has been linked to extrapyramidal symp
unknown whether paliperidone could lead to similar neonatal effects. Until further data are available, it is recc
paliperidone be used during pregnancy only if the potential benefit to the mother justifies the potential risk to
INVEGA(TM) extended-release oral tablets, 2006).

4) Literature Reports

a) No human studies of pregnancy outcomes after exposure to paliperidone have been published, and there
of outcomes after inadvertent exposure during pregnancy. In studies in rats and rabbits, no increases in fetal
noted at the highest oral paliperidone dose, which was approximately 8 times the maximum recommended hu
Paliperidone is the major active metabolite of risperidone. In rat reproduction studies with risperidone, increas
noted at oral doses that were less than the MRHD of risperidone. Use of first-generation antipsychotic drugs
trimester of pregnancy has been linked to extrapyramidal symptoms in neonates. However, it is unknown whe
could lead to similar neonatal effects (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk wh
breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this dr
breastfeeding.

2) Literature Reports

a) Lactation studies with paliperidone have not been conducted in humans. In animal studies, paliperidone w
milk. Paliperidone is the major active metabolite of risperidone, which is excreted into human milk. Therefore,
paliperidone recommended that women receiving paliperidone should not breast-feed infants (Prod Info INVE
release oral tablets, 2006).

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Acecainide

Ajmaline

Amiodarone

Arsenic Trioxide

Azimilide

Bretylium

Carbamazepine

Chlorpromazine

Disopyramide

Dofetilide

Gatifloxacin

Hydroquinidine

Ibutilide

Iloperidone

Lapatinib

Levodopa

Mesoridazine

Methadone

Moxifloxacin

Nilotinib

Paroxetine

Pirmenol

Prajmaline

Procainamide

Prochlorperazine

Ranolazine

Sematilide

Sotalol

Tedisamil

Tetrabenazine

Thioridazine

Trifluoperazine

3.5.1.A Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventr ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info sotal 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) e tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents sh this may result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2(
7) Probable Mechanism: additive QT prolongation

3.5.1.B Ajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006 Duenas-Laita et al, 1999b; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.C Amiodarone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventr ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info sotal 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) e tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents sh this may result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2(
7) Probable Mechanism: additive QT prolongation

3.5.1.D Arsenic Trioxide

1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes
2) Summary: Arsenic trioxide can prolong the QT interval in some patients, which may result in ventricular ta fibrillation, and torsades de pointes and should not be administered with other drugs that may prolong the QT Trisenox(R), 2001a). Several antipsychotic agents have demonstrated QT prolongation including amisulpride 1999), haloperidol (O'Brien et al, 1999), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2 (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), quetiapine (Owens, 2001), sultopride (Lande et al (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of arsenic trioxide and antipsychotics is not recomme
7) Probable Mechanism: additive effects on QTc prolongation

8) Literature Reports

a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointe heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL t trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic triox returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Inf

3.5.1.E Azimilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventri ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info sotal 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) e tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents sh this may result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 20

7) Probable Mechanism: additive QT prolongation

3.5.1.F Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventri ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info sotal 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) e tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents sh this may result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 20

7) Probable Mechanism: additive QT prolongation

3.5.1.G Carbamazepine

1) Interaction Effect: decreased paliperidone concentration

2) Summary: Concomitant use of paliperidone and carbamazepine decreased the maximum concentration (C under the concentration-time curve (AUC) values of paliperidone by 37%. Coadministration with carbamazep inducer, could increase paliperidone renal clearance by 35%. The dose of paliperidone should be evaluated v concurrently with carbamazepine. If therapy with carbamazepine is discontinued, the dose of paliperidone sh necessary (Prod Info INVEGA(TM) extended-release oral tablets, 2007).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of paliperidone and carbamazepine resulted in decreased paliperi Dosing of paliperidone should be evaluated when it is administered concurrently with carbamazepine. If thera carbamazepine is discontinued, the dose of paliperidone should be decreased if necessary(Prod Info INVEGA release oral tablets, 2007).

7) Probable Mechanism: induction of paliperidone metabolism

8) Literature Reports

a) Coadministration of paliperidone 6 mg daily and carbamazepine 200 mg twice daily decreased the pa steady-state maximum concentration (Cmax) and area under the concentration-time curve (AUC) by app decrease is caused by a 35% increase in renal clearance of paliperidone. There is little effect on the met bioavailability of paliperidone when coadministered with carbamazepine. Carefully evaluate paliperidone discontinuation of carbamazepine (Prod Info INVEGA(TM) extended-release oral tablets, 2007).

3.5.1.H Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Co Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info haloperidol (O'Brien et al, 1999a), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), 2001a), risperidone (Duenas-Laita et al, 1999a), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 199 (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).

3) Severity: major

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phen antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.I Disopyramide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006 Duenas-Laita et al, 1999b; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperi day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.J Dofetilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventr ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info sotal 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) e tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents sh this may result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2
7) Probable Mechanism: additive QT prolongation

3.5.1.K Gatifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Gatifloxacin may prolong the QTc interval in some patients, which may result in ventricular tach ventricular fibrillation. Additionally, rare cases of torsades de pointes have been reported with quinolones, inc post-marketing surveillance (Prod Info TEQUIN(R) tablets, injection, 2006). Modest increases in the QTc inte with paliperidone use (Prod Info INVEGA(TM) extended-release oral tablets, 2006). Although pharmacokineti gatifloxacin and other drugs which prolong the QT interval have not been performed, an additive effect canno Therefore, the concurrent administration of gatifloxacin and paliperidone should be avoided (Prod Info INVEG release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of gatifloxacin and paliperidone should be avoided as additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.L Hydroquinidine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM

Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006 Duenas-Laita et al, 1999b; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).

3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports

a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther Norpace(R), 1997).

c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.M Ibutilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventr ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info sotal 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) e tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents sh this may result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 20
7) Probable Mechanism: additive QT prolongation

3.5.1.N Iloperidone

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de poin used when iloperidone and drugs that prolong the QT interval are given concomitantly. Consideration should cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) le iloperidone in patients with persistent QTc measurements greater than 500 msec (Prod Info FANAPT(TM) ora
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of iloperidone and drugs that prolong the QT interval may result in the QT interval and an increased risk of torsade de pointes. Iloperidone should be avoided in patients with sig cardiovascular illness, eg, cardiac arrhythmia, QT prolongation, recent acute myocardial infarction, and uncon failure. If concomitant use is necessary, consider monitoring cardiac function periodically with on-treatment E electrolyte (ie, magnesium, potassium) levels. Discontinue iloperidone in patients with persistent QTc measur 500 msec(Prod Info FANAPT(TM) oral tablets, 2009).
7) Probable Mechanism: additive effects on the QT interval
8) Literature Reports

a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

3.5.1.O Lapatinib

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de poin used when lapatinib and drugs that prolong the QT interval are given concomitantly. Consideration should be cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) le TYKERB oral tablets, 2008). Thirteen patients had either QTcF (corrected QT by the Friedericia method) grea an increase in QTcF of greater than 60 msec in an uncontrolled, open-label, dose escalation study in advanc (n=81) who received lapatinib doses ranging from 175 mg/day to 1800 mg/day, with serial ECGs collected on Info TYKERB oral tablets, 2008).
3) Severity: major

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of lapatinib and drugs that prolong the QT interval may result in ac QT interval and an increased risk of torsade de pointes. Therefore, caution should be used when these agent concomitantly. Consider monitoring cardiac function periodically with on-treatment ECGs and evaluating elec magnesium, potassium) levels (Prod Info TYKERB oral tablets, 2008).
7) Probable Mechanism: additive effects on the QT interval

3.5.1.P Levodopa

1) Interaction Effect: loss of levodopa efficacy
2) Summary: Because paliperidone is an antagonist with a high affinity for dopamine type 2 receptors, it is ex the effects of levodopa and other dopamine agonists (Prod Info INVEGA(TM) extended-release oral tablets, 2 paliperidone is used concurrently in patients receiving levodopa. Monitor patients for loss of levodopa efficacy
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use with paliperidone is expected to antagonize the effects of levodopa agonists due to pharmacologic antagonism (Prod Info INVEGA(TM) extended-release oral tablets, 2006). Us paliperidone is used concurrently in patients receiving levodopa. Monitor patients for loss of levodopa efficacy
7) Probable Mechanism: pharmacologic antagonism

3.5.1.Q Mesoridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of mesoridazine states that concomitant use with oth prolong the QT interval is contraindicated (Prod Info Serentil(R), 2001). Several antipsychotic agents have de prolongation including amisulpride (Prod Info Solian(R), 1999d), haloperidol (O'Brien et al, 1999d), paliperido (TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001d), risperidone (Duenas-Laita et al, 1999 et al, 2001c), sultopride (Lande et al, 1992d), ziprasidone (Prod Info GEODON(R) intramuscular injection, ora zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antips mesoridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.R Methadone

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Cases of QT interval prolongation and serious arrhythmias, including torsade de pointes, have methadone use (Prod Info DOLOPHINE(R) HYDROCHLORIDE oral tablets, 2006). Treatment with paliperido associated with QTc prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2006a). The coadm paliperidone and other drugs known to prolong the QTc interval, including methadone, should be avoided due additive QT interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2006a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive effects on the QT interval, avoid concomitant use of methadone (Prod Info INVEGA(TM) extended-release oral tablets, 2006a).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.S Moxifloxacin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Moxifloxacin has been shown to prolong the QTc interval in some patients (Prod Info AVELOX injection, 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVE release oral tablets, 2006). Although pharmacokinetic studies between moxifloxacin and paliperidone have no additive effect cannot be excluded. Therefore, the concurrent administration of moxifloxacin and paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of moxifloxacin and paliperidone should be avoided a additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.T Nilotinib

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de poir of nilotinib with drugs that prolong the QT interval should be avoided. However, if concomitant use is required

closely monitored for prolongation of the QT interval (Prod Info TASIGNA(R) oral capsules, 2007).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of nilotinib with drugs that prolong the QT interval should be avoid for additive effects on the QT interval and increased risk of torsade de pointes. However, if concurrent therap patient closely for prolongation of the QT interval (Prod Info TASIGNA(R) oral capsules, 2007).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.U Paroxetine
1) Interaction Effect: increased plasma concentrations of paliperidone
2) Summary: Concurrent use of paliperidone and paroxetine may result in increased paliperidone plasma co Paliperidone (9-hydroxyrisperidone) is the major active metabolite of risperidone (Prod Info INVEGA(TM) exte tablets, 2007). Concomitant use of paroxetine and risperidone has resulted in increased plasma concentratio and 9-hydroxyrisperidone, particularly at higher (40 mg) paroxetine doses (Saito et al, 2005; Spina et al, 200 paliperidone and paroxetine are used concomitantly. Consider monitoring for increased paliperidone side effe neuroleptic malignant syndrome, QTc prolongation, or tardive dyskinesia.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when paliperidone and paroxetine are used concomitantly as this may paliperidone plasma concentrations (Prod Info INVEGA(TM) extended-release oral tablets, 2007). Consider r increased paliperidone side effects, including neuroleptic malignant syndrome, QTc prolongation, or tardive d
7) Probable Mechanism: inhibition of the CYP2D6-mediated metabolism of paliperidone
8) Literature Reports
a) In a drug interaction study, paliperidone exposures were a significant 16% (90% confidence interval, average in CYP2D6 extensive metabolizers who were treated concomitantly with a single dose of palipe paroxetine 20 mg/day. Studies with higher paroxetine doses have not been conducted. The clinical relev (Prod Info INVEGA(TM) extended-release oral tablets, 2007).
b) Paroxetine, a potent inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, prim CYP2D6-mediated alpha-hydroxylation and, to a lesser extent, by simultaneously affecting the further m hydroxyrisperidone (9-OH-risperidone) or other pathways of risperidone biotransformation. In a study inc diagnosed with schizophrenia (n=7) or schizoaffective disorder depressive type (n=3), risperidone plasm increased when paroxetine was coadministered with risperidone. Patients were stabilized on risperidone and received adjunctive paroxetine 20 mg/day to treat negative symptoms, concomitant depression, or b dosage remained constant throughout the duration of the study. A significant elevation in risperidone pla less than 0.01) and a slight, nonsignificant decrease in 9-OH-risperidone occurred. After 4 weeks of parc total concentration of risperidone and 9-OH-risperidone was increased by 45% (p less than 0.05). The m risperidone to 9-OH-risperidone ratio also changed significantly (p less than 0.001) with concomitant par Extrapyramidal side effects occurred in one patient during the second week of paroxetine coadministratio of risperidone in this patient increased 62% over baseline values during paroxetine coadministration. The extrapyramidal symptoms in patients after addition of SSRIs to antipsychotics might also be caused by a pharmacodynamic effect of paroxetine (Spina et al, 2001).
c) Risperidone plasma concentrations increased when risperidone-treated inpatients (n=12) with schizo symptoms were coadministered incremental doses of paroxetine. Prior to initiating paroxetine, patients w risperidone 2 mg twice daily for at least 6 weeks and steady-state plasma concentrations of risperidone a hydroxyrisperidone (9-OH-risperidone) had been achieved. Paroxetine doses were administered in 3 cor increments of 10 mg/day, 20 mg/day, and 40 mg/day. Mean risperidone plasma concentrations during 1(paroxetine treatment were 3.8- (95% confidence interval (CI), 3.2 to 5.8; p less than 0.01) , 7.1- (95% CI than 0.01), and 9.7-fold (95% CI, 7.8 to 22.5; p less than 0.01) higher compared with baseline. Increases concentrations were not significant with paroxetine use. Mean active moiety (risperidone plus 9-OH-rispe concentrations increased by 1.8-fold (95% CI, 1.4 to 2.7; p less than 0.05) during the 40-mg paroxetine c not significant with 10- or 20-mg doses. Metabolic ratio was significantly increased (p less than 0.01) by to 6.2) with 10 mg of paroxetine, by 8.2-fold (95% CI, 6 to 16) with 20 mg, and by 12.6-fold (95% CI, 9.6 Negative symptom scores were significantly improved during all paroxetine doses; however, extrapyrami were significantly higher during 20- and 40-mg doses. The authors suggest that low-dose coadministratio risperidone may be safe and effective for treating schizophrenia with negative symptoms (Saito et al, 20(

3.5.1.V Pirmenol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006 Duenas-Laita et al, 1999b; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.W Prajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006 Duenas-Laita et al, 1999b; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.X Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006 Duenas-Laita et al, 1999b; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperic day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide ther Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine

treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.Y Prochlorperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Co Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info haloperidol (O'Brien et al, 1999a), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), 2001a), risperidone (Duenas-Laita et al, 1999a), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 199 (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phen antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.Z Ranolazine

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Paliperidone causes an increase of QTc interval and ranolazine prolongs the QTc interval in a If concomitant administration is unavoidable, use caution when paliperidone is coadministered with ranolazin for additive effects on QT interval prolongation (Prod Info INVEGA(R) extended-release oral tablets, 2008a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Paliperidone causes an increase of QTc interval and ranolazine prolongs the QTc i related manner. If concomitant administration is unavoidable, use caution when paliperidone is coadministere to the potential for additive effects on QT interval prolongation (Prod Info INVEGA(R) extended-release oral t
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.AA Sematilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in venti ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info sotal 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents sh this may result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2
7) Probable Mechanism: additive QT prolongation

3.5.1.AB Sotalol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in venti ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info sotal 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents sh this may result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2
7) Probable Mechanism: additive QT prolongation

3.5.1.AC Tedisamil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in venti ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info sotal 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM)

tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents sh this may result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2(
7) Probable Mechanism: additive QT prolongation

3.5.1.AD Tetrabenazine
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de poir of tetrabenazine with drugs that prolong the QT interval should be avoided. However, if concomitant use is re should be closely monitored for prolongation of the QT interval (Prod Info XENAZINE(R) oral tablets, 2008). I double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg or 50 mg do the QT interval was studied with moxifloxacin as a positive control. The 50 mg dose of tetrabenazine caused millisecond mean increase in QT (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tetrabenazine with drugs that prolong the QT interval should be potential for additive effects on the QT interval and increased risk of torsade de pointes. However, if concurre monitor patient closely for prolongation of the QT interval (Prod Info XENAZINE(R) oral tablets, 2008).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.AE Thioridazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Several antipsychotic agents have demonstra including amisulpride (Prod Info Solian(R), 1999c), haloperidol (O'Brien et al, 1999c), pimozide (Prod Info Ora quetiapine (Owens, 2001c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risper et al, 1999c), sertindole (Agelink et al, 2001c), sultopride (Lande et al, 1992c), ziprasidone (Prod Info GEODO injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antips thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.AF Trifluoperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Co Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info haloperidol (O'Brien et al, 1999a), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), 2001a), risperidone (Duenas-Laita et al, 1999a), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 199 (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phen antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Therapeutic

1) Physical Findings

a) Schizophrenia

1) Patients should be monitored for signs of improvement in the target positive and negative symptoms as improved communication, decreased hallucinations and delusions, improved socialization, and decrea of improvement in socialization, grooming, and attention to activities of daily living should also be monito

B) Toxic

1) Laboratory Parameters

a) Fasting glucose test in patients with a diagnosis or with risk factors for diabetes mellitus at the initiation of periodically during treatment (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

2) Physical Findings

a) Hyperglycemia symptom monitoring in all patients for polydipsia, polyuria, polyphagia, and weakness (Prc extended-release oral tablets, 2006)

b) Neuroleptic malignant syndrome has been reported and patients should be monitored for the signs and sy syndrome (hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability) (Prod Info INVEGA release oral tablets, 2006).

c) Orthostatic vital sign monitoring in patients susceptible to hypotension (Prod Info INVEGA(TM) extended-r 2006)

d) QT prolongation has been reported with paliperidone, a baseline EKG may be considered (Prod Info INVE release oral tablets, 2006)

e) Suicide monitoring in high-risk patients (Prod Info INVEGA(TM) extended-release oral tablets, 2006)

4.2 Patient Instructions

A) Paliperidone (By mouth)

Paliperidone

Treats schizophrenia (a mental disorder).

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to paliperidone or risperidone.

How to Use This Medicine:
Long Acting Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed order to find out what works best for you. Do not use more medicine or use it more often than your doctor tell
You may take this medicine with or without food.
Swallow the extended-release tablet whole. Do not crush, break, or chew it. Swallow the tablet with a liquid, s
While taking the extended-release form of this medicine, part of the tablet may pass into your stools. This is r to worry about.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next d use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a

Make sure your doctor knows if you are using medicines for heart rhythm problems (such as amiodarone, qui sotalol, Betapace®, Cordarone®, Procanbid®) or a diuretic, also called a "water pill" (such as furosemide, hy Aldactazide®, Aldactone®, Lasix®, Maxzide®).
Tell your doctor if you are using levodopa (Dopar®, Larodopa®), any medicine for mental illness (such as chl thioridazine, Thorazine®, Mellaril®), or certain antibiotic medicines (such as gatifloxacin, moxifloxacin, Tequi
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant, planning to become pregnant, or if you are breastfeeding. T
have a history of seizures, heart disease, kidney disease, stroke, or breast cancer. Make sure your doctor kn
Parkinson's disease, any trouble with swallowing, or a history of blocked bowels or stomach and intestine pro
doctor if you have ever had thoughts of hurting yourself.

Make sure your doctor knows if you or a family member has a heart condition called congenital long QT synd
if you have ever had a condition called neuroleptic malignant syndrome (NMS) that was caused by a medicin
disorders.

This medicine may cause an increase in your blood sugar. If you have diabetes, you may need to check your
often. If you are using medicine for diabetes, your doctor may need to change your dose.

This medicine is not approved to treat behavior disorders in older people who have dementia. Using this med
problem could increase the risk of death. This risk has not been shown for the approved uses of this medicin
Some side effects are more likely to happen in elderly people who have memory problems or other reduced r
sure the doctor knows if the person who will be using this medicine has Alzheimer's disease or similar proble
"dementia").

This medicine may cause tardive dyskinesia, which is a movement disorder. If you have muscle spasms, twit
body, or uncontrolled tongue or jaw movements, stop taking this medicine and call your doctor right away. Ta
the risk of this side effect.

This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
are not alert. You may also feel lightheaded or dizzy when you get up quickly from a sitting or lying position. I
should get up slowly.

This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If
hot, you might feel dizzy, weak, tired, or confused. You might vomit or have an upset stomach. Do not get too
exercising. Avoid places that are very hot. Call your doctor if you are too hot and cannot cool down.

Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke
If your symptoms do not improve or if they get worse, call your doctor.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, c
breathing.

Dry mouth, increased thirst, muscle cramps, nausea, or vomiting.

Fast, slow, pounding, or irregular heartbeat.

Fever, confusion, sweating, or muscle stiffness.

Lightheadedness, dizziness, or fainting.

Neck muscle spasm, throat tightness, difficulty swallowing or breathing, or sticking out of the tongue.

Painful or prolonged erection of the penis.

Pinpoint red spots on skin.

Problems with speech, balance, or walking.

Seizures or tremors.

Swelling of breasts or unusual milk production.

Twitching or muscle movements you cannot control (often in your face, tongue, or jaw).

If you notice these less serious side effects, talk with your doctor:

Anxiety or restlessness.

Drooling.

Headache.

Sleepiness or unusual drowsiness.

Stomach pain or upset stomach.

Unusual tiredness or weakness.

Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Current users of atypical antipsychotic drugs (including paliperidone) and typical antipsychotic drugs had a similar
of sudden cardiac death, according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600
The study included patients age 30 to 74 years (mean 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline
filled prescription and had 1 outpatient visit in each of the 2 preceding years. Sudden cardiac death was defined as oc
community and excluded deaths of patients admitted to the hospital, non-sudden deaths, deaths due to extrinsic caus
related to ventricular tachyarrhythmia. Current use was defined as the interval between the time the prescription was f
the day's supply. Low and high doses was defined as comparable to less than 100 milligrams (mg) of chlorpromazine,
comparable to chlorpromazine 300 mg or greater, respectively. The adjusted rate of sudden cardiac death (incidence-
users of atypical antipsychotic drugs in 79,589 person-years was 2.26 (95% CI, 1.88 to 2.72, p less than 0.001) which
in current users of typical antipsychotic drugs in 86,735 person-years which was 1.99 (95% CI, 1.68 to 2.34, p less tha
sudden cardiac death significantly increased with increasing dose in both the typical and atypical antipsychotic drug gr
antipsychotic use, the incidence rate ratio increased from 1.59 (95% CI, 1.03 to 2.46) in low-dose use to 2.86 (95% CI
dose use. To limit the effects of confounding of the study results, there was a secondary analysis performed in a coho

by propensity score, which resulted in a similar risk of sudden death as the primary cohort analysis (Ray et al, 2009). I New England Journal of Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with benefit, but in vulnerable populations with cardiac risk profiles (eg, elderly patients), there should be an age-dependen prior to administration. It has also been suggested (although not formally tested) that ECGs be performed before and s of antipsychotic therapy to screen for existing or emergent QT interval prolongation (Schneeweiss & Avorn, 2009).
B) Paliperidone is a benzisoxazole derivative, and an active metabolite of risperidone. It is indicated for the treatment efficacy in improving positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, anxiety/depression among patients with schizophrenia has been established in three 6-week, multinational, fixed-dose and active-controlled (olanzapine) trials. While the mechanism of action of paliperidone is unclear, it is thought to bloc dopamine Type 2 (D(2)) and serotonin Type 2 (5HT(2A)) receptors, and has antagonistic effects on the alpha-1 adren adrenergic, and H1 histaminergic receptors (Prod Info INVEGA(TM) extended-release oral tablets, 2006). Due to the l efficacy data with haloperidol, fluphenazine, risperidone, and other conventional neuroleptics, the role of paliperidone i schizophrenia is unclear. Concomitant use of paliperidone with risperidone has not been studied.
C) Paliperidone extended-release is also being investigated as a monotherapy and as an adjunctive therapy to lithium treatment of acute manic and mixed episodes associated with bipolar I disorder, as well as in schizoaffective disorder.
See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHREN

4.4 Mechanism of Action / Pharmacology

A) Paliperidone is the major active metabolite of risperidone. While the mechanism of action is unknown, its proposed antagonism of both the central dopamine Type 2 (D(2)) and serotonin Type 2 (5HT(2A)) receptors. It also has antagon alpha-1 adrenergic, alpha-2 adrenergic, and H1 histaminergic receptors; however, the degree of affinity is unclear. Pal known affinity for cholinergic muscarinic or beta-1 and beta-2 adrenergic receptors (Prod Info INVEGA(TM) extended- 2006).

4.5 Therapeutic Uses

4.5.A Schizophrenia

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Paliperidone is indicated for the treatment of schizophrenia (Prod Info INVEGA(TM) extended-release or
A 6-week, randomized, double-blind, placebo- and active-controlled, dose-response study (n=630) demo daily paliperidone (6 milligrams (mg), 9 mg, and 12 mg) extended-release (ER) was effective in significar schizophrenia symptoms, personal functioning, and social functioning (Kane et al, 2007).
In a randomized, double-blind, placebo-controlled study (n=113), paliperidone extended-release (ER) tab delayed time-to-recurrence of schizophrenia symptoms and maintained symptom stability relative to plac 2007).
Geriatric patients (n=114) were safely treated with paliperidone extended-release tablets and although n for efficacy or safety and tolerability, clinical improvements were seen, according to a prospective, 6-wee randomized, placebo-controlled, optional 24-week open-label extension safety trial (Tzimos et al, 2008).

3) Adult:

a) Acute Therapy

1) A 6-week, randomized, double-blind, placebo- and active-controlled, dose-response study demonstra paliperidone (6 milligrams (mg), 9 mg, and 12 mg) extended-release (ER) was effective in significantly in symptoms, personal functioning, and social functioning. The enrolled patients (n=630) were greater than of age (mean age, 37.1 years), experiencing an acute episode of schizophrenia (Positive and Negative S (PANSS) score between 70 and 120), and had a diagnosis of schizophrenia according to the Diagnostic of Mental Disorders Fourth Edition (DSM-IV) for at least 1 year. After discontinuation of previous medicat antiparkinsonian drugs, beta-blockers or other psychotropic agents) for three days prior to randomization group (n=628) received either paliperidone ER 6 mg (n=123), paliperidone ER 9 mg (n=122), paliperidon olanzapine 10 mg (n=128), or placebo (n=126) once daily for 6 weeks. The primary efficacy variable was PANSS score from baseline to 6 weeks for each dose of paliperidone ER compared to placebo. The mea deviation (SD)) decrease in PANSS score was 17.9 (+/-22.2), 17.2 (+/-20.2), 23.3 (+/-20.1) for the 6 mg, paliperidone ER groups (p less than 0.001 vs placebo), respectively, compared with 4.1 (+/-23.2), and 19 placebo and olanzapine groups, respectively. All doses of paliperidone ER resulted in statistically signific placebo (p less than 0.001) in all PANSS Marder factor scores. Clinical response (defined as a greater th decrease in PANSS total score) was achieved in 56%, 51%, 61%, and 30% for the paliperidone ER 6 mg placebo groups, respectively (p less than 0.001 for all groups vs placebo). Improvement in personal and (+/- SD) scores was 9.1 (+/-15.5), 8.1 (+/-14.5), 11.5 (+/-16), and 0.5 (+/-15.5) for the paliperidone 6 mg, placebo groups, respectively (p less than 0.001). At 6 weeks, fewer patients were classified as marked o the Clinical and Global Impressions-Severity scale scores (paliperidone ER 6 mg: 62.6% at baseline vs 2 paliperidone ER 9 mg: 57.3% at baseline vs 23% at 6 weeks, paliperidone ER 12 mg: 64.4% at baseline placebo: 59.5% at baseline vs 50.8% at 6 weeks, p less than 0.001 for all doses vs placebo). The numbe

adverse effects in the safety analysis group (n=629) was similar among all groups. The most common ac
to discontinuation of the study was tachycardia (2% for paliperidone ER 12 mg, 1% in all other groups). F
showed no observable dose-response relationship for the severity of adverse events. The most common
effect was psychosis which occurred in 2% of the paliperidone ER 12 mg group, 1% of the placebo, palip
olanzapine groups, and in 0% of the paliperidone ER 9 mg group. Most movement disorder-related adve
to moderate in severity; 3 patients discontinued the study because of movement disorder-related adverse
paliperidone ER 6 mg group, 2 in the 12 mg group) (Kane et al, 2007).

b) Maintenance Therapy

1) In a randomized, double-blind, placebo-controlled study, paliperidone extended-release (ER) tablets s
time-to-recurrence of schizophrenia symptoms and maintained symptom stability relative to placebo. The
65 years old and had a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of
Fourth Edition (DSM-IV) for at least 1 year. The patients were also experiencing an acute episode of sch
and Negative Syndrome Scale (PANSS) total score of 70-120). The study consisted of an 8-week run-in
patients received open-label paliperidone ER, starting at 9 milligrams (mg) once daily and adjusted until
for at least 2 weeks (dose range: 3 to 15 mg once daily). This was followed by a 6-week open-label stabi
they remained on their stabilized dose. Patients then entered a double-blinded treatment phase in which
randomized to receive paliperidone ER or placebo for maintenance therapy. The patients remained in th
until they experienced a recurrence event (defined as: psychiatric hospitalization, a pre-defined increase
Clinical and Global Impression-Severity (CGI-S) score, deliberate self-injury, aggressive behavior, suicid
homicidal ideation), until they withdrew from the study or until the end of the study. The time to first recur
double-blind phase was the primary efficacy variable. At the interim analysis (n=113), the study was term
significant efficacy was established; 14 patients (25%) in the paliperidone ER group experienced a recur
to 29 patients (53%) in the placebo group. In the final analysis (n=205), paliperidone ER significantly dela
recurrence (25% quantile of time-to-recurrence was 83 days for paliperidone ER vs 23 days for placebo,
open-label phases of the trial, 73% of patients reported treatment-related adverse events while 37% of p
treatment-related adverse events in the double-blind phase. A 2 fold increase in treatment-related advers
reported for the placebo group than for the paliperidone ER group; most related to the underlying psycho
psychosis and aggressive reaction occurred more frequently in the placebo group (n=102, 23% and 6%,
the paliperidone ER group (n=104, 7% and 1%, respectively) (Kramer et al, 2007).

c) Geriatric

1) According to a prospective, 6-week, double-blind, randomized, placebo-controlled, optional 24-week
safety trial, paliperidone treatment was well tolerated in the geriatric population compared with placebo.
adverse events in geriatric patients receiving paliperidone extended-release tablets in general were simil
increased age-related incidences of somnolence and elevated pulse rate. Although the study was not su
efficacy or safety and tolerability, clinical improvements were seen in the Positive and Negative Syndrom
paliperidone-treated (n=76) versus placebo-treated patients (n=38) during the 6-week double-blind perio
difference in the change from baseline of -14.6 vs -9.9, respectively yielding a difference between groups
confidence interval, -9.9 to -1.1, p=0.014). There were nonsignificant differences seen between treatmen
Clinical Global Impressions Severity (CGI-S) scale, Personal and Social Performance Scale, and the Scl
Life Scale. The study included 114 patients (mean age of 70 years) with 99% having moderate to severe
receiving either placebo or median mean dose of paliperidone ER 8.4 milligrams/day (mg/day) during the
and median mean doses of 7.4 mg and 8.5 mg in the placebo/paliperidone ER and paliperidone ER/palip
respectively during the open-label phase (Tzimos et al, 2008).

4.6 Comparative Efficacy / Evaluation With Other Therapies

4.6.A Quetiapine Fumarate

4.6.A.1 Schizophrenia, Recent exacerbation, in hospitalized patients

a) In a randomized, double-blind, placebo- and active-controlled clinical trial (n=394), treatment with paliperid
(ER) produced significantly improved Positive and Negative Syndrome Scale (PANSS) total scores compared
hospitalized patients with a recent exacerbation of schizophrenia. Hospitalized patients 18 to 65 years of age
(defined as lasting less than 4 weeks but more than 4 days) of schizophrenia (paranoid, disorganized, or und
diagnosed using Diagnostic and Statistical Manual of Mental Disorders Fourth edition (DSM-IV)), a Clinical G
Severity (CGI-S) scale score of 5 or greater, and symptom scores of 4 or greater on 2 or more of the following
hostility, excitement, tension, uncooperativeness, and poor impulse control (with a combined score of these it
were eligible for enrollment. Following the discontinuation of all psychotropic agents, patients were randomize
paliperidone ER (n=157; baseline mean PANSS total score, 102.8 +/- 13.1 points), quetiapine (n=157; baseli
score, 101.3 +/- 13.3 points), or placebo (n=80; baseline mean PANSS total score, 103.8 +/- 15.7 points). In a
phase, paliperidone ER was initiated at 6 milligrams (mg)/day on days 1 to 3 and then increased to 9 mg/day
an optional dose increase to 12 mg/day starting on day 8 if necessary (mean dose, 10.4 +/- 1.7 mg/day) and
at 50 mg/day on day 1, 100 mg/day on day 2, 200 mg/day on day 3, 400 mg/day on day 4, 600 mg/day on da
dose increase to 800 mg/day on day 8 (mean dose, 690.9 +/- 134.3 mg/day). Psychotropic medications (excl
additional paliperidone ER or quetiapine) could be added following the 14-day monotherapy phase (one or m
agents: paliperidone ER, 52.9%; quetiapine, 55.4%; placebo, 66.7%). The least-squares mean PANSS total s
baseline to day 14 was significantly decreased in the paliperidone ER arm (-23.4 +/- 1.8 (standard error (SE)
with the quetiapine arm (-17.1 +/- 1.8 (SE) points; p less than 0.001) (primary endpoint) and the placebo arm
between group analyses (using a least-squares mean differences in change scores with the last observation

patients in the paliperidone ER arm had significantly improved PANSS total score, PANSS scale negative sy
PANSS scale disorganized thoughts scores, PANSS scale uncontrolled hostility/excitement scores, and CGI-
with patients in the quetiapine and placebo arms at day 14 and at the end of 6 weeks of treatment (day 42) (T
the PANSS scale positive symptoms score (PANSS-P) and Clinical Global Impression of Change (CGI-C) sc
improved in the paliperidone ER arm compared with the quetiapine and placebo arms at day 14 and paliperic
improved PANSS-P and CGI-C compared with placebo at day 42 (Table 1). Serious adverse events were rep
and 2.5% of patients in the paliperidone ER, quetiapine, and placebo arms, respectively. Extrapyramidal sym
significantly (p less than 0.001) higher in the paliperidone ER arm following the 14-day monotherapy phase c
quetiapine using the Simpson-Angus Rating Scale (total score). The incidence of movement disorders at day
significantly different between the 3 arms using the Barnes Akathisia Rating Scale and the Abnormal Involunt
(Canuso et al, 2009).

Table 1: Between Group Analyses

Outcome measures	Day 14			Day 42	
PANSS score Mean (SE)	Paliperidone ER versus Quetiapine	Paliperidone ER versus Placebo	Quetiapine versus Placebo	Paliperidone ER versus Quetiapine	Paliperidc ER versus Placebc
Total	-6.3* (1.8)	-8.4* (2.2)	-2.1 (2.2)	-4.7* (2)	-7.8* (2.
Positive symptoms	-1.6* (0.6)	-2.1* (0.7)	-0.5 (0.7)	-1.1 (0.6)	-1.9* (0.
Negative symptoms	-1.3* (0.5)	-2.2* (0.6)	-0.9 (0.6)	-1.2* (0.5)	-2.1* (0.
Anxiety/depression	-0.5 (0.3)	-0.6 (0.4)	-0.1 (0.4)	-0.4 (0.3)	-0.5 (0.4
Disorganized thoughts	-1.3* (0.4)	-2.1* (0.5)	-0.8 (0.5)	-1* (0.5)	-2* (0.6
Uncontrolled hostility/excitement	-1.5* (0.4)	-1.6* (0.5)	-0.1 (0.5)	-1* (0.4)	-1.3* (0.
CGI-S (Mean SE)	-0.3* (0.1)	-0.4* (0.1)	-0.1 (0.1)	-0.3* (0.1)	-0.5* (0.
CGI-C (Mean SE)	-0.4* (0.1)	-0.5* (0.1)	-0.2 (0.1)	-0.1 (0.1)	-0.4* (0.

*p less than 0.05

PANSS, Positive and Negative Syndrome Scale; SE, standard error; CGI-S, Clinical Global Impression
Clinical Global Impression of Change

6.0 References

1. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. Int J 2001; 5:33-40.
2. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. Int J 2001a; 5:33-40.
3. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. Int J 2001b; 5:33-40.
4. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. Int J 2001c; 5:33-40.
5. Amiel JM, Mangurian CV, Ganguli R, et al: Addressing cardiometabolic risk during treatment with antipsychotic me Psychiatry 2008; 21(6):613-618.
6. Ananth J: Tardive dyskinesia: myths and realities. Psychosomatics 1980; 21:394-396.
7. Batey SR: Schizophrenic disorders In: DiPiro JT, Talbert RL, Hayes PE, et al (Eds): Pharmacotherapy A Pathophys Elsevier, New York, NY, 1989.
8. Bostwick JR, Guthrie SK, & Ellingrod VL: Antipsychotic-induced hyperprolactinemia. Pharmacotherapy 2009; 29(1)
9. Canuso CM, Dirks B, Carothers J, et al: Randomized, double-blind, placebo-controlled study of paliperidone extenc quetiapine in inpatients with recently exacerbated schizophrenia. Am J Psychiatry 2009; 166(6):691-701.
10. Chien CP: Past history of drug and somatic treatments in tardive dyskinesia In: Fann WE, Smith RC, David JM, et a Dyskinesia. Research and Treatment, SP Medical & Scientific Books, New York, NY, 1980, pp 315-324.
11. Crane GE: Persistant dyskinesia. Br J Psychiatry 1973; 122:395-405.
12. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidone pc Toxicol 1999; 37(7):893-894.
13. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidone pc Toxicol 1999a; 37(7):893-894.
14. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidone pc Toxicol 1999b; 37(7):893-894.

15. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidone pc Toxicol 1999c; 37(7):893-894.
16. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidone pc Toxicol 1999d; 37(7):893-894.
17. Ereshefsky L & Richards A: Psychoses In: Ereshefsky L & Richards A: Young LY & Koda-Kimble MA: Applied Ther Use of Drugs, 4th. Applied Therapeutics Inc, Vancouver, WA, 1988.
18. Gill SS, Bronskill SE, Normand SL, et al: Antipsychotic drug use and mortality in older adults with dementia. Ann In (11):775-786.
19. Gilman AG, Goodman LS, Rall TW, et al: Goodman and Gilman's The Pharmacologic Basis of Therapeutics, 7th ec Publishing, New York, NY, 1985. Jeste DV & Wyatt RJ: Changing epidemiology of tardive dyskinesia: an overview. 1981; 138:297-309.
20. Hasnain M, Vieweg WV, Fredrickson SK, et al: Clinical monitoring and management of the metabolic syndrome in p atypical antipsychotic medications. Prim Care Diabetes 2008; Epub:1-.
21. Jimenez-Jimenez FJ, Garcia-Ruiz PJ, & Molina JA: Drug-induced movement disorders. Drug Saf 1997; 16(3):180-2
22. Jin H, Meyer JM, & Jeste DV: Atypical antipsychotics and glucose dysregulation: a systematic review. Schizophr R 212.
23. Kane J, Canas F, Kramer M, et al: Treatment of schizophrenia with paliperidone extended-release tablets: A 6-wee trial. Schizophr Res 2007; 90(1-3):147-161.
24. Khakee A & Hess GF: Mellaril(R) in the treatment of chronically disturbed patients. Am J Psychiatry 1960; 116:102
25. Kramer M, Simpson G, Maciulis V, et al: Paliperidone extended-release tablets for prevention of symptom recurren schizophrenia: a randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol 2007; 27(1):6-14.
26. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electro correlation. Ann Fr Anesth Reanim 1992; 11:629-635.
27. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electro correlation. Ann Fr Anesth Reanim 1992a; 11:629-635.
28. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electro correlation. Ann Fr Anesth Reanim 1992b; 11:629-635.
29. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electro correlation. Ann Fr Anesth Reanim 1992c; 11:629-635.
30. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electro correlation. Ann Fr Anesth Reanim 1992d; 11:629-635.
31. Leucht S, Corves C, Arbter D, et al: Second-generation versus first-generation antipsychotic drugs for schizophreni Lancet 2008; 373(9657):31-41.
32. Lieberman JA, Stroup TS, McEvoy JP, et al: Effectiveness of antipsychotic drugs in patients with chronic schizophr 2005; 353(12):1209-1223.
33. Lohr JB, Caligiuri MP, Edson R, et al: Treatment predictors of extrapyramidal side effects in patients with tardive dy Veterans Affairs Cooperative Study 394. J Clin Psychopharmacol 2002; 22(2):196-200.
34. Marder SR, Essock SM, Miller AL, et al: Physical health monitoring of patients with schizophrenia. Am J Psychiatry 1349.
35. Newcomer JW: Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. J Cli 68(Suppl 1):20-27.
36. Newcomer JW: Metabolic syndrome and mental illness. Am J Manag Care 2007; 13(7 Suppl):S170-S177.
37. None Listed: Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care
38. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999; 33:1046-1
39. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999a; 33:1046-
40. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999b; 33:1046-
41. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999c; 33:1046-
42. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999d; 33:1046-
43. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacotl 319.
44. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacotl 319.
45. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacotl 319.
46. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacotl 319.
47. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacotl 319.
48. Product Information: AVELOX(R) oral tablets, IV injection, moxifloxacin hcl oral tablets, IV injection. Schering-Plouc 2005.
49. Product Information: CORDARONE(R) oral tablets, amiodarone hcl oral tablets. Wyeth Pharmaceuticals,Inc, Philac
50. Product Information: Compazine(R), prochlorperazine maleate spansule. GlaxoSmithKline, Research Triangle Park
51. Product Information: DOLOPHINE(R) HYDROCHLORIDE oral tablets, methadone hcl oral tablets. Roxane Laborat OH, 2006.
52. Product Information: FANAPT(TM) oral tablets, iloperidone oral tablets. Vanda Pharmaceuticals, Rockville, MD, 20
53. Product Information: GEODON(R) intramuscular injection, oral capsule, ziprasidone hydrochloride oral capsule, zip intramuscular injection. Pfizer Inc, NY, NY, 2005.
54. Product Information: INVEGA(R) extended-release oral tablets, paliperidone extended-release oral tablets. Alza Cc

NJ, 2008b.
55. Product Information: INVEGA(R) extended-release oral tablets, paliperidone extended-release oral tablets. Janssen
56. Product Information: INVEGA(R) extended-release oral tablets, paliperidone extended-release oral tablets. Janssen 2008a.
57. Product Information: INVEGA(TM) extended-release oral tablets, paliperidone extended-release oral tablets. Alza C View, CA, 2006.
58. Product Information: INVEGA(TM) extended-release oral tablets, paliperidone extended-release oral tablets. Janss 2006a.
59. Product Information: INVEGA(TM) extended-release oral tablets, paliperidone extended-release oral tablets. Janss 2007.
60. Product Information: Mellaril(R), thioridazine. Mylan Pharmaceuticals Inc., Morgantown, WV, 2001.
61. Product Information: Norpace(R), disopyramide. G.D. Searle & Co., Chicago, IL, 1997.
62. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 2000.
63. Product Information: Quinaglute(R), quinidine gluconate. Berlex Laboratories, Wayne, NJ, 1999.
64. Product Information: Serentil(R), mesoridazine. Novartis Pharmaceuticals Corporation, East Hanover, NJ, 2001.
65. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999.
66. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999a.
67. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999b.
68. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999c.
69. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999d.
70. Product Information: Stelazine(R), trifluoperazine hydrochloride. GlaxoSmithKline, Research Triangle Park, NC, 20
71. Product Information: TASIGNA(R) oral capsules, nilotinib oral capsules. Novartis Pharmaceuticals Corporation, Eas
72. Product Information: TEQUIN(R) tablets, injection, gatifloxacin tablets, injection, gatifloxacin in 5% dextrose injectio Squibb Company, Princeton, NJ, 2006.
73. Product Information: TYKERB oral tablets, lapatinib oral tablets. GlaxoSmithKline, Research Triangle Park, NC, 20
74. Product Information: Thorazine(R), chlorpromazine. Smithkline Beecham Pharmaceuticals, Philadelphia, PA, 2002.
75. Product Information: Trisenox(R), arsenic trioxide injection. Cell Therapeutics, Inc., Seattle, WA, 2001.
76. Product Information: Trisenox(R), arsenic trioxide injection. Cell Therapeutics, Inc., Seattle, WA, 2001a.
77. Product Information: XENAZINE(R) oral tablets, tetrabenazine oral tablets. Prestwick Pharmaceuticals,Inc, Washin
78. Product Information: sotalol hcl oral tablets, sotalol hcl oral tablets. Teva Pharmaceuticals USA, Sellersville, PA, 20
79. Ray WA, Chung CP, Murray KT, et al: Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J M 235.
80. Saito M, Yasui-Furukori N, & Kaneko S: [Clinical pharmacogenetics in the treatment of schizophrenia]. Nihon Shink Zasshi 2005; 25(3):129-135.
81. Schneeweiss S & Avorn J: Antipsychotic agents and sudden cardiac death — How should we manage the risk?. N (3):294-296.
82. Schneeweiss S, Setoguchi S, Brookhart A, et al: Risk of death associated with the use of conventional versus atypi drugs among elderly patients. CMAJ 2007; 176(5):627-632.
83. Shader RI & DiMascio A (Eds): Psychotropic Drug Side Effects, Williams and Wilkins Company, Maryland, 1977.
84. Spina E, Avenoso A, Facciola G, et al: Plasma concentrations of risperidone and 9-hydroxyrisperidone during comb paroxetine. Ther Drug Monit 2001; 23:223-227.
85. Stroup TS, Lieberman JA, McEvoy JP, et al: Results of phase 3 of the CATIE schizophrenia trial. Schizophr Res 20
86. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version, M Greenwood Village, Colorado, Edition expires 06/2003.
87. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version, M Greenwood Village, Colorado, Edition expires 06/2003a.
88. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version, M Greenwood Village, Colorado, Edition expires 06/2003b.
89. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version, M Greenwood Village, Colorado, Edition expires 06/2004.
90. Tzimos A, Samokhvalov V, Kramer M, et al: Safety and tolerability of oral paliperidone extended-release tablets in e schizophrenia: a double-blind, placebo-controlled study with six-month open-label extension. Am J Geriatr Psychiat
91. Vermeir M, Naessens I, Remmerie B, et al: Absorption, metabolism, and excretion of paliperidone, a new monoami humans. Drug Metab Dispos 2008; 36(4):769-779.
92. Young D, Midha KK, Fossler MJ, et al: Effect of quinidine on the interconversion kinetics between haloperidol and r humans: implications for the involvement of cytochrome P450IID6. Eur J Clin Pharmacol 1993; 44:433-438.

Last Modified: June 25, 2009

DRUGDEX® Evaluations

LAMOTRIGINE

0.0 Overview

1) Class

a) This drug is a member of the following class(es):
Anticonvulsant
Phenyltriazine

2) Dosing Information

a) Adult

1) caution for potential for dispensing errors involving similarly named medications (Prod Info LAMICTAL chewab disintegrating tablets, 2009)

2) safety and efficacy as initial monotherapy, for conversion to monotherapy from a non-enzyme-inducing antiepi conversion to monotherapy from 2 or more concomitant antiepileptic drugs has not been established (Prod Info L orally disintegrating tablets, 2009)

a) Bipolar I disorder

1) (patients not taking enzyme-inducing drugs or valproic acid) 25 mg/day orally for 2 weeks, then 50 m 200 mg/day; usual maintenance dose of lamotrigine in patients not taking enzyme-inducing drugs or valp dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

2) (added to valproic acid regimen) 25 mg/day orally every other day for 2 weeks, then 25 mg/day for 2 usual maintenance dose of lamotrigine in patients taking valproic acid is 100 mg/day (Prod Info LAMICT disintegrating tablets, 2009)

3) (added to enzyme-inducing antiepileptic drug regimen without valproic acid) 50 mg/day orally for 2 we then 200 mg/day for 1 week (in divided doses), then 300 mg/day for 1 week (in divided doses), then may mg/day (in divided doses) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disi

b) Lennox-Gastaut syndrome; Adjunct

1) (added to antiepileptic drug regimen with valproic acid) 25 mg/day ORALLY every OTHER day for 2 dosage by 25 to 50 mg/day ORALLY every 1 to 2 weeks to the usual maintenance dose of 100 to 400 m of patients adding lamotrigine to valproic acid ALONE ranges from 100 to 200 mg/day (Prod Info LAMIC disintegrating tablets, 2009)

2) (added to antiepileptic drug regimen not containing enzyme-inducing antiepileptic drugs or valproic ac 2 weeks; may increase dosage by 50 mg/day every 1 to 2 weeks to the usual maintenance dose of 225 chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

3) (added to enzyme-inducing antiepileptic drug regimen without valproic acid) 50 mg/day ORALLY for 2 weeks; may increase dosage by 100 mg/day ORALLY every 1 to 2 weeks to the usual maintenance dos LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

c) Partial seizure, Adjunct or monotherapy

1) (chewable dispersible or orally disintegrating tablets; added to antiepileptic drug regimen with valproic then 25 mg/day for 2 weeks; may increase dosage by 25 to 50 mg/day ORALLY every 1 to 2 weeks to th 2 divided doses; usual maintenance dose of patients adding lamotrigine to valproic acid ALONE ranges dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

2) (chewable dispersible or orally disintegrating tablets; added to antiepileptic drug regimen not containi ORALLY for 2 weeks, then 50 mg/day for 2 weeks; may increase dosage by 50 mg/day every 1 to 2 wee in 2 divided doses (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrati

3) (chewable dispersible or orally disintegrating tablets; added to antiepileptic drug regimen containing e mg/day orally for 2 weeks, then 100 mg/day (in 2 divided doses) for 2 weeks; may increase dosage by 1 maintenance dose of 300 to 500 mg/day (in 2 divided doses) (Prod Info LAMICTAL chewable dispersible 2009)

4) (chewable dispersible or orally disintegrating tablets; conversion to monotherapy in patients, 16 yr an inducing antiepileptic drug) 500 mg/day orally (in 2 divided doses); titrate lamotrigine to the targeted dos withdraw the other drug by 20% decrements each week over a 4-week period (Prod Info LAMICTAL che disintegrating tablets, 2009)

5) (chewable dispersible or orally disintegrating tablets; conversion to monotherapy in patients, 16 yr an lamotrigine to 200 mg/day while maintaining valproic acid dose, the maintain lamotrigine dose at 200 mg by decrements no greater than 500 mg/day per week and then maintain the dose at 500 mg/day for 1 we while simultaneously decreasing the valproic acid to 250 mg/day and maintain this for 1 week, finally dis 100 mg/day each week until the maintenance dose of 500 mg/day is reached(Prod Info LAMICTAL chew disintegrating tablets, 2009)

6) (extended-release tablets; added to antiepileptic drug regimen with valproic acid) weeks 1 and 2, 25 mg/day; week 5, 50 mg/day; week 6, 100 mg/day; week 7, 150 mg/day; weeks 8 onwards to maintenanc 200 to 250 mg/day (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

7) (extended-release tablets; added to antiepileptic drug regimen not containing enzyme-inducing drugs weeks 3 and 4, 50 mg/day; week 5, 100 mg/day; week 6, 150 mg/day; week 7, 200 mg/day; weeks 8 on at weekly intervals), 300 to 400 mg/day (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

8) (extended-release tablets; added to antiepileptic drug regimen containing enzyme-inducing drugs and ORALLY; weeks 3 and 4, 100 mg/day; week 5, 200 mg/day; week 6, 300 mg/day; week 7, 400 mg/day; v 100 mg/day at weekly intervals), 400 to 600 mg/day (Prod Info LAMICTAL XR oral extended-release tab
9) (extended-release tablets; conversion from immediate-release lamotrigine tablets) initial, should matc need adjustments depending on therapeutic response after conversion (Prod Info LAMICTAL XR oral ex

d) Tonic-clonic seizure, Primary generalized; Adjunct

1) (added to antiepileptic drug regimen with valproic acid) 25 mg/day orally every other day for 2 weeks, 25 to 50 mg/day orally every 1 to 2 weeks to the usual maintenance dose of 100 to 400 mg/day in 1 to 2 adding lamotrigine to valproic acid alone ranges from 100 to 200 mg/day (Prod Info LAMICTAL chewable disintegrating tablets, 2009)
2) (added to antiepileptic drug regimen not containing enzyme-inducing antiepileptic drugs or valproic ac weeks; may increase dosage by 50 mg/day every 1 to 2 weeks to the usual maintenance dose of 225 to chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)
3) (added to enzyme-inducing antiepileptic drug regimen without valproic acid) 50 mg/day orally for 2 we may increase dosage by 100 mg/day orally every 1 to 2 weeks to the usual maintenance dose of 300 to chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

b) Pediatric

1) safety and efficacy of extended-release lamotrigine in patients below 13 years of age has not been established tablets, 2009)
2) safety and efficacy in pediatric patients with acute mood disorders has not been established (Prod Info LAMIC 2007)
3) efficacy in pediatric patients (age range, 1 to 24 months) for the treatment of partial seizures was not demonst tablets, oral tablets, orally disintegrating tablets, 2009)

a) Lennox-Gastaut syndrome; Adjunct

1) (2 to 12 yr; added to antiepileptic drug regimen with valproic acid) 0.15 mg/kg/day (rounded down to t doses for 2 weeks, then 0.3 mg/kg/day (rounded down to the nearest whole tablet) in 1 to 2 divided dose every 1 to 2 weeks (rounded down to the nearest whole tablet) to the usual maintenance dose of 1 to 5 r usual maintenance dose for children adding lamotrigine to valproic acid ALONE ranges from 1 to 3 mg/k tablets, oral tablets, orally disintegrating tablets, 2009)
2) (2 to 12 yr; added to antiepileptic drug regimen not containing enzyme-inducing antiepileptic drugs or nearest whole tablet) ORALLY in 1 to 2 divided doses for 2 weeks, then 0.6 mg/kg/day (rounded down to weeks; may increase dosage by 0.6 mg/kg/day every 1 to 2 weeks (rounded down to the nearest whole t mg/kg/day in 2 divided doses (max 300 mg/day) (Prod Info LAMICTAL chewable dispersible oral tablets,
3) (2 to 12 yr; added to enzyme-inducing antiepileptic drug regimen without valproic acid) 0.6 mg/kg/day 2 divided doses for 2 weeks, then 1.2 mg/kg/day (rounded down to the nearest whole tablet) in 2 divided mg/kg/day every 1 to 2 weeks (rounded down to the nearest whole tablet) to the usual maintenance dose mg/day) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets
4) (over age 12; added to antiepileptic drug regimen with valproic acid) 25 mg/day ORALLY every OTHE increase dosage by 25 to 50 mg/day ORALLY every 1 to 2 weeks to the usual maintenance dose of 100 maintenance dose of patients adding lamotrigine to valproic acid ALONE ranges from 100 to 200 mg/day tablets, oral tablets, orally disintegrating tablets, 2009)
5) (over age 12; added to antiepileptic drug regimen not containing enzyme-inducing antiepileptic drugs 50 mg/day for 2 weeks; may increase dosage by 50 mg/day every 1 to 2 weeks to the usual maintenanc Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)
6) (over age 12; added to enzyme-inducing antiepileptic drug regimen without valproic acid) 50 mg/day doses) for 2 weeks; may increase dosage by 100 mg/day ORALLY every 1 to 2 weeks to the usual main (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

b) Partial seizure, Adjunct or monotherapy

1) (chewable dispersible or orally disintegrating tablets; 2 to 12 yr; added to antiepileptic drug regimen w nearest whole tablet) ORALLY in 1 to 2 divided doses for 2 weeks, then 0.3 mg/kg/day (rounded down to weeks; may increase dosage by 0.3 mg/kg/day every 1 to 2 weeks (rounded down to the nearest whole t mg/kg/day in 1 to 2 divided doses (max 200 mg/day); usual maintenance dose for children adding lamotr mg/kg/day (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating table
2) (chewable dispersible or orally disintegrating tablets; 2 to 12 yr; added to antiepileptic drug regimen n valproic acid) 0.3 mg/kg/day (rounded down to the nearest whole tablet) ORALLY in 1 to 2 divided doses nearest whole tablet) in 2 divided doses for 2 weeks; may increase dosage by 0.6 mg/kg/day every 1 to 2 the usual maintenance dose of 4.5 to 7.5 mg/kg/day in 2 divided doses (max 300 mg/day) (Prod Info LAM orally disintegrating tablets, 2009)
3) (chewable dispersible or orally disintegrating tablets; 2 to 12 yr; added to enzyme-inducing antiepilept (rounded down to the nearest whole tablet) ORALLY in 2 divided doses for 2 weeks, then 1.2 mg/kg/day doses for 2 weeks; may increase dosage by 1.2 mg/kg/day every 1 to 2 weeks (rounded down to the nea 15 mg/kg/day in 2 divided doses (max 400 mg/day) (Prod Info LAMICTAL chewable dispersible oral table
4) (chewable dispersible or orally disintegrating tablets, over age 12; added to antiepileptic drug regimen day for 2 weeks, then 25 mg/day for 2 weeks; may increase dosage by 25 to 50 mg/day ORALLY every 400 mg/day in 1 to 2 divided doses; usual maintenance dose of patients adding lamotrigine to valproic ac LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)
5) (chewable dispersible or orally disintegrating tablets; over age 12; added to antiepileptic drug regimen valproic acid) 25 mg/day ORALLY for 2 weeks, then 50 mg/day for 2 weeks; may increase dosage by 50

dose of 225 to 375 mg/day in 2 divided doses (Prod Info LAMICTAL chewable dispersible oral tablets, or
6) (chewable dispersible or orally disintegrating tablets; over age 12; added to enzyme-inducing antiepil
ORALLY for 2 weeks, then 100 mg/day (in 2 divided doses) for 2 weeks; may increase dosage by 100 m
maintenance dose of 300 to 500 mg/day (in 2 divided doses) (Prod Info LAMICTAL chewable dispersible
2009)
7) (extended-release tablets; age 13 and older; added to antiepileptic drug regimen with valproic acid) w
weeks 3 and 4, 25 mg/day; week 5, 50 mg/day; week 6, 100 mg/day; week 7, 150 mg/day; week 8 onwa
100 mg/day at weekly intervals), 200 to 250 mg/day (Prod Info LAMICTAL XR oral extended-release tab
8) (extended-release tablets; age 13 and older; added to antiepileptic drug regimen not containing enzy
mg/day ORALLY; weeks 3 and 4, 50 mg/day; week 5, 100 mg/day; week 6, 150 mg/day; week 7, 200 mg
should not exceed 100 mg/day at weekly intervals), 300 to 400 mg/day (Prod Info LAMICTAL XR oral ex
9) (extended-release tablets; age 13 and older; added to antiepileptic drug regimen containing enzyme-i
2, 50 mg/day ORALLY; weeks 3 and 4, 100 mg/day; week 5, 200 mg/day; week 6, 300 mg/day; week 7,
increase should not exceed 100 mg/day at weekly intervals), 400 to 600 mg/day (Prod Info LAMICTAL X
10) (extended-release tablets; age 13 and older; conversion from immediate-release lamotrigine tablets)
release lamotrigine; may need adjustments depending on therapeutic response after conversion (Prod In

c) Tonic-clonic seizure, Primary generalized; Adjunct
1) (2 to 12 yr; added to antiepileptic drug regimen with valproic acid) 0.15 mg/kg/day (rounded down to t
for 2 weeks, then 0.3 mg/kg/day (rounded down to the nearest whole tablet) in 1 to 2 divided doses for 2
to 2 weeks (rounded down to the nearest whole tablet) to the usual maintenance dose of 1 to 5 mg/kg/da
maintenance dose for children adding lamotrigine to valproic acid ALONE ranges from 1 to 3 mg/kg/day
oral tablets, orally disintegrating tablets, 2009)
2) (2 to 12 yr; added to antiepileptic drug regimen not containing enzyme-inducing antiepileptic drugs or
nearest whole tablet) ORALLY in 1 to 2 divided doses for 2 weeks, then 0.6 mg/kg/day (rounded down to
weeks; may increase dosage by 0.6 mg/kg/day every 1 to 2 weeks (rounded down to the nearest whole t
mg/kg/day in 2 divided doses (max 300 mg/day) (Prod Info LAMICTAL chewable dispersible oral tablets,
3) (2 to 12 yr; added to enzyme-inducing antiepileptic drug regimen without valproic acid) 0.6 mg/kg/day
divided doses for 2 weeks, then 1.2 mg/kg/day (rounded down to the nearest whole tablet) in 2 divided d
mg/kg/day every 1 to 2 weeks (rounded down to the nearest whole tablet) to the usual maintenance dose
mg/day) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets
4) (over age 12; added to antiepileptic drug regimen with valproic acid) 25 mg/day orally every other day
increase dosage by 25 to 50 mg/day ORALLY every 1 to 2 weeks to the usual maintenance dose of 100
maintenance dose of patients adding lamotrigine to valproic acid alone ranges from 100 to 200 mg/day (
oral tablets, orally disintegrating tablets, 2009)
5) (over age 12; added to antiepileptic drug regimen not containing enzyme-inducing antiepileptic drugs
mg/day for 2 weeks; may increase dosage by 50 mg/day every 1 to 2 weeks to the usual maintenance d
LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)
6) (over age 12; added to enzyme-inducing antiepileptic drug regimen without valproic acid) 50 mg/day
for 2 weeks; may increase dosage by 100 mg/day ORALLY every 1 to 2 weeks to the usual maintenance
Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

3) Contraindications
a) hypersensitivity to lamotrigine or any component of the product (Prod Info LAMICTAL chewable dispersible oral tab
Prod Info LAMICTAL XR oral extended-release tablets, 2009)

4) Serious Adverse Effects
a) Anemia
b) Angioedema
c) Disseminated intravascular coagulation
d) Eosinophil count raised
e) Erythema multiforme
f) Leukopenia
g) Liver failure
h) Stevens-Johnson syndrome
i) Thrombocytopenia
j) Toxic epidermal necrolysis

5) Clinical Applications
a) FDA Approved Indications
1) Bipolar I disorder
2) Lennox-Gastaut syndrome; Adjunct
3) Partial seizure, Adjunct or monotherapy
4) Tonic-clonic seizure, Primary generalized; Adjunct

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In

B) Synonyms

Lamotrigine

C) Orphan Drug Status

1) Lamotrigine has been designated an orphan product for use in the treatment of Lennox-Gastaut syndrome.

D) Physicochemical Properties

1) Molecular Weight

a) 256.09 (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) pKa

a) 5.7 (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

3) Solubility

a) Lamotrigine is very slightly soluble in water (0.17 mg/mL at 25 degrees C) and slightly soluble in 0.1 mola LAMICTAL XR oral extended-release tablets, 2009).

1.2 Storage and Stability

A) Preparation

1) Oral route

a) Chewable Dispersible Tablets

1) Chewable dispersible tablets may be swallowed whole, chewed, or dispersed in water or diluted fruit nearest whole tablet. Disperse by adding tablets to a small amount of liquid (1 teaspoon, or enough to co dispersed (approximately 1 min), swirl solution and consume entire volume immediately (Prod Info LAMI orally disintegrating tablets, 2009).

b) Orally Disintegrating Tablets

1) Orally disintegrating tablets should be placed onto the tongue and moved around in the mouth. The ta without water and may be taken with or without food (Prod Info LAMICTAL chewable dispersible oral tab

c) Extended-Release Tablets

1) Extended-release tablets must be swallowed whole with or without food. The tablet must not be chew extended-release tablets, 2009).

B) Lamotrigine 25 milligrams (mg) tablets and lamotrigine chewable dispersible 2 mg, 5 mg and 25 mg tablets should Fahrenheit (F)) with excursions permitted between 15 and 30 degrees C (59 to 86 degrees F) in a dry place. Lamotrigi stored at 25 degrees C (77 degrees F) with excursions permitted between 15 to 30 degrees C (59 to 86 degrees F) in (R), 2003f).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Other Disease States

1.3.1 Normal Dosage

1.3.1.A Oral route

Bipolar I disorder

Lennox-Gastaut syndrome; Adjunct

Partial seizure, Adjunct or monotherapy

Tonic-clonic seizure, Primary generalized; Adjunct

1.3.1.A.1 Bipolar I disorder

a) Not Taking Enzyme-Inducing Antiepileptic Drugs or Valproic Acid

1) The target dose of lamotrigine is 200 milligrams (mg)/day. Doses up to 400 mg/day as monothera benefit was observed at 400 mg/day as compared to 200 mg/day (Prod Info LAMICTAL chewable di tablets, 2009)

2) For patients not taking carbamazepine (or other enzyme-inducing drugs) or valproic acid:

Weeks 1 and 2:	25 mg/day
Weeks 3 and 4:	50 mg/day
Week 5:	100 mg/day
Week 6:	200 mg/day
Week 7:	200 mg/day (target dose)

b) Added to Valproic Acid Regimen

1) The target dose of lamotrigine in combination with valproic acid is 100 mg/day (Prod Info LAMIC disintegrating tablets, 2009):

2) For patients taking valproic acid:

Weeks 1 and 2:	25 mg every other day
Weeks 3 and 4:	25 mg/day
Week 5:	50 mg/day
Week 6:	100 mg/day
Week 7:	100 mg/day (target dose)

c) Added to Enzyme-Inducing Antiepileptic Drug Regimen (Without Valproic Acid)

1) The target dose of lamotrigine in combination with carbamazepine or other enzyme-inducing dru dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).

2) For patients taking carbamazepine (or other enzyme-inducing drugs), but not taking valproic acid

Weeks 1 and 2:	50 mg/day
Weeks 3 and 4:	100 mg/day (divided doses)
Week 5:	200 mg/day (divided doses)
Week 6:	300 mg/day (divided doses)
Week 7:	400 mg/day (divided doses) (target dose)

d) Adjustment - Discontinuation of Psychotropics

1) For discontinuation of psychotropic drugs excluding valproic acid, carbamazepine, or other enzyr dose (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablet

e) Adjustment - Discontinuation of Valproic Acid

1) For patients discontinuing valproic acid, the dose of lamotrigine should be doubled over a 2-weel LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):

AFTER DISCONTINUATION OF VALPROIC ACID	
Current lamotrigine dose:	100 mg/day
Week 1:	150 mg/day
Week 2:	200 mg/day
Week 3 and onward:	200 mg/day

f) Adjustment - Discontinuation of Carbamazepine

1) For patients discontinuing carbamazepine or other enzyme-inducing agents, the dose of lamotrig should be decreased by half over a 2-week period in equal weekly decrements. The dose may then mg/day (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tab

AFTER DISCONTINUATION OF CARBAMAZEPINE OR OTHER ENZYME-INDUCING DRUGS	
Current lamotrigine dose:	400 mg/day
Week 1:	400 mg/day
Week 2:	300 mg/day
Week 3 and onward:	200 mg/day

1.3.1.A.2 Lennox-Gastaut syndrome; Adjunct

a) With Valproic Acid

1) For adult patients adding lamotrigine to an antiepileptic drug (AED) regimen containing valproic a tablets, oral tablets, orally disintegrating tablets, 2009):

Lamotrigine added to antiepileptic drug (AED) regimen containing valproic acid:

Weeks 1 and 2: 25 milligrams (mg) every other day

Weeks 3 and 4: 25 mg every day

Week 5 and onward: Doses may be increased by 25 to 50 mg/day every 1 to 2 weeks to ac
Usual maintenance dose: 100 to 400 mg/day (1 or 2 divided doses)
The usual maintenance dose in patients adding lamotrigine to valproic acid alone rang

b) Without Valproic Acid

1) For adult patients receiving enzyme-inducing antiepileptic drugs (EIAED) (carbamazepine, phen
(Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 20(
Lamotrigine added to EIAED regimen without valproic acid:
Weeks 1 and 2: 50 mg/day
Weeks 3 and 4: 100 mg/day (in 2 divided doses)
Week 5 and onward: Doses may be increased by 100 mg/day every 1 to 2 weeks to achiev
Usual maintenance dose: 300 to 500 mg/day (in two divided doses)

c) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid

1) For adult patients adding lamotrigine to an antiepileptic drug (AED) regimen not containing enzyr
LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009) :
Lamotrigine added to AED regimen not containing drug-inducing AED or valproic acid:
Weeks 1 and 2: 25 mg/day
Weeks 3 and 4: 50 mg/day
Wee 5 and onward: Doses may be increased by 50 mg/day every 1 to 2 weeks to achieve
Usual maintenance dose: 225 to 375 mg/day (in 2 divided doses)

1.3.1.A.3 Partial seizure, Adjunct or monotherapy

a) With Valproic Acid

1) For patients age 13 years or older adding extended-release lamotrigine to an antiepileptic drug (
LAMICTAL XR oral extended-release tablets, 2009):
Extended-release lamotrigine added to AED regimen containing valproic acid:
Weeks 1 and 2: 25 milligrams (mg) once every other day
Weeks 3 and 4: 25 mg once daily
Week 5: 50 mg once daily
Week 6: 100 mg once daily
Week 7: 150 mg once daily
Week 8 onwards to maintenance: 200 to 250 mg once daily
Dose increase at week 8 or later should not exceed 100 mg daily at weekly intervals

2) For adult patients adding chewable dispersible or orally disintegrating lamotrigine to an antiepilep
Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):
Chewable dispersible or orally disintegrating lamotrigine added to AED regimen containing valp
Weeks 1 and 2: 25 milligrams (mg) every other day
Weeks 3 and 4: 25 mg every day
Week 5 and onward: Doses may be increased by 25 to 50 mg/day every 1 to 2 weeks to ac
Usual maintenance dose: 100 to 400 mg/day (1 or 2 divided doses)
The usual maintenance dose in patients adding lamotrigine to valproic acid alone rang

b) Without Valproic Acid

1) (extended-release tablets) For patients 13 years or older receiving enzyme-inducing antiepileptic
phenobarbital, or primidone) without valproic acid (Prod Info LAMICTAL XR oral extended-release ta
Extended-release lamotrigine added to EIAED regimen without valproic acid:
Weeks 1 and 2: 50 mg once daily
Weeks 3 and 4: 100 mg once daily
Week 5: 200 mg once daily
Week 6: 300 mg once daily
Week 7: 400 mg once daily
Week 8 onwards to maintenance: 400 to 600 mg once daily
Dose increase at week 8 or later should not exceed 100 mg daily at weekly intervals

2) (chewable dispersible or orally disintegrating tablets) For adult patients receiving enzyme-inducir
phenytoin, phenobarbital, or primidone) without valproic acid (Prod Info LAMICTAL chewable disper
tablets, 2009):
Chewable dispersible or orally disintegrating lamotrigine added to EIAED regimen without valpr
Weeks 1 and 2: 50 mg/day
Weeks 3 and 4: 100 mg/day (in 2 divided doses)
Week 5 and onward: Doses may be increased by 100 mg/day every 1 to 2 weeks to achiev
Usual maintenance dose: 300 to 500 mg/day (in two divided doses)

c) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid

1) For patients 13 years or older adding extended-release lamotrigine to an antiepileptic drug (AED)
valproic acid (Prod Info LAMICTAL XR oral extended-release tablets, 2009):
Extended-release lamotrigine added to EIAED regimen without valproic acid:
Weeks 1 and 2: 25 mg once daily
Weeks 3 and 4: 50 mg once daily
Week 5: 100 mg once daily
Week 6: 150 mg once daily
Week 7: 200 mg once daily

Week 8 onwards to maintenance: 300 to 400 mg once daily
Dose increase at week 8 or later should not exceed 100 mg daily at weekly intervals

2) For adult patients adding chewable dispersible or orally disintegrating lamotrigine to an antiepilep properties or valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orall

Chewable dispersible or orally disintegrating lamotrigine added to AED regimen not containing

Weeks 1 and 2: 25 mg/day
Weeks 3 and 4: 50 mg/day
Week 5 and onward: Doses may be increased by 50 mg/day every 1 to 2 weeks to achieve
Usual maintenance dose: 225 to 375 mg/day (in 2 divided doses)

d) Conversion from Immediate-Release to Extended-Release Formulation

1) The initial dose of extended-release lamotrigine in patients age 13 years and older should match Depending on the therapeutic response after conversion, the total daily dose may need to be adjust Info LAMICTAL XR oral extended-release tablets, 2009).

e) Conversion to Monotherapy, With Enzyme-Inducing Antiepileptic Drug

1) The recommended dose for conversion from adjunctive therapy with a single-enzyme-inducing a patients 16 years-old and older, is 500 milligrams/day (mg/day) given in 2 divided doses. Lamotrigin maintaining the first drug at a fixed level. Lamotrigine should be titrated as follows (Prod Info LAMIC orally disintegrating tablets, 2009):

Weeks 1 and 2: 50 mg/day
Weeks 3 and 4: 100 mg/day (in two divided doses)
Doses may be increased by 100 mg/day every 1 to 2 weeks to achieve maintenance.
After achieving a dose of 500 mg/day of lamotrigine, withdrawal of the concomitant drug should each week.

f) Conversion to Monotherapy, With Valproic Acid

The recommended dose for conversion from adjunctive therapy with valproic acid to monotherapy w 500 milligrams/day (mg/day) given in 2 divided doses. The conversion regimen involves 4 steps. Firs dose while maintaining the valproic acid dose at a fixed level. Lamotrigine should be titrated as follo tablets, oral tablets, orally disintegrating tablets, 2009):

Weeks 1 and 2: 25 mg every other day
Weeks 3 and 4: 25 mg every day
Doses may be increased by 25 to 50 mg/day every 1 to 2 weeks to achieve the target dose.

Secondly, while maintaining the lamotrigine dose at 200 mg/day, valproic acid should be gradually d 500 mg/day per week. This regimen should be maintained for 1 week. Thirdly, the lamotrigine dose acid is simultaneously decreased to 250 mg/day. This regimen should also be maintained for 1 weel completely and lamotrigine should be increased by 100 mg/day every week until the recommended LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).

g) Conversion to Monotherapy, With Non-Enzyme-Inducing Antiepileptic Drug

1) The effects of non-enzyme-inducing antiepileptic drugs other than valproic acid on the metabolis no dosing guidelines can be provided for the safe and effective conversion to monotherapy with lam tablets, oral tablets, orally disintegrating tablets, 2009).

h) Partial Seizures - Refractory

1) In the treatment of simple and complex partial seizures refractory to multiple combinations of ant milligrams/day has been effective. Dose adjustments are made based on clinical response rather th had trough plasma levels in the range of 1 to 4 micrograms/milliliter (Graves & Leppik, 1991; Jawad

1.3.1.A.4 Tonic-clonic seizure, Primary generalized; Adjunct

a) With Valproic Acid

1) For adult patients adding lamotrigine to an antiepileptic drug (AED) regimen containing valproic a tablets, oral tablets, orally disintegrating tablets, 2009):

Lamotrigine added to antiepileptic drug (AED) regimen containing valproic acid:

Weeks 1 and 2: 25 milligrams (mg) every other day
Weeks 3 and 4: 25 mg every day
Week 5 and onward: Doses may be increased by 25 to 50 mg/day every 1 to 2 weeks to ac
Usual maintenance dose: 100 to 400 mg/day (1 or 2 divided doses)
The usual maintenance dose in patients adding lamotrigine to valproic acid alone rang

b) Without Valproic Acid

1) For adult patients receiving enzyme-inducing antiepileptic drugs (EIAED) (carbamazepine, pheny (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 20

Lamotrigine added to EIAED regimen without valproic acid:

Weeks 1 and 2: 50 mg/day
Weeks 3 and 4: 100 mg/day (in 2 divided doses)
Week 5 and onward: Doses may be increased by 100 mg/day every 1 to 2 weeks to achiev
Usual maintenance dose: 300 to 500 mg/day (in two divided doses)

c) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid

1) For adult patients adding lamotrigine to an antiepileptic drug (AED) regimen not containing enzyr LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):

Lamotrigine added to AED regimen not containing drug-inducing AED or valproic acid:

Weeks 1 and 2: 25 mg/day

Weeks 3 and 4: 50 mg/day
Wee 5 and onward: Doses may be increased by 50 mg/day every 1 to 2 weeks to achieve
Usual maintenance dose: 225 to 375 mg/day (in 2 divided doses)

1.3.1.B Important Note

1) Use caution when dispensing lamotrigine (Lamictal(R), Lamisil(R), lamivudine, Ludiomil(R), labetalol, and errors involving these similarly named medications (Prod Info LAMICTAL chewable dispersible oral tablets, o

2) Safety and efficacy of lamotrigine has not been established (Prod Info LAMICTAL chewable dispersible or 2009):

- as initial monotherapy
- for conversion to monotherapy from a non-enzyme-inducing antiepileptic agent other than valproic acid
- for simultaneous conversion to monotherapy from 2 or more concomitant antiepileptic drugs

1.3.1.C Withdrawal

1) In patients requiring discontinuation of lamotrigine, the dosage should be decreased by about 50% per we patient's safety require a more rapid withdrawal. Discontinuing an enzyme-inducing antiepileptic agent should valproic acid should shorten the half-life of lamotrigine (Prod Info LAMICTAL(R) oral tablets, chewable disper extended-release tablets, 2009).

1.3.2 Dosage in Renal Failure

A) Use reduced maintenance doses in patients with significant renal impairment. Use with caution in patients with Prod Info LAMICTAL XR oral extended-release tablets, 2009).

B) Twenty volunteers with chronic renal failure (mean creatinine clearance 13 milliliters/minute) were given a sing prolonged compared to that observed in volunteers with normal renal function (50 hours vs 25 hours). Another 6 p milligram dose of lamotrigine. On average, approximately 17% (range 5.6% to 35.1%) of lamotrigine was removed life in these patients during hemodialysis was 12.2 hours, while that between sessions was 59.6 hours (Fillastre e

C) Dosage of lamotrigine need not be altered in the presence of impaired renal function since lamotrigine disposi the pharmacokinetics of lamotrigine in 10 subjects with renal failure (estimated creatinine clearance of 10.6 to 25. maximum concentration and area-under-the curve were similar since lamotrigine was largely cleared by metabolis to accumulate. Therefore, impaired renal function would have little effect on the plasma concentrations of lamotrig

1.3.3 Dosage in Hepatic Insufficiency

A) The manufacturer recommends that in patients with moderate and severe liver impairment without ascites, the reduced by approximately 25%. In patients with severe hepatic impairment with ascites, the initial, escalation, and approximately 50%. Clinical response should also be considered during escalation and maintenance dosing (Prod oral tablets, 2006) (Prod Info LAMICTAL XR oral extended-release tablets, 2009).

1.3.6 Dosage in Other Disease States

A) Hyperbilirubinemia

1) Elimination of lamotrigine is not significantly impaired in patients with Gilbert's syndrome (unconjugated hy

B) Pregnancy

1) Dose-normalized lamotrigine concentrations progressively decreased during pregnancy with a 40% and 6 women on lamotrigine monotherapy in 2 retrospective studies (n=12 and n=11. respectively). Lamotrigine cle trimester in a retrospective (n=12) and prospective (n=14) study, respectively. The clearance and concentrati delivery. Other evidence suggest that there was a less pronounced reduction in lamotrigine plasma concentra enzyme-inducing antiepileptic drugs or valproic acid (Tomson & Battino, 2007).

2) Lamotrigine clearance increased by more than 50% in some women at the onset of pregnancy with a drar reversed soon after delivery. Increased doses of lamotrigine may be required to maintain therapeutic levels d following pregnancy (Tran et al, 2002a).

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Other Disease States

1.4.1 Normal Dosage

1.4.1.A Oral route

Convulsions in the newborn, Intractable

Epilepsy, Refractory

Lennox-Gastaut syndrome; Adjunct

Partial seizure, Adjunct or monotherapy

Status epilepticus

Tonic-clonic seizure, Primary generalized; Adjunct

1.4.1.A.1 Convulsions in the newborn, Intractable

a) Adjunctive lamotrigine was successful in reducing the number of seizures in patients with intractable label study. In neonates who were taking enzyme-inducing agents, doses up to 10 milligrams per kilogra between 1 and 12 months of age, who were taking enzyme- inducing agents, final doses ranged betwee of age, taking valproate and enzyme inducers, were dosed between 5 to 10 mg/kg/day. In infants betwee mg/kg/day was the final dose (Mikati et al, 2002).

1.4.1.A.2 Epilepsy, Refractory

a) Lamotrigine is effective in intractable childhood epilepsy. Doses of lamotrigine 2 to 15 milligrams/kilog (maximum of 15 milligrams/kilogram/day used in patients on enzyme-inducing antiepileptic drugs (AEDs) valproate only) (Gibbs et al, 1992); (Yven et al, 1992)(Mims, 1992; Hosking, 1993; Pons, 1993).

1.4.1.A.3 Lennox-Gastaut syndrome; Adjunct

a) Age 2 to 12 Years

1) With Valproic Acid

a) For patients 2 to 12 years of age adding lamotrigine to an antiepileptic drug (AED) regimen dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):

Lamotrigine added to AED regimen containing valproic acid in patients 2 to 12 years of age

Weeks 1 and 2: 0.15 milligram/kilogram/day (mg/kg/day) in one or two divided doses, tablets should be used for dosing

Weeks 3 and 4: 0.3 mg/kg/day in one or two divided doses, rounded down to the neare

Week 5 and onward: Doses may be increased every 1 to 2 weeks by 0.3 mg/kg/day, r the previously administered daily dose to achieve maintenance.

Usual maintenance dose: 1 to 5 mg/kg/day (maximum 200 mg/day in 1 or 2 divided do

The usual maintenance dose in patients adding lamotrigine to valproic acid alone

Maintenance doses in patients weighing less than 30 kg may need to be increase

INITIAL WEIGHT BASED DOSING GUIDE:

Patient weight 6.7 to 14 kg, dose for weeks 1 and 2 is 2 mg every other day; dose

Patient weight 14.1 to 27 kg, dose for weeks 1 and 2 is 2 mg every day; dose for

Patient weight 27.1 to 34 kg, dose for weeks 1 and 2 is 4 mg every day; dose for

Patient weight 34.1 to 40 kg, dose for weeks 1 and 2 is 5 mg every day; dose for

2) Without Valproic Acid

a) For patients age 2 to 12 years old receiving enzyme-inducing antiepileptic drugs (EIAED) (c without valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally

Lamotrigine added to EIAED regimen without valproic acid in patients 2 to 12 years of age:

Weeks 1 and 2: 0.6 milligram/kilogram/day (mg/kg/day) in two divided doses, rounded

Weeks 3 and 4: 1.2 mg/kg/day in two divided doses, rounded down to the nearest whc

Week 5 and onward: Doses may be increased every 1 to 2 weeks by 1.2 mg/kg/day, r the previously administered daily dose to achieve maintenance.

Usual maintenance dose: 5 to 15 mg/kg/day (maximum 400 mg/day in 2 divided doses

Maintenance doses in patients weighing less than 30 kg may need to be increase

3) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid

a) For patients 2 to 12 years of age adding lamotrigine to an antiepileptic drug (AED) regimen acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating ta

Lamotrigine added to an antiepileptic drug (AED) regimen not containing drug-inducing AE

Weeks 1 and 2: 0.3 milligram/kilogram/day (mg/kg/day) in one or two divided doses, r tablets should be used for dosing.

Weeks 3 and 4: 0.6 mg/kg/day in two divided doses, rounded down to the nearest whc

Week 5 and onward: Doses may be increased every 1 to 2 weeks by 0.6 mg/kg/day, r the previously administered daily dose to achieve maintenance.

Usual maintenance dose: 4.5 to 7.5 mg/kg/day (maximum 300 mg/day in 2 divided dos

Maintenance doses in patients weighing less than 30 kg may need to be increase

b) Age 12 Years and Older

1) With Valproic Acid

a) For patients 12 years and older adding lamotrigine to an antiepileptic drug (AED) regimen cc
dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):
Lamotrigine added to antiepileptic drug (AED) regimen containing valproic acid:
Weeks 1 and 2: 25 milligrams (mg) every other day
Weeks 3 and 4: 25 mg every day
Week 5 and onward: Doses may be increased by 25 to 50 mg/day every 1 to 2 weeks
Usual maintenance dose: 100 to 400 mg/day (1 or 2 divided doses)
The usual maintenance dose in patients adding lamotrigine to valproic acid alone

2) Without Valproic Acid

a) For patients 12 years and older receiving enzyme-inducing antiepileptic drugs (EIAED) (carb
without valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally
Lamotrigine added to EIAED regimen without valproic acid:
Weeks 1 and 2: 50 mg/day
Weeks 3 and 4: 100 mg/day (in 2 divided doses)
Week 5 and onward: Doses may be increased by 100 mg/day every 1 to 2 weeks to ac
Usual maintenance dose: 300 to 500 mg/day (in two divided doses)

3) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid

a) For patients 12 years and older adding lamotrigine to an antiepileptic drug (AED) regimen nc
acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating ta
Lamotrigine added to AED regimen not containing drug-inducing AED or valproic acid:
Weeks 1 and 2: 25 mg/day
Weeks 3 and 4: 50 mg/day
Wee 5 and onward: Doses may be increased by 50 mg/day every 1 to 2 weeks to achi
Usual maintenance dose: 225 to 375 mg/day (in 2 divided doses)

1.4.1.A.4 Partial seizure, Adjunct or monotherapy

a) Extended-release Tablets, Age 13 Years and Older

1) With Valproic Acid

a) For patients 13 years of age and older adding extended-release lamotrigine to an antiepilept
Info LAMICTAL XR oral extended-release tablets, 2009):
Extended-release lamotrigine added to AED regimen containing valproic acid:
Weeks 1 and 2: 25 milligrams (mg) once every other day
Weeks 3 and 4: 25 mg once daily
Week 5: 50 mg once daily
Week 6: 100 mg once daily
Week 7: 150 mg once daily
Week 8 onwards to maintenance: 200 to 250 mg once daily
Dose increase at week 8 or later should not exceed 100 mg daily at weekly intervals

1) Without Valproic Acid

a) (extended-release tablets) For patients 13 years or older receiving enzyme-inducing ant
phenobarbital, or primidone) without valproic acid (Prod Info LAMICTAL XR oral extended-
Extended-release lamotrigine added to EIAED regimen without valproic acid:
Weeks 1 and 2: 50 mg once daily
Weeks 3 and 4: 100 mg once daily
Week 5: 200 mg once daily
Week 6: 300 mg once daily
Week 7: 400 mg once daily
Week 8 onwards to maintenance: 400 to 600 mg once daily
Dose increase at week 8 or later should not exceed 100 mg daily at weekly interva

2) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid

a) For patients 13 years or older adding extended-release lamotrigine to an antiepileptic dr
properties or valproic acid (Prod Info LAMICTAL XR oral extended-release tablets, 2009):
Extended-release lamotrigine added to EIAED regimen without valproic acid:
Weeks 1 and 2: 25 mg once daily
Weeks 3 and 4: 50 mg once daily
Week 5: 100 mg once daily
Week 6: 150 mg once daily
Week 7: 200 mg once daily
Week 8 onwards to maintenance: 300 to 400 mg once daily
Dose increase at week 8 or later should not exceed 100 mg daily at weekly interva

2) Conversion from Immediate-Release to Extended-Release Formulation

a) The initial dose of extended-release lamotrigine in patients age 13 years and older should m
lamotrigine. Depending on the therapeutic response after conversion, the total daily dose may r
instructions (Prod Info LAMICTAL XR oral extended-release tablets, 2009).

b) Chewable Dispersible or Orally Disintegrating Tablets, Age 2 to 12 Years

1) With Valproic Acid

a) For patients 2 to 12 years of age adding chewable dispersible or orally disintegrating lamotri
valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disinteg

Chewable dispersible or orally disintegrating lamotrigine added to AED regimen containing
Weeks 1 and 2: 0.15 milligram/kilogram/day (mg/kg/day) in one or two divided doses,
tablets should be used for dosing
Weeks 3 and 4: 0.3 mg/kg/day in one or two divided doses, rounded down to the neare
Week 5 and onward: Doses may be increased every 1 to 2 weeks by 0.3 mg/kg/day, r
the previously administered daily dose to achieve maintenance.
Usual maintenance dose: 1 to 5 mg/kg/day (maximum 200 mg/day in 1 or 2 divided do
The usual maintenance dose in patients adding lamotrigine to valproic acid alone
Maintenance doses in patients weighing less than 30 kg may need to be increase
INITIAL WEIGHT BASED DOSING GUIDE:
Patient weight 6.7 to 14 kg, dose for weeks 1 and 2 is 2 mg every OTHER day; do
Patient weight 14.1 to 27 kg, dose for weeks 1 and 2 is 2 mg every day; dose for
Patient weight 27.1 to 34 kg, dose for weeks 1 and 2 is 4 mg every day; dose for
Patient weight 34.1 to 40 kg, dose for weeks 1 and 2 is 5 mg every day; dose for

2) Without Valproic Acid

a) For patients age 2 to 12 years old receiving enzyme-inducing antiepileptic drugs (EIAED) (ca
without valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally
Chewable dispersible or orally disintegrating lamotrigine added to EIAED regimen without
Weeks 1 and 2: 0.6 milligram/kilogram/day (mg/kg/day) in two divided doses, rounded
Weeks 3 and 4: 1.2 mg/kg/day in two divided doses, rounded down to the nearest whc
Week 5 and onward: Doses may be increased every 1 to 2 weeks by 1.2 mg/kg/day, r
the previously administered daily dose to achieve maintenance.
Usual maintenance dose: 5 to 15 mg/kg/day (maximum 400 mg/day in 2 divided doses
Maintenance doses in patients weighing less than 30 kg may need to be increase

3) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid

a) For patients 2 to 12 years of age adding chewable dispersible or orally disintegrating lamotri
containing enzyme-inducing properties or valproic acid (Prod Info LAMICTAL chewable dispers
2009):
Chewable dispersible or orally disintegrating lamotrigine added to an antiepileptic drug (AE
valproic acid in patients 2 to 12 years of age:
Weeks 1 and 2: 0.3 milligram/kilogram/day (mg/kg/day) in one or two divided doses, r
tablets should be used for dosing.
Weeks 3 and 4: 0.6 mg/kg/day in two divided doses, rounded down to the nearest whc
Week 5 and onward: Doses may be increased every 1 to 2 weeks by 0.6 mg/kg/day, r
the previously administered daily dose to achieve maintenance.
Usual maintenance dose: 4.5 to 7.5 mg/kg/day (maximum 300 mg/day in 2 divided dos
Maintenance doses in patients weighing less than 30 kg may need to be increase

c) Chewable Dispersible or Orally Disintegrating Tablets, Age 12 Years and Older

1) With Valproic Acid

a) For patients 12 years and older adding chewable dispersible or orally disintegrating lamotrig
valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disinteg
Chewable dispersible or orally disintegrating lamotrigine added to antiepileptic drug (AED)
Weeks 1 and 2: 25 milligrams (mg) every other day
Weeks 3 and 4: 25 mg every day
Week 5 and onward: Doses may be increased by 25 to 50 mg/day every 1 to 2 weeks
Usual maintenance dose: 100 to 400 mg/day (1 or 2 divided doses)
The usual maintenance dose in patients adding lamotrigine to valproic acid alone

2) Without Valproic Acid

a) For patients 12 years and older receiving enzyme-inducing antiepileptic drugs (EIAED) (carb
without valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally
Chewable dispersible or orally disintegrating lamotrigine added to EIAED regimen without
Weeks 1 and 2: 50 mg/day
Weeks 3 and 4: 100 mg/day (in 2 divided doses)
Week 5 and onward: Doses may be increased by 100 mg/day every 1 to 2 weeks to a
Usual maintenance dose: 300 to 500 mg/day (in two divided doses)

3) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid

a) For patients 12 years and older adding chewable dispersible or orally disintegrating lamotrig
containing enzyme-inducing properties or valproic acid (Prod Info LAMICTAL chewable dispers
2009):
Chewable dispersible or orally disintegrating lamotrigine added to AED regimen not contair
Weeks 1 and 2: 25 mg/day
Weeks 3 and 4: 50 mg/day
Wee 5 and onward: Doses may be increased by 50 mg/day every 1 to 2 weeks to achi
Usual maintenance dose: 225 to 375 mg/day (in 2 divided doses)

1.4.1.A.5 Status epilepticus

a) Successful control of status epilepticus refractory to parenteral diazepam was achieved in one 17-yea
over 24 hours followed by 200 milligrams twice a day. Although this case report was encouraging, more

lamotrigine in status epilepticus (Pisani et al, 1991).

1.4.1.A.6 Tonic-clonic seizure, Primary generalized; Adjunct

a) Age 2 to 12 Years

1) With Valproic Acid

a) For patients 2 to 12 years of age adding lamotrigine to an antiepileptic drug (AED) regimen c
dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):

Lamotrigine added to AED regimen containing valproic acid in patients 2 to 12 years of age
Weeks 1 and 2: 0.15 milligram/kilogram/day (mg/kg/day) in one or two divided doses,
tablets should be used for dosing
Weeks 3 and 4: 0.3 mg/kg/day in one or two divided doses, rounded down to the neare
Week 5 and onward: Doses may be increased every 1 to 2 weeks by 0.3 mg/kg/day, r
the previously administered daily dose to achieve maintenance.
Usual maintenance dose: 1 to 5 mg/kg/day (maximum 200 mg/day in 1 or 2 divided do
The usual maintenance dose in patients adding lamotrigine to valproic acid alone
Maintenance doses in patients weighing less than 30 kg may need to be increase
INITIAL WEIGHT BASED DOSING GUIDE:
Patient weight 6.7 to 14 kg, dose for weeks 1 and 2 is 2 mg every other day; dose
Patient weight 14.1 to 27 kg, dose for weeks 1 and 2 is 2 mg every day; dose for
Patient weight 27.1 to 34 kg, dose for weeks 1 and 2 is 4 mg every day; dose for
Patient weight 34.1 to 40 kg, dose for weeks 1 and 2 is 5 mg every day; dose for

2) Without Valproic Acid

a) For patients age 2 to 12 years old receiving enzyme-inducing antiepileptic drugs (EIAED) (ca
without valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally

Lamotrigine added to EIAED regimen without valproic acid in patients 2 to 12 years of age:
Weeks 1 and 2: 0.6 milligram/kilogram/day (mg/kg/day) in two divided doses, rounded
Weeks 3 and 4: 1.2 mg/kg/day in two divided doses, rounded down to the nearest whc
Week 5 and onward: Doses may be increased every 1 to 2 weeks by 1.2 mg/kg/day, r
the previously administered daily dose to achieve maintenance.
Usual maintenance dose: 5 to 15 mg/kg/day (maximum 400 mg/day in 2 divided doses
Maintenance doses in patients weighing less than 30 kg may need to be increase

3) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid

a) For patients 2 to 12 years of age adding lamotrigine to an antiepileptic drug (AED) regimen
acid (valproic acid) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally d

Lamotrigine added to an antiepileptic drug (AED) regimen not containing drug-inducing AE
Weeks 1 and 2: 0.3 milligram/kilogram/day (mg/kg/day) in one or two divided doses, rc
tablets should be used for dosing.
Weeks 3 and 4: 0.6 mg/kg/day in two divided doses, rounded down to the nearest whc
Week 5 and onward: Doses may be increased every 1 to 2 weeks by 0.6 mg/kg/day, r
the previously administered daily dose to achieve maintenance.
Usual maintenance dose: 4.5 to 7.5 mg/kg/day (maximum 300 mg/day in 2 divided dos
Maintenance doses in patients weighing less than 30 kg may need to be increase

b) Age 12 Years and Older

1) With Valproic Acid

a) For patients 12 years and older adding lamotrigine to an antiepileptic drug (AED) regimen co
tablets, chewable dispersible oral tablets, 2006):

Lamotrigine added to antiepileptic drug (AED) regimen containing valproic acid:
Weeks 1 and 2: 25 milligrams (mg) every other day
Weeks 3 and 4: 25 mg every day
Week 5 and onward: Doses may be increased by 25 to 50 mg/day every 1 to 2 weeks
Usual maintenance dose: 100 to 400 mg/day (1 or 2 divided doses)
The usual maintenance dose in patients adding lamotrigine to valproic acid alone

2) Without Valproic Acid

a) For patients 12 years and older receiving enzyme-inducing antiepileptic drugs (EIAED) (carb
without valproic acid (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

Lamotrigine added to EIAED regimen without valproic acid:
Weeks 1 and 2: 50 mg/day
Weeks 3 and 4: 100 mg/day (in 2 divided doses)
Week 5 and onward: Doses may be increased by 100 mg/day every 1 to 2 weeks to ac
Usual maintenance dose: 300 to 500 mg/day (in two divided doses)

3) With Antiepileptic Drugs Not Containing Enzyme-Inducing Properties or Valproic Acid

a) For patients 12 years and older adding lamotrigine to an antiepileptic drug (AED) regimen nc
acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating ta

Lamotrigine added to AED regimen not containing drug-inducing AED or valproic acid:
Weeks 1 and 2: 25 mg/day
Weeks 3 and 4: 50 mg/day
Wee 5 and onward: Doses may be increased by 50 mg/day every 1 to 2 weeks to achi
Usual maintenance dose: 225 to 375 mg/day (in 2 divided doses)

1.4.1.B Important Note

1) Safety and efficacy of extended-release lamotrigine has not been established in patients below 13 years c tablets, 2009)

2) The risk of developing a potentially life-threatening rash is appreciably higher in children than in adults. Do escalation regimens (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2007) (Prod Info may also be higher with concomitant valproic acid and divalproex sodium use (Prod Info LAMICTAL(R) oral t Info LAMICTAL XR oral extended-release tablets, 2009).

3) Only whole tablets of the chewable dispersible tablets should be used. Doses should be rounded down to tablets, chewable dispersible oral tablets, 2007).

1.4.2 Dosage in Renal Failure

A) Use reduced maintenance doses in patients with significant renal impairment. Use with caution in patients with (Prod Info LAMICTAL XR oral extended-release tablets, 2009).

B) Dosage of lamotrigine need not be altered in the presence of impaired renal function since lamotrigine disposi the pharmacokinetics of lamotrigine in 10 subjects with renal failure (estimated creatinine clearance of 10.6 to 25. maximum concentration and area-under-the curve were similar since lamotrigine was largely cleared by metabolis to accumulate. Therefore, impaired renal function would have little effect on the plasma concentrations of lamotrig

C) Twenty volunteers with chronic renal failure (mean creatinine clearance 13 milliliters/min) were given a single prolonged compared to that observed in volunteers with normal renal function (50 hours vs 25 hours). Another 6 p milligrams dose of lamotrigine. On average, approximately 17% (range 5.6 to 35.1%) of lamotrigine was removed life in these patients during hemodialysis was 12.2 hours, while that between sessions was 59.6 hr (Fillastre et al,

1.4.3 Dosage in Hepatic Insufficiency

A) The manufacturer recommends that in patients with moderate and severe liver impairment without ascites, the reduced by approximately 25%. In patients with severe hepatic impairment with ascites, the initial, escalation, and approximately 50%. Clinical response should also be considered during escalation and maintenance dosing (Proc oral tablets, 2006; Prod Info LAMICTAL XR oral extended-release tablets, 2009).

1.4.5 Dosage in Other Disease States

A) Hyperbilirubinemia

1) Elimination of lamotrigine is not significantly impaired in patients with Gilbert's syndrome (unconjugated hy

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) Seizure, oral: 3 months (Gibbs et al, 1992a; Jawad et al, 1989c).

B) Duration

1) Multiple Dose

a) Seizure, oral: at least 6 months (Gibbs et al, 1992a).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Seizure, 1 to 4 mcg/mL (not well-established) (Garnett, 1997; Cohen et al, 1987a).

a) The therapeutic concentration range for lamotrigine has not been determined (Brodie, 1992) (Goa et al, 19 dosage titration should be based on clinical response rather than plasma concentrations (Goa et al, 1993b; M

b) Many patients have required higher levels (Garnett, 1997).

c) In children optimal levels have been between 0.5 to 5.4 mcg/ml (Battino et al, 1996)(Battino et al, 1995a).

d) Pharmacokinetics remained approximately linear within individuals (Battino et al, 1997; Bartoli et al, 1997;

e) Adults have a higher concentration to dose ratio than children (Battino et al, 1997; Bartoli et al, 1997).

f) Extended Release Tablets

1) In an open-label, crossover study of 44 epileptic patients on concomitant ant-epileptic drugs (AEDs) a extended-release lamotrigine once daily with immediate-release lamotrigine twice daily showed that stea lamotrigine were not significantly different from those of the immediate-release product. The degree of flu decreased by 17%, 34% and 37% for extended-release lamotrigine administered concomitantly with enz phenytoin, phenobarbital, and primidone), valproic acid, or all other AEDS, respectively, compared with t release lamotrigine was associated with lower peaks, longer time to peaks and lower peak-to-trough fluc lamotrigine (Prod Info LAMICTAL XR oral extended-release tablets, 2009).

B) Peak Concentration

1) Oral, single dose: 0.58 to 4.63 mg/L (50 to 400 mg)(Goa et al, 1993b; Prod Info Lamictal, 94; Prod Info Lamicta

a) Peak plasma concentrations increased linearly from 0.58 to 4.63 mg/L in healthy subjects administered si mg(Goa et al, 1993b; Prod Info Lamictal, 94; Prod Info Lamictal, 97; Goa et al, 1993b).

b) In two small studies of patients with epilepsy, plasma concentrations increased linearly with doses of 50 t 11/22/95.).

c) Extended Release Tablet

1) In an open-label, crossover study of 44 epileptic patients on concomitant anti-epileptic drugs (AEDs) extended-release lamotrigine once daily with immediate-release lamotrigine twice daily showed a mean release lamotrigine. Analysis of the data based on concomitant AED use showed, the decrease in Cmax inducing AEDs (ie, carbamazepine, phenytoin, phenobarbital, and primidone), 12% for patients receiving receiving all other AEDs. Some of the patients receiving the extended-release lamotrigine with concomita reduction in Cmax (Prod Info LAMICTAL XR oral extended-release tablets, 2009).

d) Rectal Administration

1) A peak concentration of 0.54 mcg/mL was achieved in 6.5 hours in 12 healthy adults after rectal adm with a peak concentration of 1.43 mcg/mL in 0.79 hour after oral administration of lamotrigine 100 mg ch 2001).

C) Time to Peak Concentration

1) Oral: (adult) 1.4 hours to 4.8 hours (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally hours (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009).

2) Oral: (pediatric) 1.6 hours to 5.2 hours (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, ora (Mikati et al, 2003)

a) Adults

1) Immediate-Release

a) In healthy volunteers and adult patients with epilepsy, peak plasma concentration was achieved administration (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrat

b) A second peak has been reported at 4 to 6 hours, possibly due to enterohepatic recycling (Garne

2) Extended Release Tablet

a) In an open-label, crossover study of 44 epileptic patients on concomitant anti-epileptic drugs (AE comparison of extended-release lamotrigine once daily with immediate-release lamotrigine twice dai (Tmax) following administration of extended-release lamotrigine was 4 to 11 hours compared with 1 Specifically, in patients receiving concomitant enzyme inducing AEDs (ie carbamazepine, phenytoin approximately 4 to 6 hours; in patients receiving concomitant valproic acid, the Tmax was 9 to 11 ho was 6 to 10 hours (Prod Info LAMICTAL XR oral extended-release tablets, 2009).

3) Rectal Administration

a) A peak concentration of 0.54 mcg/mL was achieved in 6.5 hours in 12 healthy adults after rectal compared with a peak concentration of 1.43 mcg/mL in 0.79 hour after oral administration of lamotri (Birnbaum et al, 2001).

b) Pediatrics

1) In pediatric patients with epilepsy, ages 10 months to 5.3 years old, the peak concentration was achie concomitant carbamazepine, phenytoin, phenobarbital or valproate. The mean time to peak was 5.2 hou drugs with no known effect on the apparent clearance of lamotrigine (Prod Info LAMICTAL chewable dis tablets, 2009).

2) In pediatric patients with epilepsy, ages 5 to 11 years old, the mean peak concentration of lamotrigine concomitant carbamazepine, phenytoin, phenobarbital, or primidone; to 4.5 hours among patients taking dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).

3) Peak concentrations in 3 neonates between the ages of 3 and 4 weeks, were obtained at 4 hours, wit lamotrigine (Mikati et al, 2003).

D) Area Under the Curve

1) Oral, (adult) 56.6 mg x hr/L (Garnett, 1997).

2) Oral (elderly) 91.8 mg x hr/L (Garnett, 1997)

3) Oral (pediatric) 61 mcg x hr/mL (Chen et al, 1999)

a) The AUC in adults was 56.6 mg x hr/L (Garnett, 1997)

b) Area under the curve was 55% higher in the elderly (91.8 mg x hr/L) (Garnett, 1997).

c) The AUC in children was 61 mcg x hr/mL (Chen et al, 1999).

d) Extended Release Tablet

1) In an open-label, crossover study of 44 epileptic patients on concomitant anti-epileptic drugs (AEDs) extended-release lamotrigine once daily with immediate-release lamotrigine twice daily, showed the mea lamotrigine was approximately 21% lower than immediate-release lamotrigine in patients receiving conc phenytoin, phenobarbital, and primidone), 6% lower in patients receiving concomitant valproic acid, and patients in this study, experienced up to 70% decrease in AUC when switched to the extended-release l release tablets, 2009).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption

A) Bioavailability

1) Oral tablets: 98% (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating

a) Lamotrigine is rapidly and completely absorbed after oral administration with an absolute bioavailabili oral tablets, oral tablets, orally disintegrating tablets, 2009).

b) Lamotrigine chewable/dispersible tablets are equivalent to the compressed tablets in terms of rate an dispersed in water, chewed, swallowed as whole or disintegrated in the mouth (Prod Info LAMICTAL che disintegrating tablets, 2009).

c) The relative bioavailability was 0.52 when a lamotrigine 100-mg chewable dispersible tablet was adm orally and swallowed whole in 12 healthy adults (Birnbaum et al, 2001). The rectal suspension was prepa and placing it into 6 mL of tap water (room temperature), followed by two 2-mL syringe-tubing rinses, wit under the curve (AUC) for rectally administered lamotrigine was 29.68 mcg/mL x hr compared with 54.94 than 0.001).

B) Effects of Food

1) No effect on systemic availability (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, oral

a) The bioavailability of lamotrigine is not affected by food (Prod Info LAMICTAL chewable dispersible o 2009; Prod Info LAMICTAL XR oral extended-release tablets, 2009).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) Plasma protein: 55% (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disin

1) Lamotrigine is approximately 55% bound to human plasma proteins at concentration from 1 to 10 oral tablets, oral tablets, orally disintegrating tablets, 2009).

B) Distribution Kinetics

1) Volume of Distribution

a) adult, 0.9 to 1.3 L/kg(Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disinte 1999)

1) The mean apparent volume of distribution of lamotrigine after oral administration ranges from 0.9 volunteers (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating

2) The volume of distribution in patients receiving concurrent antiepileptic therapy is 1.2 to 1.5 L/kg

3) The volume of distribution in children was 1.5 L/kg (Chen et al, 1999).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver, extensive (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating t

2) Lamotrigine is metabolized primarily by glucuronic acid conjugation into inactive metabolites. When given metabolism; however, in patients receiving other anticonvulsants this may not occur (Prod Info LAMICTAL ch disintegrating tablets, 2009).

2.3.4 Excretion

A) Kidney

1) Renal Clearance (rate)

a) Adult, (healthy volunteers) 0.18 to 0.58 mL/min/kg; (epilepsy), 0.28 to 1.21 mL/min/kg(Prod Info LAMI orally disintegrating tablets, 2009)

1) The mean apparent plasma clearance of lamotrigine was between 0.44 and 0.58 mL/min/kg in he medications, between 0.18 and 0.3 mL/min/kg in patients taking concomitant valproic acid (n=24) (P oral tablets, orally disintegrating tablets, 2009).

2) The mean apparent plasma clearance of lamotrigine in adult patients with epilepsy taking concor When lamotrigine was taken concomitantly with valproic acid and an enzyme-inducing antiepileptic r 0.53 mL/min/kg (n=25). When taken concomitantly with an enzyme-inducing antiepileptic medicatior mL/min/kg (n=41) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disinte

b) Elderly, 0.26 to 0.48 mL/min/kg (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, o

1) In 12 elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance, 61 mL

was 0.40 mL/min/kg (range, 0.26 to 0.48 mL/min/kg) following a single 150-mg dose of lamotrigine (oral tablets, orally disintegrating tablets, 2009).

c) Gender, no effect(Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegra

1) In general, the clearance of lamotrigine is not affected by gender. However, during dose escalati dose of valproic acid (n=77), the mean trough lamotrigine concentrations, unadjusted for weight, we than in males (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrati

d) Hepatic Impairment, 0.15 to 0.3 mL/min/kg (Prod Info LAMICTAL chewable dispersible oral tablets, o

1) Following a single 100-mg dose of lamotrigine the mean apparent clearances of lamotrigine in pa ascites (n=2), and severe with ascites (n=5) hepatic impairment were 0.30 +/- 0.09, 0.24 +/- 0.1, 0.2 compared with 0.37 +/- 0.1 mL/min/kg in the healthy control patients (Prod Info LAMICTAL chewable disintegrating tablets, 2009).

e) Pediatric, 0.24 to 3.62 mL/min/kg (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets

1) The mean apparent plasma clearance of lamotrigine in pediatric patients with epilepsy (age rang enzyme-inducing antiepileptic medication regimen was 3.62 mL/min/kg (n=10). When lamotrigine wa antiepileptic medication regimen, the mean plasma clearance was 1.2 mL/min/kg (n=7), and was 0.4 acid (n=8) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating

2) The mean apparent plasma clearance of lamotrigine in pediatric patients with epilepsy (age rang inducing antiepileptic medication regimen was 2.54 mL/min/kg (n=7). When lamotrigine was taken c antiepileptic medication regime, the mean plasma clearance was 0.89 mL/min/kg (n=8), and was 0.2 acid (n=3) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating

3) The mean apparent plasma clearance of lamotrigine in pediatric patients with epilepsy (age rang inducing antiepileptic medication regimen was 1.3 mL/min/kg (n=11). When lamotrigine was taken c antiepileptic medication regimen, the mean plasma clearance was 0.5 mL/min/kg (n=8), and was 0.3 (n=4) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating table

4) The mean apparent clearance in infants less than 2 months old was 0.119 liter per hour per kilog 2 to 12 months old and who were administered oral lamotrigine (Mikati et al, 2003).

f) Race, 25% lower in non-Caucasians (Prod Info LAMICTAL chewable dispersible oral tablets, oral tabl

1) The apparent clearance of lamotrigine was 25% lower in non-Caucasians than in Caucasians (Pr oral tablets, orally disintegrating tablets, 2009).

g) Renal Impairment, 2 mL/min (Garnett, 1997)

1) The clearance was reduced to 2 mL/min in patients with renal failure (Garnett, 1997).

2) Renal Excretion (%)

a) 94% (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets,

1) Following oral administration in healthy volunteers, 94% of the drug was recovered in the urine (F oral tablets, orally disintegrating tablets, 2009; Peck, 1991e).

B) Feces

1) Feces, 2% (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablet

a) After oral administration of lamotrigine, 2% was recovered in the feces (Prod Info LAMICTAL chewab disintegrating tablets, 2009).

2.3.5 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) Adult, (healthy volunteers) 25.4 to 70.3 hours; (epilepsy), 12.6 to 58.8 hours (Prod Info LAMICTAL ch disintegrating tablets, 2009)

1) The elimination half-life of lamotrigine in healthy adult volunteers (n=215) taking no other medica between 48.3 and 70.3 hours taken concomitantly with valproic acid (n=24) (Prod Info LAMICTAL ch disintegrating tablets, 2009).

2) The elimination half-life of lamotrigine in adult patients with epilepsy taking lamotrigine concomita when taken concomitantly with valproic acid and an enzyme-inducing antiepileptic medication regim concomitantly with an enzyme-inducing antiepileptic medication regimen (n=41) (Prod Info LAMICTA disintegrating tablets, 2009).

b) Elderly, 31.2 hours(Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disinteg

1) In 12 elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance, 61 mL half-life was 31.2 hours (range, 24.5 to 43.4 hours) following a single 150-mg dose of lamotrigine (P oral tablets, orally disintegrating tablets, 2009).

c) Hepatic Impairment, 46 +/- 20 hours to 100 +/- 48 hours(Prod Info LAMICTAL chewable dispersible o 2009)

1) Following a single 100-mg dose of lamotrigine the mean half-life elimination of lamotrigine in pati ascites (n=2), and severe with ascites (n=5) hepatic impairment were 46 +/- 20 hours, 72 +/- 44 hou as compared with 33 +/- 7 hours in healthy control patients (Prod Info LAMICTAL chewable dispersi 2009).

d) Pediatric, 7 hours to 65.8 hours (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets,

1) The elimination half-life of lamotrigine in pediatric patients with epilepsy (age range, 10 months t concomitantly with an enzyme-inducing antiepileptic medication regimen (n=10). When taken conco medication regimen, the half-life was 19 hours (n=7). When taken concomitantly with valproic acid (dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).

2) The mean elimination half-life of lamotrigine in pediatric patients with epilepsy (age range, 5 to 1

antiepileptic medication regimen was 7 hours (n=7). When lamotrigine was taken concomitantly with
medication regimen, the elimination half-life was 19.1 hours (n=8). When taken concomitantly with v
LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
3) The estimated half-life of lamotrigine in neonates taking enzyme-inducing agents was 23.4 hours
e) Renal Impairment, 13 hours to 57.4 hours (Prod Info LAMICTAL chewable dispersible oral tablets, or
1) Following a single 100-mg dose of lamotrigine, volunteers with chronic renal failure (n=12; mean
patients undergoing hemodialysis (n=6) the mean plasma half-lives were 42.9 hours (chronic renal f
(between hemodialysis) compared with 26.2 hours in healthy volunteers (Prod Info LAMICTAL chew
disintegrating tablets, 2009).

2.3.6 Extracorporeal Elimination

A) Hemodialysis

1) Dialyzable: Yes (Prod Info Lamictal(R), 2003g; Garnett, 1997).

a) Approximately 20% (range, 5.6% to 35.1%) of the amount of lamotrigine present in the body was elim
Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Oral (Tablet; Tablet, Chewable; Tablet, Disintegrating; Tablet, Extended Release)

a) Serious Skin Rashes: Lamotrigine can cause serious rashes requiring hospitalization and discontinuation of tre
included Stevens-Johnson syndrome, is approximately 0.8% (8 per 1,000) in pediatric patients (2 to 16 years of a
lamotrigine as adjunctive therapy for epilepsy and 0.3% (3 per 1,000) in adults on adjunctive therapy for epilepsy.
patients (2 to 16 years of age) with epilepsy taking adjunctive immediate-release formulation of lamotrigine, there
experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported in adult and pe
a precise estimate of the rate.

b) The risk of serious rash caused by treatment with lamotrigine is not expected to differ from that with the immed
relatively limited treatment experience with lamotrigine makes it difficult to characterize the frequency and risk of s

c) Other than age, there are as yet no factors identified that are known to predict the risk of occurrence or the sev
suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration of lamotrigine w
sodium), (2) exceeding the recommended initial dose of lamotrigine, or (3) exceeding the recommended dose esc
in the absence of these factors.

d) Nearly all cases of life-threatening rashes caused by the immediate-release formulation of lamotrigine have oc
However, isolated cases have occurred after prolonged treatment (eg, 6 months). Accordingly, duration of therapy
potential risk heralded by the first appearance of a rash.

e) Although benign rashes are also caused by lamotrigine, it is not possible to predict reliably which rashes will p
lamotrigine should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug-related. D
becoming life-threatening or permanently disabling or disfiguring (Prod Info LAMICTAL chewable dispersible oral
Prod Info LAMICTAL XR oral extended-release tablets, 2009).

3.1 Contraindications

A) hypersensitivity to lamotrigine or any component of the product (Prod Info LAMICTAL chewable dispersible oral tal
Prod Info LAMICTAL XR oral extended-release tablets, 2009)

3.2 Precautions

A) skin rash, serious and potentially life-threatening, has been reported; discontinue drug if alternate etiology for react
dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009; Prod Info LAMICTAL XR oral extended-release
B) concomitant use with valproic acid; dose adjustment may be required (Prod Info LAMICTAL chewable dispersible
2009; Prod Info LAMICTAL XR oral extended-release tablets, 2009)
C) pediatric patients (2 to 16 years of age); higher rate of serious rash (Prod Info LAMICTAL chewable dispersible ora
Prod Info LAMICTAL XR oral extended-release tablets, 2009)
D) abrupt drug discontinuation should be avoided due to the potential for increased seizure frequency (Prod Info LAM
orally disintegrating tablets, 2009; Prod Info LAMICTAL XR oral extended-release tablets, 2009)
E) allergy to other antiepileptic drugs, preexisting; lamotrigine may increase risk of nonserious rash (Prod Info LAMIC
disintegrating tablets, 2009; Prod Info LAMICTAL XR oral extended-release tablets, 2009)

F) bipolar disorder, treatment of; possible increased risk for worsening depression or suicidality (Prod Info LAMICTAL disintegrating tablets, 2009; Prod Info LAMICTAL XR oral extended-release tablets, 2009)
G) blood dyscrasias (ie, neutropenia, anemia, leukopenia, pancytopenia, thrombocytopenia, aplastic anemia, pure red LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009; Prod Info LAMICTAL XR
H) hypersensitivity reactions, including life-threatening or fatal reactions, have occurred; discontinuation of therapy ma dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009; Prod Info LAMICTAL XR oral extended-release
I) multiorgan failure, acute, including fatal and irreversible cases, has occurred (Prod Info LAMICTAL chewable dispe tablets, 2009; Prod Info LAMICTAL XR oral extended-release tablets, 2009)
J) status epilepticus, sudden and unexplained deaths, may occur (Prod Info LAMICTAL chewable dispersible oral tab Info LAMICTAL XR oral extended-release tablets, 2009)
K) suicidality, increased risk of; monitoring recommended (Prod Info LAMICTAL XR oral extended-release tablets, 20 tablets, 2009; US Food and Drug Administration, 2008)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Chest pain

EKG finding

Hypotension

3.3.1.A Chest pain

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)
2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, chest pain was treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod

2009).

3.3.1.B EKG finding

1) Premarketing studies have shown a minor incidence of increased PR interval, which were not clinically sig (Matsuo et al, 1993a). One case of a patient who had first-degree heart block was also reported (Betts et al,

2) Literature Reports

a) First-degree heart block was reported in one patient receiving lamotrigine therapy; however, this was an athlete, continued to run marathons while continuing lamotrigine treatment. Another patient had invert electrocardiogram (EKG) performed 2 weeks after discontinuing lamotrigine was still abnormal, so this e 1991).

3.3.1.C Hypotension

1) Two children had hypotensive episodes, with blood pressure 77/45 millimeters of mercury in one child, aft Both children subsequently suffered multiorgan dysfunction, which reversed several days following discontinu represents lamotrigine-associated anticonvulsant hypersensitivity syndrome (Chattergoon et al, 1997b).

3.3.2 Dermatologic Effects

Alopecia

Erythema multiforme

Fixed drug eruption

Flushing

Rash

Stevens-Johnson syndrome

Summary

Toxic epidermal necrolysis

3.3.2.A Alopecia

1) Incidence: 2% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, alopecia was e treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod 2009).

3.3.2.B Erythema multiforme

1) Summary

a) Multiforme erythema has been rarely reported during clinical trials of pediatric and adult patients rece tablets, chewable dispersible oral tablets, 2006).

2) Incidence: rare (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)

3.3.2.C Fixed drug eruption

1) Case Report

a) Lamotrigine was associated with an extensive fixed drug eruption developed in a 54-year-old man. La Rapid improvement occurred (Hsiao et al, 2001).

2) Literature Reports

a) A 54-year-old man developed an extensive fixed drug eruption caused by lamotrigine. His medical his spinocerebellar degeneration; his medications were haloperidol 1 to 5 milligrams (mg) as required, baclo daily, and bisacodyl 10 mg at bedtime. For the previous month and one-half, the patient had been taking seizures. Due to poor control of his seizures, lamotrigine 50 mg twice daily was added to the valproate. T developed a rash, described as red to violaceous, round patches and plaques with central erosions or ve periorbital area and subsequently spread to the trunk and extremities. Skin biopsy revealed extensive va infiltration of lymphocytes, histiocytes, eosinophils, and melanophages. Fixed drug eruption due to lamot withdrawn, and Solu-Medrol 40 mg/day initiated. Rapid improvement occurred. Nine weeks later, patch t lamotrigine was the causal agent. When patch-test lamotrigine was applied to previously uninvolved area appeared only on the previously involved areas (Hsiao et al, 2001).

3.3.2.D Flushing

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)
2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, hot flush was e
treatment with lamotrigine extended-release (n=118) compared with 0% who received placebo (n=121) (Prod
2009).

3.3.2.E Rash

1) Incidence: 10% adult; 14% pediatric (immediate-release) (Prod Info LAMICTAL(R) oral tablets, chewable
(Prod Info LAMICTAL XR oral extended-release tablets, 2009)
2) Immediate Release
a) Maculopapular and erythematous rashes have been reported with therapeutic doses of lamotrigine (F
dispersible oral tablets, 2006; Messenheimer et al, 1998; Matsuo et al, 1993a). Retrospective evaluation
United Kingdom epilepsy clinics identified 12 cases of serious skin rash (1.1%). Nonserious rashes occu
determined the following significant (p less than 0.05) risk factors: higher starting dose, concomitant sodi
Reports from clinical use have suggested (although not proven) that, besides age below 16 years, the fo
developing a severe potentially life-threatening rash (Prod Info LAMICTAL(R) oral tablets, chewable disp
Concomitant use of valproic acid or antibiotics known to cause skin rashes; 2) Administration of lamotrigi
manufacturer; 3) Escalating the lamotrigine dose at a faster rate than recommended by the manufacture
3) Literature Reports
a) Retrospective evaluation of 1050 records of lamotrigine recipients from five United Kingdom epilepsy
The relative risk of lamotrigine- related rash in females compared to males was 1.83 (95% confidence int
serious rash included concomitant sodium valproate (n=12), female gender (n=10), and starting daily dos
serious rash decreased following the manufacturer- recommended initial dose reduction in 1994, the ove
after this time point (Wong et al, 1999).
b) PEDIATRIC REVIEW - A comprehensive review of manufacturer data encompassing 13 clinical trials
profile in the pediatric population. As add-on therapy, the mean lamotrigine dose and duration were 5.5 r
respectively. As monotherapy, the mean dose and duration were 2.9 mg/kg/day and 22 weeks, respectiv
effect was rash. (Messenheimer et al, 2000). One such add-on study, involving 1983 pediatric patients, r
oral tablets, chewable dispersible oral tablets, 2006). In all monotherapy trials, the corresponding event v
rash was 12.6%, leading to discontinuation in 4.7% of children (Messenheimer et al, 2000).
c) In a series of 68 consecutive children treated with lamotrigine at a pediatric medical center, five (7%)
hospitalization, one with Stevens-Johnson syndrome. The authors conclude that lamotrigine should be d
within two to eight weeks of initiation of therapy; if rechallenge is considered, it should be done with a ver
In a study of 14 children, lamotrigine was withdrawn due to rash (two cases) and hirsutism (one case) (B
d) A 25-year-old man who had developed rash with lamotrigine was rechallenged and developed the ras
previously started on lamotrigine 25 milligrams/day titrated by 25 mg every 3 days for 2 weeks, and then
to a daily dose of 300 mg/day. A slower titration was attempted and again after reaching 300 mg (after 7
made to decrease the dose to 150 mg and begin prednisone 20 mg, however, the rash persisted and lan
4) Management
a) Among 44 patients rechallenged with lamotrigine following lamotrigine-induced rash, 39 were succes
systematic review including 2 case series, 2 case reports, and 1 retrospective record review of adults wit
2 case reports of adults with bipolar disorder. The authors concluded that very slow titration is essential i
The following table outlines the number of successful lamotrigine rash rechallenges and the titration sche

Patients/study design	Total patients rechallenged or continued	Successful rechallenge/ continuation	
Children epilepsy case series (age 5 to 19 years)	7	7	Re-initiated after a m mg/day; week 2: 0.1 and 5: 1 mg/day; wee 10: 6.25 mg/day; wee doubled in increment dose of 50 mg/day. T mg/day.
Adult epilepsy case series	6	6	Rechallenged with 12 specified
Adult epilepsy case series	8	7	Titration doses varied varying from 24 days
Adult epilepsy case reports	2	2	Re-initiated at a dose dose of 50 mg/day
Adult epilepsy retrospective review	19	16	5 mg/day or every se weeks to 25 mg/day.
Adult bipolar disorder case report	1	0	Rechallenged with 5 dose of 300 mg/day
Adult bipolar disorder case	1	1	Restarted at 12.5 mg

report			wks, 50 mg/day for 2
Total	44	39	

(Lorberg et al, 2009)

5) Extended Release

a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, rash was e treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121). extended-release is not expected to be different from the immediate-release formulation (Prod Info LAMI

3.3.2.F Stevens-Johnson syndrome

1) Incidence: 0.08% to 0.8% (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)

2) Severe and potentially life-threatening rashes, including Stevens-Johnson syndrome, have been reported and 0.8% of pediatric epilepsy patients. Serious rashes were also reported in clinical trials of adult patients w lamotrigine as initial monotherapy and 0.13% for adjunctive therapy. Most cases have presented within 2 to 8 occurred after long-term treatment (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3) A Stevens-Johnson-like syndrome appeared in one of 16 patients during the first year of lamotrigine treatr discontinuation (Cocito et al, 1994).

4) Literature Reports

a) A case of Stevens-Johnson-Syndrome associated with lamotrigine therapy in a 30-year-old male was initiation of lamotrigine, which was added to valproic acid therapy (2500 milligrams/day) and was diagnos to the drug. The patient developed a skin eruption and had complaints of influenza-like symptoms (Sachs

3.3.2.G Summary

1) Lamotrigine should be discontinued at the first sign of a rash, unless the rash is clearly not drug related. P also been noted. The risk of severe rash may be increased by the coadministration of lamotrigine with valproi lamotrigine or by exceeding the recommended dose escalation recommendations. However, cases have bee manufacturer recommends that lamotrigine not be restarted in patients who have previously discontinued lam drug clearly outweigh the risks. If a patient has discontinued lamotrigine for greater than 5 half-lives, the initia LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3.3.2.H Toxic epidermal necrolysis

1) Incidence: 0.08% to 0.8% (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)

2) Severe and potentially life-threatening rashes, including toxic epidermal necrolysis (TEN), have been repo adult and 0.8% of pediatric epilepsy patients. Serious rashes were also reported in clinical trials of adult patie receiving lamotrigine as initial monotherapy and 0.13% for adjunctive therapy. Most cases have presented wi but some occurred after long-term treatment (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral

3) Literature Reports

a) A 54-year-old man developed fatal toxic epidermal necrolysis (TEN) 4 weeks after beginning lamotrig glioblastoma multiforme brain tumor. The patient was also receiving allopurinol, captopril, and valproic a started and was then increased to 50 mg twice daily within 1 week. He died 17 days after the onset of TE

b) A 74-year-old man developed toxic epidermal necrolysis (TEN) 14 days after beginning lamotrigine th rash, which progressed in 4 days to TEN. After 5 days the lamotrigine was discontinued and the patient & Davis, 1997).

c) A 22-month-old child developed toxic epidermal necrolysis 14 days after the addition of lamotrigine to maculopapular rash developed and worsened involving the conjunctivae, oral cavity and trachea. Lamot weeks (Vukelic et al, 1997).

d) Three cases of toxic epidermal necrolysis (TEN), verified by skin biopsies, were reported, which deve were treated in burn units of hospitals. The authors speculated immune sensitization occurred; however, incidence of rash with lamotrigine is especially high when combined with valproic acid, but it is unknown 1996).

3.3.3 Endocrine/Metabolic Effects

Hyponatremia

Weight gain

3.3.3.A Hyponatremia

1) Hyponatremia occurred in 2 young girls (12 and 15 years of age) with cranial diabetes insipidus who were had primary panhypopituitarism, and the second patient developed panhypopituitarism secondary to removal desmopressin therapy at the time lamotrigine was introduced. The first patient was given lamotrigine 50 millig had lamotrigine dose increases of 7 milligrams/kilogram (mg/kg) (initial dose not specified). In both cases, the requirements as lamotrigine doses increased. The authors suggested that the effect of lamotrigine on fluid ba 2000).

3.3.3.B Weight gain

1) Incidence: 2% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, weight gain was treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod 2009).

3) Lamotrigine is not associated with clinically significant weight gain. Based on a retrospective review of ma the average weight change was only 0.5 kilogram at a mean lamotrigine daily dose and duration of 259 millig age- or gender-related differences in body weight changes (Devinsky et al, 2000).

3.3.4 Gastrointestinal Effects

Abdominal pain

Constipation

Diarrhea

Indigestion

Loss of appetite

Nausea

Vomiting

Xerostomia

3.3.4.A Abdominal pain

1) Incidence: 10% (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)

2) Abdominal pain has been reported in 10% of pediatric epilepsy patients receiving lamotrigine compared w tablets, chewable dispersible oral tablets, 2006).

3) Incidence: 6% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

4) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, abdominal pain treatment with lamotrigine extended-release (n=118) compared with 4% who received placebo (n=121) (Prod 2009).

3.3.4.B Constipation

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, constipation wa treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod 2009).

3.3.4.C Diarrhea

1) Incidence: 8% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, diarrhea was ev treatment with lamotrigine extended-release (n=118) compared with 5% who received placebo (n=121) (Prod 2009).

3.3.4.D Indigestion

1) Incidence: 7% (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)

2) In a monotherapy trial for adults with partial seizures, 7% of patients receiving lamotrigine reported dyspep valproate (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3.3.4.E Loss of appetite

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, decreased appe adjunctive treatment with lamotrigine extended-release (n=118) compared with 2% who received placebo (n= tablets, 2009).

3.3.4.F Nausea

1) Incidence: 7% to 25%(immediate-release) (Prod Info LAMICTAL(R) oral tablets, chewable dispersible ora LAMICTAL XR oral extended-release tablets, 2009)

2) Immediate Release

a) Nausea has been reported in 7% of adult partial seizure patients treated with lamotrigine compared w epilepsy patients receiving lamotrigine compared with 10% of placebo patients, and in 10% of pediatric e 2% of placebo patients. A randomized trial of adult epilepsy patients found that incidence of nausea was with 500 mg, compared with 11% with placebo (Prod Info LAMICTAL(R) oral tablets, chewable dispersib

3) Extended Release

a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, nausea wa treatment with lamotrigine extended-release (n=118) compared with 2% who received placebo (n=121) (2009)

3.3.4.G Vomiting

1) Incidence: 9%(immediate-release) (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets

2) Immediate Release

a) Vomiting has been reported in 9% of adult epilepsy patients receiving lamotrigine compared with 4% seizure patients treated with lamotrigine compared with none of the patients treated with low-dose valproc that incidence of vomiting was dose-related, increasing from 11% with 300 mg to 18% with 500 mg, com oral tablets, chewable dispersible oral tablets, 2006).

3) Extended Release

a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, vomiting w treatment with lamotrigine extended-release (n=118) compared with 2% who received placebo (n=121) (2009).

3.3.4.H Xerostomia

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, dry mouth was treatment with lamotrigine extended-release (n=118) compared with 2% who received placebo (n=121) (Prod 2009).

3.3.5 Hematologic Effects

Anemia

Disseminated intravascular coagulation

Eosinophil count raised

Leukopenia

Neutropenia

Pure red cell aplasia

Thrombocytopenia

Thrombocytosis

3.3.5.A Anemia

1) Anemia has been reported as an uncommon adverse effect of lamotrigine. Anemias (aplastic anemia, her reversible after discontinuation of lamotrigine. Patients with anemias were also taking other anticonvulsants, LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006; Pulik et al, 2000; Esfahani & Dasheiff, 19

2) Literature Reports

a) Complete erythroblastopenia occurred several weeks after initiation of lamotrigine (50 milligrams (mg for uncontrolled epilepsia in a 29- year-old woman who had been diagnosed at age 4 months with Diamo aplasia). Treatment with folinic acid 25 mg/day returned hemoglobin levels to normal within 2 months, ar et al, 2000).

b) In one patient, lamotrigine treatment was stopped after 23 months due to macrocytic anemia (Cocito

3.3.5.B Disseminated intravascular coagulation

1) Two children (3.5- and 11-years-old) suffered multiorgan dysfunction and disseminated intravascular coag current valproic acid therapy. Symptoms began 9 days after starting lamotrigine therapy and included a syndr urticarial/maculopapular rash, hepatic, and renal dysfunction, hypoalbuminemia, and changes in alertness. D were also reported, along with evidence of rhabdomyolysis in one patient. No seizures were noted during this lamotrigine. This probably represents lamotrigine- associated anticonvulsant hypersensitivity syndrome (Cha

2) Disseminated intravascular coagulation has been reported in a 45-year-old female after 2 weeks of upwar

previously been maintained on carbamazepine and clonazepam for seizures with poor control prior to lamotri
partial thromboplastin times were significantly prolonged, fibrinogen was decreased, and fibrin degradation pr

3.3.5.C Eosinophil count raised

1) Eosinophilia has been infrequently reported with lamotrigine use (Prod Info LAMICTAL(R) oral tablets, che

3.3.5.D Leukopenia

1) Although uncommon, leukopenia has resulted from therapeutic dosages of lamotrigine. Neutropenia, panc
in postmarketing experiences, causality has not been established (Prod Info LAMICTAL(R) oral tablets, chew
2) Leukopenia progressing to agranulocytosis occurred within days of discontinuing lamotrigine due to rash i
lamotrigine 50 milligrams/day two weeks prior to this event. No concomitant medications were taken. The agr
count of 3.1 x 10(9)/liter (92% lymphocytes and 8% monocytes) and accompanied by slight transaminase ele
improved to 6.5 x 10(9)/liter with 50% neutrophils (Kraus de Camargo & Bode, 1999).
3) A 35-year-old woman presented with leukopenia, which progressed to sepsis following 10 days of therapy
valproate sodium and propranolol. On admission to the hospital she was hypoxic, hypotensive and feverish, v
therapy, her condition stabilized and she fully recovered (Nicholson et al, 1995).

3.3.5.E Neutropenia

1) Neutropenia induced by lamotrigine was experienced by a 50-year-old woman with schizoaffective disorde
the patient presented with mood swings, alopecia, and weight gain. Lamotrigine was administered at 12.5 mg
and then by 50 mg/day every 2 weeks until a total of 150 mg twice daily was reached. Sodium valproate was
in mood symptoms. Her WBC count and absolute neutrophil count was 4.9 x 10(9) and 2.8 x 10(9)/L, respect
months later, her WBC count was 3.8 x 10(9)/L and absolute neutrophil count was 2.2 x 10(9)/L. Due to decli
decreased by 50 mg/day. Briefly her counts returned to baseline only to continue downward. Consequently, l
on therapy for approximately 10 months. Her WBC count and neutrophil count at discontinuation was 2.8 x 10
returned to baseline without any recurrence of neutropenia. A year and a half later, the patient was rechallen
decreased once again after 2 months of lamotrigine therapy. Following discontinuation, her counts returned t
al, 2007).

3.3.5.F Pure red cell aplasia

1) Incidence: rare (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)
2) Pure red cell aplasia, possibly related to hypersensitivity syndrome, has been noted as an adverse reactio
experiences (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3.3.5.G Thrombocytopenia

1) A 15-year-old female with therapy-resistant Lennox-Gastaut syndrome experienced severe thrombocytop
mucosal edema two weeks after initiation of add-on lamotrigine therapy (25 milligrams every other day). The
valproate sodium 2400 milligrams/day. After discontinuation of lamotrigine and introduction of prednisone 10
edema cleared and the thrombocyte level returned to the normal range. The authors assume that the thromb
close time relationship involved, although other possible causes (hypersensitivity reaction, bone marrow aller
(Laengler & Meusers, 1995).

3.3.5.H Thrombocytosis

1) Two cases of decreased hematocrit with thrombocytosis were reported approximately 2 months after begi
reversed after discontinuation of lamotrigine.

3.3.6 Hepatic Effects

Hepatitis

Hyperbilirubinemia

Increased liver enzymes

Liver failure

3.3.6.A Hepatitis

1) Acute hepatitis occurred in a 28-year-old woman after lamotrigine (25 milligrams every other day) was adc
had used for 12 years to treat a generalized seizure disorder (Sauve et al, 2000).
2) Twelve days after initiation of lamotrigine, a 28-year-old patient developed headache, fever, and diplopia a
day. The lamotrigine had been added to her current dose of valproate 14 milligrams/kilogram/day. Clinical sy
amoxicillin therapy, and the patient was admitted. An atypical headache, hyperthermia, drowsiness, and majc
results showed a 10-fold increase in aspartate aminotransferase and alanine aminotransferase, plus a low pr
indicating coagulopathy). All medications were immediately withdrawn. To prevent seizures, gabapentin (400

by clonazepam (1 milligram/day continuous intravenous infusion). Two days after admission, the patient bega peaked on day 3, then declined and became normal within 2 weeks, when she was discharged. A liver biopsy lymphocytes and eosinophils; focal acidophil hepatocellular necrosis was also noted (Sauve et al, 2000).

3.3.6.B Hyperbilirubinemia

1) Slight elevations in plasma bilirubin have been reported with lamotrigine (Cohen et al, 1987b); however, th

3.3.6.C Increased liver enzymes

1) A case report described acute liver failure with significant elevations in liver enzymes in a 21-year-old mal time of admission to the inpatient psychiatry unit for paranoid delusions, home medications included aripiprazo nonadherence to aripiprazole was reported by the patient's family. Although the overall duration and titration 200 mg/day for 2 months prior to admission. While acute findings were not present on physical examination, based on aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum levels of 960 units/L were normal, and the patient was afebrile with no signs of infection. Liver function tests 2 months prior to adm serology and autoimmune tests ruled out other etiologies of hepatic failure, lamotrigine was determined to be Instead, the patient was restarted on aripiprazole, titrating up to 25 mg/day. Five days after stopping lamotrigi (102 units/L). The Naranjo Probability Scale indicated a probable causative relationship of lamotrigine and ac

2) Elevated aspartate transaminase (AST) (1,066 units/liter (L)), alanine aminotransferase (ALT) (279 units/L units/L), and alkaline phosphatase (ALP) (145 units/L) serum levels were reported in an 11-year-old female a therapy. Multiorgan dysfunction developed, with rhabdomyolysis and no seizures. After discontinuation of her returned to normal over 10 days (Chattergoon et al, 1997b). This probably represents lamotrigine-associated

3.3.6.D Liver failure

1) A case report described acute liver failure with significant elevations in liver enzymes in a 21-year-old mal time of admission to the inpatient psychiatry unit for paranoid delusions, home medications included aripiprazo nonadherence to aripiprazole was reported by the patient's family. Although the overall duration and titration 200 mg/day for 2 months prior to admission. While acute findings were not present on physical examination, based on aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum levels of 960 units/L were normal, and the patient was afebrile with no signs of infection. Liver function tests 2 months prior to adm serology and autoimmune tests ruled out other etiologies of hepatic failure, lamotrigine was determined to be Instead, the patient was restarted on aripiprazole, titrating up to 25 mg/day. Five days after stopping lamotrigi (102 units/L). The Naranjo Probability Scale indicated a probable causative relationship of lamotrigine and ac

2) A 35-year-old woman, with a history of bipolar disorder and poly substance abuse, developed a fatal prog treatment. Thirty-nine days after starting lamotrigine 400 milligrams/day, she had a four-day history of fevers, addition to lamotrigine she was also receiving Tylenol 3, chloral hydrate, olanzapine, topiramate, and trazodo papular rash, fever (104 degrees Farenheit) and elevated liver function tests were noted. On day 48 lamotrigi chloral hydrate, olanzapine, and trazodone were discontinued. On day 55, a liver biopsy showed centrilobular hepatocytes. Despite treatment, the liver necrosis progressed over the next 3 weeks and the patient died. An extensive, well developed, bile duct proliferation which was suggestive of a protracted and subacute course. damage, the authors suspected that lamotrigine was the cause of the hepatic necrosis due to the rash preced 2002).

3) An 8-year-old boy developed acute hepatic failure 2 weeks after beginning lamotrigine therapy. The patien 50 milligrams, 3 times daily (6 milligrams/kilogram/day) with 3 days of overlapping drugs. Two weeks later, he coagulopathy. His lamotrigine level was 30.2 micrograms/milliliter (mcg/mL) (normal 1 to 3 mcg/mL). He reco and supportive care (Arnon, 1998).

3.3.7 Immunologic Effects

3.3.7.A Immune hypersensitivity reaction

1) Some fatal or life-threatening hypersensitivity reactions have occurred which included clinical features of r vasculitis, lupus-like syndrome, flu-like symptoms and/or disseminated intravascular coagulation. Even thoug hypersensitivity are present, such as fever, or lymphadenopathy, the patient should be evaluated immediately dispersible oral tablets, 2006; Schlienger et al, 1998).

2) Literature Reports

a) Anticonvulsant hypersensitivity syndrome (AHS) - consisting of fever, skin eruption or lymphadenopat associated with lamotrigine therapy in 26 reported cases. Effects appear similar to AHS induced by other have fever (100%), exanthematous rashes (77%), eosinophilia (19%) and lymphadenopathy (12%). Four intravascular coagulopathy. The most commonly reported internal organ toxicities were hematologic and followed by renal (23%) and musculoskeletal (8%). Concomitant anticonvulsant drugs were used in all 26

b) Acute granulomatous interstitial nephritis, along with colitis and ileitis, occurred in a 17-year-old woma weeks after the start of lamotrigine, she developed an pruritic rash; lamotrigine was withdrawn. A week la she developed a fever and progressing flu-like symptoms (sore throat, nausea/vomiting, diarrhea, and ur Lymphadenopathy was found to be present, and liver enzymes were abnormal. Occult blood was found i necrotizing epithelioid granuloma. Renal function deteriorated, with development of oliguria requiring her steroid treatment. The authors concluded that this was a case of anticonvulsant hypersensitivity syndrom

c) A 6-year-old boy being treated with lamotrigine and valproic acid for generalized tonic-clonic seizures lamotrigine, he developed a pruritic eruption (predominantly trunk and extremities), facial swelling, nause white blood cell count had increased to 9500 cells/cubic millimeter, liver enzymes were elevated, and che

Lamotrigine was discontinued but the symptoms persisted until valproic acid was discontinued 2 days lat
laboratory abnormalities (Brown et al, 1999).
d) A 27-year-old female developed multisystem hypersensitivity reaction, with disseminated intravascula
dysfunction, 11 days after starting lamotrigine therapy. Adjunctive therapy included phenobarbital. After s
spontaneously with no interventions other than steroid therapy (Sarris & Wong, 1999).
e) A 47-year-old man developed a hypersensitivity syndrome to lamotrigine that included neuralgic amy
valproate and had lamotrigine titrated to 50 milligrams/day over 1 month. He developed a rash, fever, an
was discontinued but 3 days later he developed left shoulder pain and numbness. Neuralgic amyotrophy
followed by focal neurologic symptoms restricted to that limb. It resolved over 8 months (Hennessy et al,
f) A 35-year-old man developed pseudolymphoma (which may develop as a hypersensitivity reaction to
patient was receiving lamotrigine 225 milligrams along with valproic acid, carbamazepine, and clobazam
The frozen section diagnosis was consistent with lymphoma. With further testing a pathologic diagnosis
of lymphoid hyperplasia was established. Lymphadenopathy resolved 1 month after lamotrigine was disc

3.3.8 Musculoskeletal Effects

Asthenia

Myalgia

Rhabdomyolysis

3.3.8.A Asthenia

1) Summary

a) In premarketing clinical trials of monotherapy for epilepsy, asthenia has been reported in at least 5%
(Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

b) Asthenia led to discontinuation of therapy in 2.4% of adult patients (n=420)(Prod Info LAMICTAL(R) o

2) Incidence: 5% or greater (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)

3.3.8.B Myalgia

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, muscle pain wa
treatment with lamotrigine extended-release (n=118) compared with 0% who received placebo (n=121) (Prod
2009).

3.3.8.C Rhabdomyolysis

1) Rhabdomyolysis has been reported in hypersensitive patients during postmarketing surveillance (Prod Inf
tablets, 2006).

2) Rhabdomyolysis in the absence of seizures is reported in an 11-year-old female 9 days after the addition
dose was halved). Serum creatine kinase level was reported to be 40,952 units/liter (normal less than 255 un
creatine kinase levels returned to normal. This probably represents lamotrigine-associated anticonvulsant hy

3) A case of myopathy with elevated creatine kinase levels (7770 International Units/liter) and myoglobin lev
absence of generalized seizures following a 2 week period of lamotrigine initialization and increasing therape

3.3.9 Neurologic Effects

Amnesia

Aphasia

Aseptic meningitis

Ataxia

Aura, Loss

Blepharospasm

Coordination problem

Dizziness

Drug withdrawal seizure

Encephalopathy

Gilles de la Tourette's syndrome

Headache

Insomnia

Myoclonus

Nystagmus

Somnolence

Status epilepticus

Tremor

Unsteady gait

Vertigo

3.3.9.A Amnesia

1) Incidence: greater than 1% to less than 5% (Prod Info LAMICTAL(R) chewable dispersible oral tablets, or

2) Amnesia has been reported in greater than 2% and less than 5% of adult patients with epilepsy who recei received placebo (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 2009).

3) Amnesia has also been reported in greater than 1% and less than 5% of adult patients with bipolar disord more frequently than in those who received placebo (Prod Info LAMICTAL(R) oral tablets, chewable dispersib

3.3.9.B Aphasia

1) An 11-year-old girl with atypical, benign partial epilepsy showed a loss of previously acquired communicat milligrams/kilogram/day for a recurrence of absence seizures. An increase in the dose of lamotrigine to 2.5 m age 5, she had been treated successfully for absence seizures with valproate and phenobarbital. At the onse the normal range. The girl at age 6 had shown mild learning difficulties, and tests showed low normal intellige was accompanied by marked electroencephalographic (EEG) activation, especially during sleep, when a patt weaning from lamotrigine, EEG patterns and language function returned to pre-lamotrigine levels (Battaglia e

3.3.9.C Aseptic meningitis

1) A 25-year-old woman developed aseptic meningitis 8 days after starting lamotrigine 25 mg/day for epileps resolved; however the symptoms returned upon rechallenge with lamotrigine. The patient presented with mer glutamyl transpeptidase (GGT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and cerebros erythrocytes, and leukocytes were elevated; however, CSF cultures for bacteria, fungi, and viruses were nega empiric ceftriaxone 2 g twice daily was initiated The patient had mild leukopenia and thrombocytopenia were viral meningitis. One hour after lamotrigine was re-initiated on day 19, the patient experienced a severe head dysesthesia, tachycardia, and a fever of 39.9 degrees C. Lab findings showed leukopenia, an elevated GGT Again, the CSF cultures for bacteria, fungi, and viruses were negative. Subsequently, lamotrigine was discon initiated until CSF results were negative. Symptoms improved; however, a mild right abducens nerve palsy w good recovery with the exception of incomplete resolution of the abducens palsy. Upon questioning, the patie eyes and mouth, was diagnosed with Sjogren's syndrome that was confirmed by a positive antinuclear antibo with a stabilized erythrocyte sedimentation rate. (Boot, 2009).

2) Lamotrigine-induced aseptic meningitis was reported in a 50-year-old female after the first dose of lamotri mixed episode of bipolar disorder with suicidal thoughts. Within a few hours of the first dose of lamotrigine 25 40.1 degrees C, difficult breathing, tachycardia, headache, photophobia, neck stiffness and increasing myalg inflammation; however, cerebrospinal fluid (CSF) Gram-stains and bacterial cultures found no evidence of an subsequently discontinued and the symptoms improved over the next few days. It was then discovered that t was started on lamotrigine 25 mg daily 7 months prior to the current incident. Lamotrigine was also discontinu subsequently discharged with a presumptive diagnosis of aseptic meningitis. The time between the administr of meningitis, which completely resolved upon discontinuation, as well as recurrence of symptoms upon rech aseptic meningitis in this patient. Aseptic meningitis is a rare side effect of lamotrigine with only 4 cases previ

3.3.9.D Ataxia

1) Incidence: adults, greater than 2% to 28%; children, 11% (Prod Info LAMICTAL(R) chewable dispersible o

2) In premarketing clinical trials of adjunctive epilepsy therapy, ataxia was reported in 22% of adult patients r those receiving placebo (n=419) (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 200

3) In a randomized, placebo-controlled, parallel study, ataxia was one of the more common dose-related adv adult patients with epilepsy treated with lamotrigine 300 mg/day (n=71), lamotrigine 500 mg/day (n=72), and chewable dispersible oral tablets, oral tablets, 2009).

4) In a controlled, monotherapy trial, ataxia was reported in greater than 2% and less than 5% of adult patier (n=43) following discontinuation of carbamazepine or phenytoin and was reported at a greater frequency thar (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 2009).

5) In placebo-controlled, adjunctive trials, ataxia was reported in 11% of pediatric patients with epilepsy rece 750 mg/day (n=168) compared to 3% of patients receiving placebo (n=171) (Prod Info LAMICTAL(R) chewab

3.3.9.E Aura, Loss

1) Three patients experienced loss of aura after switching from conventional antiepileptic therapy to lamotrig had been refractory to conventional therapy. Two of the patients sustained injuries due to loss of aura (Deleu

3.3.9.F Blepharospasm

1) Blepharospasm was attributed to lamotrigine monotherapy in a 51-year-old male with secondarily general blepharospasm appeared 4 months after lamotrigine initiation, his current dose and serum level were 500 mg remitted after a 4-week gradual taper and withdrawal of lamotrigine. The authors discuss possible mechanisn inhibitory effect on glutamate release, which may indirectly affect basal ganglia function (Verma et al, 1999).

3.3.9.G Coordination problem

1) Incidence: 5% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, cerebellar coor who received adjunctive treatment with lamotrigine extended-release (n=118) compared with 0% who receive extended-release tablets, 2009).

3.3.9.H Dizziness

1) Incidence: adults, 7% to 54%; children, 14% (immediate-release) (Prod Info LAMICTAL(R) chewable disp release)

2) Immediate Release

a) In premarketing clinical trials of adjunctive epilepsy therapy, dizziness was reported in 38% of adult p 13% of those receiving placebo (n=419) (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral

b) In a randomized, placebo-controlled, parallel study, dizziness was one of the more common dose-rel and 27% of adult patients with epilepsy treated with lamotrigine 300 mg/day (n=71), lamotrigine 500 mg/ LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 2009).

c) In a controlled, monotherapy trial, dizziness was reported in 7% of adult patients with epilepsy who re discontinuation of carbamazepine or phenytoin compared to 0% of those who received valproate monoth dispersible oral tablets, oral tablets, 2009).

d) In placebo-controlled, adjunctive trials, dizziness was reported in 14% of pediatric patients with epilep maximum of 750 mg/day (n=168) compared to 4% of patients receiving placebo (n=171) (Prod Info LAM 2009).

3) Extended Release

a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, dizziness v treatment with lamotrigine extended-release (n=118) compared with 5% who received placebo (n=121) (2009).

3.3.9.I Drug withdrawal seizure

1) Drug withdrawal seizure has been reported in patients with bipolar disorder in clinical trials (Prod Info LAM tablets, 2009; Guerrini et al, 1999).

3.3.9.J Encephalopathy

1) Reversible encephalopathy associated with high lamotrigine blood levels (19 mg/L), with a concurrent urir Concomitant medication included valproic acid, which remained at therapeutic blood levels. Symptoms includ incontinence and primitive reflexes. Symptoms improved concurrent with a fall in lamotrigine levels after her l mg/day (Hennessy & Wiles, 1996).

3.3.9.K Gilles de la Tourette's syndrome

1) Lamotrigine caused dose-related symptoms of Tourette syndrome in 3 children (Lombroso, 1999).

2) A 7-year-old girl with partial motor seizures with secondary generalization was treated with valproic acid a developed tic-like movements and vocalizations. Lamotrigine was discontinued and all symptoms abated. Se up to 250 mg daily. Vocalizations were worse but abated after lamotrigine was reduced to 175 mg daily. A 12 lamotrigine 450 mg added to carbamazepine. He began tic-like movements, vocalizations, and rituals consist Lamotrigine was discontinued and the ticks resolved within 2 weeks and the OCD symptoms resolved over s and the symptoms have not returned. An 8-year-old boy with complex partial seizures received lamotrigine 2 repetitive head shaking, hand rubbing, throat clearing, and facial grimaces. His tics abated within a few days

remained under control with lamotrigine 200 mg daily (Lombroso, 1999).

3.3.9.L Headache

1) Incidence: 29% (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 2009)

2) In a premarketing clinical trial, headache was reported in 29% of adult epilepsy patients receiving lamotrig patients, and resulted in drug discontinuation in 3.1% of lamotrigine patients (Prod Info LAMICTAL(R) chewal

3.3.9.M Insomnia

1) Incidence: 5% to 10% (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 2009)

2) In premarketing clinical trials of adjunctive epilepsy therapy, insomnia was reported in 6% of adult patients those receiving placebo (n=419) (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 200

3) In a controlled, monotherapy trial, insomnia was reported in 5% of adult patients with epilepsy who receive discontinuation of carbamazepine or phenytoin compared to 2% of those who received valproate monotherap oral tablets, oral tablets, 2009).

4) In two placebo-controlled trials, insomnia was reported in 10% of adults with bipolar I disorder receiving la after being converted from add-on therapy with other psychotropic medications compared to 6% of those rec chewable dispersible oral tablets, oral tablets, 2009).

3.3.9.N Myoclonus

1) Three case reports describe lamotrigine-associated myoclonus. Two cases involved young adult males (a epilepsies since early childhood. After 2 to 3 years of lamotrigine-valproic acid therapy resulting in a seizure-f myoclonic jerking. In both cases, the lamotrigine serum level was higher than usual (16.5 and 17.7 mg/L). My yet greatly diminished after lamotrigine was stopped or its dose reduced (Janszky et al, 2000).

3.3.9.O Nystagmus

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure nystagmus was lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod Info LAMICTA

3.3.9.P Somnolence

1) Incidence: adults, 9% to 14%; children, 17% (immediate-release) (Prod Info LAMICTAL(R) chewable disp release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) Immediate Release

a) In premarketing clinical trials of adjunctive epilepsy therapy, somnolence was reported in 14% of adul patients receiving placebo (n=419) (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral table

b) In placebo-controlled, adjunctive trials, somnolence was reported in 17% of pediatric patients with ep maximum of 750 mg/day (n=168) compared to 15% of patients receiving placebo (n=171) (Prod Info LA tablets, 2009)

c) In two placebo-controlled trials, somnolence was reported in 9% of adults with bipolar I disorder recei monotherapy after being converted from add-on therapy with other psychotropic medications compared LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 2009).

d) Somnolence and ataxia were also reported in a 45-year-old female following a 2-week upward titratio signs were present. Her neurological status improved over the next 2 weeks following discontinuation of

3) Extended Release

a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, somnolenc treatment with lamotrigine extended-release (n=118) compared with 5% who received placebo (n=121) (2009)

3.3.9.Q Status epilepticus

1) Status epilepticus has been reported in a minimum of 7 of 2,343 adult patients receiving lamotrigine (Prod oral tablets, 2009; Guerrini et al, 1999).

2) An 8-year-old female diagnosed 4 years previously with Lennox-Gastaut syndrome developed myoclonic clobazam/vigabatrin regimen. Lamotrigine had been initiated at 2 mg/kg, then gradually increased to 20 mg/k the parents reported increasingly frequent episodes of irregular multifocal jerks. Long-term electroencephalo myoclonus, which resolved shortly upon lamotrigine discontinuation (Guerrini et al, 1999).

3.3.9.R Tremor

1) Incidence: adults, 4%; children, 10% (immediate-release) (Prod Info LAMICTAL(R) chewable dispersible (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) Immediate Release

a) In premarketing clinical trials of adjunctive epilepsy therapy, tremor was reported in 4% of adult patie those receiving placebo (n=419) (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral tablets,

b) In placebo-controlled, adjunctive trials, tremor was reported in 10% of pediatric patients with epilepsy of 750 mg/day (n=168) compared to 1% of patients receiving placebo (n=171) (Prod Info LAMICTAL(R)

c) Disabling tremors with dysarthria and mild truncal ataxia have also been reported in 3 patients followi valproate sodium. Tremor resolved with reduction in dose of lamotrigine or valproate sodium (Reutens e

3) Extended Release

a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, tremor was

treatment with lamotrigine extended-release (n=118) compared with 2% who received placebo (n=121) (2009).

3.3.9.S Unsteady gait

1) Incidence: 2% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, gait disturbance treatment with lamotrigine extended-release (n=118) compared with 0% who received placebo (n=121) (Prod 2009).

3.3.9.T Vertigo

1) Incidence: 4% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, vertigo was evi treatment with lamotrigine extended-release (n=118) compared with 0% who received placebo (n=121) (Prod 2009).

3.3.10 Ophthalmic Effects

Blurred vision

Diplopia

3.3.10.A Blurred vision

1) Incidence: 11% to 25% (immediate-release) (Prod Info LAMICTAL(R) oral tablets, chewable dispersible o LAMICTAL XR oral extended-release tablets, 2009)

2) Immediate Release

a) In an adjunctive trial, blurred vision was reported in 16% of adult epilepsy patients receiving lamotrigi trial of adult epilepsy patients found that incidence of blurred vision was dose-related, increasing from 11 10% with placebo (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3) Extended Release

a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, blurred visi adjunctive treatment with lamotrigine extended-release (n=118) compared with 2% who received placeb release tablets, 2009).

3.3.10.B Diplopia

1) Incidence: 24% to 49% (immediate-release) (Prod Info LAMICTAL(R) oral tablets, chewable dispersible o LAMICTAL XR oral extended-release tablets, 2009)

2) Immediate Release

a) In an adjunctive trial, diplopia was reported in 28% of adult epilepsy patients receiving lamotrigine co of adult epilepsy patients found that incidence of diplopia was dose-related, increasing from 24% with 30 placebo (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3) A comprehensive review of manufacturer data encompassing 13 clinical trials (n=1096) characterize lamo population. As add-on therapy, the mean lamotrigine dose and duration were 5.5 milligrams/kilogram/day (m the mean dose and duration were 2.9 mg/kg/day and 22 weeks, respectively. In placebo-controlled studies, a frequency among lamotrigine recipients included diplopia at 5.4% (Messenheimer et al, 2000).

a) Extended Release

1) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, diplop adjunctive treatment with lamotrigine extended-release (n=118) compared with 0% who received pla release tablets, 2009).

3.3.12 Psychiatric Effects

Anxiety

Depression

Dyssomnia

Suicidal thoughts

Visual hallucinations

3.3.12.A Anxiety

1) Incidence: 5% (immediate release)(Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets XR oral extended-release tablets, 2009)
2) Immediate Release
a) In a monotherapy trial of adult partial seizure patients, anxiety was reported in 5% of patients treated treated with low-dose valproate (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2
3) Extended Release
a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, anxiety wa treatment with lamotrigine extended-release (n=118) compared with 0% who received placebo (n=121) (2009).

3.3.12.B Depression
1) Incidence: 4% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)
2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, depression was treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod 2009).

3.3.12.C Dyssomnia
1) A 42-year-old healthy woman experienced dose-related visual hallucinations as well as sleep disturbance citalopram 40 mg/day for 6 months for depression. She was then diagnosed with bipolar affective disorder typ subsequent dose increase to 50 mg/day, then 100 mg/day in 2 week intervals. Initial symptoms after dose inc wakening and vivid dream-like experiences without being completely asleep. Five days later she experienced headaches and hypersensitivity to noise. The hallucinations resolved over 2 to 3 days after reducing the lamo disturbances and nightmares returned within 1 week of a dose increase to 75 mg/day. Three months later, th disturbed sleep and nightmares. She continued on 100 mg/day, which resulted in visual hallucinations descri that she perceived as real. The events occurred at times of clear consciousness during both daytime and nigl in hallucinations resolving over 3 days. Hallucinations and nightmares have not recurred despite continued tr mg/day. She had no past history of hallucinations (Uher & Jones, 2006).

3.3.12.D Suicidal thoughts
1) Data reviewed by the US Food and Drug Administration suggest an increased risk of suicidal behavior or antiepileptic drugs (AEDs). The analysis included 199 placebo-controlled clinical studies covering 11 different epilepsy, selected psychiatric illnesses, and other conditions, including migraine and neuropathic pain syndro AEDs and 16,029 patients who received placebo, and patients were aged 5 years and older. There were 4 co groups versus (vs) none in the placebo groups. Suicidal behavior or ideation occurred in 0.43% of patients in patients in the placebo groups. This corresponded to an estimated 2.1 per 1000 (95% confidence interval, 0.7 having suicidal behavior or ideation than the placebo groups. The increased risk of suicidality was noted at 1 weeks. When compared to placebo, results were generally consistent among the drugs and were seen in all psychiatric disorders, or other conditions were all at an increased risk for suicidality compared to placebo. Clo or worsening of depression, suicidality and other unusual changes in behavior, which may include symptoms hypomania (US Food and Drug Administration, 2008).

3.3.12.E Visual hallucinations
1) A 42-year-old healthy woman experienced dose-related visual hallucinations as well as sleep disturbance citalopram 40 mg/day for 6 months for depression. She was then diagnosed with bipolar affective disorder typ subsequent dose increase to 50 mg/day, then 100 mg/day in 2 week intervals. Initial symptoms after dose inc wakening and vivid dream-like experiences without being completely asleep. Five days later she experienced headaches and hypersensitivity to noise. The hallucinations resolved over 2 to 3 days after reducing the lamo disturbances and nightmares returned within 1 week of a dose increase to 75 mg/day. Three months later, th disturbed sleep and nightmares. She continued on 100 mg/day, which resulted in visual hallucinations descri that she perceived as real. The events occurred at times of clear consciousness during both daytime and nigl in hallucinations resolving over 3 days. Hallucinations and nightmares have not recurred despite continued tr mg/day. She had no past history of hallucinations (Uher & Jones, 2006).

3.3.13 Renal Effects

Hematuria

Renal failure

3.3.13.A Hematuria
1) Hematuria was reported in 5% of patients receiving lamotrigine in one clinical trial (Jawad et al, 1989d); he In overall clinical experience with the drug, hematuria infrequently occurred (1% or less) (Prod Info LAMICTA 2006).

3.3.13.B Renal failure

1) Acute renal failure, in the absence of predisposing factors, occurred in a 45-year-old female after 14 days for complex partial seizures. Carbamazepine and clonazepam had been used previously by this patient. Seru Rhabdomyolysis developed and may have contributed to the renal failure. Generalized seizures were not rep

3.3.14 Reproductive Effects

3.3.14.A Dysmenorrhea

1) Incidence: 5% (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)

2) In a monotherapy trial for adults with partial seizures, 5% of female patients receiving lamotrigine reportec low-dose valproate (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3.3.15 Respiratory Effects

Apnea

Congestion of nasal sinus

Epistaxis

Influenza

Pain in throat

Rhinitis

Sinusitis

3.3.15.A Apnea

1) Summary

a) Apnea has been reported in postmarketing surveys, but causality has not been established (Prod Infc tablets, 2006).

3.3.15.B Congestion of nasal sinus

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, sinus congestic adjunctive treatment with lamotrigine extended-release (n=118) compared with 0% respectively who receivec extended-release tablets, 2009).

3.3.15.C Epistaxis

1) Incidence: 2% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, epistaxis was e treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod 2009).

3.3.15.D Influenza

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, influenza or infl received adjunctive lamotrigine extended-release (n=118) compared with 2% who received placebo (n=121) 2009).

3.3.15.E Pain in throat

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, pharyngolaryng adjunctive treatment with lamotrigine extended-release (n=118) compared with 2% who received placebo (n= tablets, 2009).

3.3.15.F Rhinitis

1) Incidence: 7% (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)

2) In a monotherapy trial of adult partial seizure patients, rhinitis was reported in 7% of patients treated with l low-dose valproate (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3.3.15.G Sinusitis

1) Incidence: 3% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, sinusitis was ev
treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod
2009).

3.3.16 Other

Angioedema

Asthenia

Drug withdrawal

Fever

Multiorgan failure, acute

Pain

3.3.16.A Angioedema

1) Incidence: rare (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006)
2) Angioedema has been rarely reported with lamotrigine therapy (Prod Info LAMICTAL(R) oral tablets, chev

3.3.16.B Asthenia

1) Incidence: 9% (extended-release) (Prod Info LAMICTAL XR oral extended-release tablets, 2009)
2) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, asthenia condit
adjunctive treatment with lamotrigine extended-release (n=118) compared with 5% who received placebo (n=
tablets, 2009).

3.3.16.C Drug withdrawal

1) A 26-year-old man developed anhedonia, visual hallucinations, tremor, slight tachycardia, and hyperhidros
discontinuation of his antiepileptic medications (valproic acid 1220 milligrams (mg) per day, lamotrigine 200 n
mg/day for the first 7 days and 2000 mg/day thereafter) in combination with valproic acid was prescribed to re
psychomotor symptoms had begun before he took the first dose of levetiracetam. Therefore, the authors attri
symptoms resolved within a few days (Gelisse et al, 2002).

3.3.16.D Fever

1) Increased temperature related to leukopenia and sepsis has been reported in a patient following 10 days
included valproate sodium and propranolol (Nicholson et al, 1995). Another case was reported of a 45-year-o
disseminated intravascular coagulation, and acute renal failure 14 days after beginning lamotrigine therapy. C
carbamazepine (Schaub et al, 1994).

3.3.16.E Multiorgan failure, acute

1) Acute multiorgan failure, which has sometimes been fatal or irreversible, has been reported in patients tak
associated with multiorgan failure and hepatic failure in 2 of 3,796 adult patients and 4 of 2,435 pediatric pati
other serious medical complications (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2
2) Two children (3.5- and 11-years-old) suffered multiorgan dysfunction and disseminated intravascular coag
current valproic acid therapy. Symptoms began 9 days after starting lamotrigine therapy and included a syndi
urticarial/maculopapular rash, hepatic, and renal dysfunction, hypoalbuminemia, and changes in alertness. D
were also reported, along with evidence of rhabdomyolysis in one patient. No seizures were noted during this
lamotrigine. This probably represents lamotrigine- associated anticonvulsant hypersensitivity syndrome (Chat

3.3.16.F Pain

1) Incidence: 5% (immediate-release)(Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets
XR oral extended-release tablets, 2009)
2) Immediate Release
a) In a monotherapy trial of adult partial seizure patients, nonspecific body pain was reported in 5% of pa
the patients treated with low-dose valproate (Prod Info LAMICTAL(R) oral tablets, chewable dispersible c
3) Extended Release
a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, pain was e
treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (
2009).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info LAMICTAL(R) oral tablets, c
a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) in women and animals are not available. Drugs should be given only if the potential benefit justifies the poten
2) Australian Drug Evaluation Committee's (ADEC) Category: B3(Australian Drug Evaluation Committee, 1999)
a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing ag or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have damage, the significance of which is considered uncertain in humans.
See Drug Consult reference: PREGNANCY RISK CATEGORIES
3) Crosses Placenta: Yes
4) Clinical Management
a) A major risk for congenital malformations or fetal loss after first trimester exposure to lamotrigine is not ev Inherently epileptic women have a greater risk of delivering a malformed infant than those without epilepsy, b with maternal seizures or with the treatment drug (Hvas et al, 2000; Morrell, 1996). Based on preliminary data Pregnancy, a possible link may exist between exposure to lamotrigine monotherapy during the first trimester and Drug Administration, 2006). A, large, case-controlled study showed a nonsignificant difference in risk of c compared with non-exposed infants(Dolk et al, 2008). In animal studies, lamotrigine decreases folate concen further data are available, lamotrigine should be used during pregnancy only if the potential benefit to the mot manufacturer maintains a Lamotrigine Pregnancy Registry to monitor outcomes of exposure to lamotrigine du encouraged to report such prenatal exposure, before fetal outcome (eg, ultrasound, amniocentesis results, bi 1-800-336-2176. Patients or prescribers may also enroll in the NAAED by calling (888) 233-2334 (Prod Info L tablets, 2007).
5) Literature Reports
a) There was not an increased risk of isolated orofacial cleft (OC) relative to other malformations in neonates with those who were not exposed to any antiepileptic drugs in a population-based, case-control study (n=85,5 5511 orofacial cleft (OC) cases and 80,052 non-OC controls. For isolated OC in lamotrigine-exposed neonate malformations (odds ratio adjusted for maternal age (adjOR) equal to 0.8, 95% confidence interval (CI), 0.11 other malformations for any of the other 3 OC categories: isolated and multiply malformed OC (adjOR equal t (adjOR equal to 1.01, 95% CI, 0.03 to 5.57), and isolated and multiply malformed CP (adjOR equal to 0.79, 9 exposure. There were 72 lamotrigine mono- or polytherapy-exposed registrations, 40 of which were lamotrigi total cases corresponded to a prevalence of 0.47 cases of OC per 1000 registrations (Dolk et al, 2008).
b) As of September 2006, preliminary data collected by the North American Antiepileptic Drug (NAAED) preg prevalence of isolated, non-syndromic, cleft palate and/or cleft lip in infants of women exposed to lamotrigine Five cases of oral cleft (2 isolated cleft lip, 3 isolated cleft palate) occurred among 564 women who received l resulting in a total prevalence of 8.9 per 1000. However, other pregnancy registries have not reported a simila until further data are available (US Food and Drug Administration, 2006).
c) A July 2005 report from the Lamotrigine Pregnancy Registry, established by the manufacturer to collect da 648 instances of mothers treated with lamotrigine monotherapy during the first trimester of pregnancy. Sixtee abnormalities were noted in this group. In mothers treated with lamotrigine plus one or more other anticonvuls presented with anomalies. However, there was no consistent pattern of anomalies among the birth defects re
d) A series of observational cohort studies suggested that lamotrigine does not cause an increased rate of c 68 pregnant women who took the drug, three discontinued the drug before the last menstrual period; 59 were second or third trimester. Of the 59 exposed during the first trimester, there were 39 births (31 without congen abortion, and nine pregnancies intentionally terminated. Three infants were delivered full term with congenita (mother also exposed to phenytoin), palatal cleft, hypospadias, and undescended testes (mother also expose ventricular septal defect (mother also exposed to phenobarbitone and valproic acid). One infant was delivered abdominal intestinal obstruction. The mother had been exposed to labetalol and had experienced pre-eclamp
e) Lamotrigine clearance increased by more than 50% in some women at the onset of pregnancy with a sign reversed soon after delivery. Increased doses of lamotrigine may be required to maintain therapeutic levels d following pregnancy (Tran et al, 2002).

B) Breastfeeding
1) Thomson Lactation Rating: Infant risk cannot be ruled out.
a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk wh benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.
2) Clinical Management
a) Lamotrigine milk to plasma (M/P) ratio was 41.3% (range, 5.7% to 147.1%) and infant/maternal ratio of tot prospective, observational study of 30 nursing mothers treated with lamotrigine and their infants (Newport et exposed to lamotrigine from the mother's breast milk are not known, breast-feeding is not recommended in w oral tablets, chewable dispersible oral tablets, 2007).
3) Literature Reports
a) Lamotrigine milk to plasma (M/P) ratio was 41.3% (95% confidence interval (CI), 33% to 49.6%) and infan 18.3% (95% CI, 9.5% to 27%) in a prospective, observational study of 30 nursing mothers treated with lamotr M/P ratio, calculated using each participant's mean breast milk concentration, ranged from 5.7% to 147.1%. U concentrations for each participant, M/P ratios were 26.5% (95% CI, 20.2% to 32.9%) and 63.1% (95% CI, 47 free lamotrigine concentration was 30.9% (95% CI, 13.4% to 48.3%), 1.7 times higher than the total. Infants h lamotrigine compared with their mothers (53.5% vs 29.5%, paired t=2.91, p less than 0.02). Theoretical infant mg/kg/d (95% CI, 0.37 to 0.65 mg/kg/d) and 9.2% (95% CI, 7.4% to 10.9%), respectively. Univariate Pearson p values less than 0.0001) positive correlations of lamotrigine concentration in breast milk with maternal daily plasma (r=0.37), and free lamotrigine in maternal plasma (r=0.51). Maternal dose (F(1147)=25.62) and free la

=17.31) were significant predictors of lamotrigine breast milk concentration (p values less than 0.0001) in a m
predictors was also significant (F(1147)=6.44, p less than 0.02). The final regression model accounted for 45
concentrations (F(3147)=41.11; p less than 0.0001) (Newport et al, 2008).
b) Evaluation of six infants who were breast fed by mothers treated with lamotrigine (mean doses of 400 mg/
infant dose of lamotrigine received through breast milk was 0.45 mg/kg/day. The mean infant plasma concen
concentration was 18% (Page-Sharp et al, 2006).
c) Lamotrigine levels were measured on day 10 of life in 4 full-term nursing infants born to epileptic mothers
ranged from less than 1 to 2 mcg/mL, and were an average of 30% (range 20 to 43%) of maternal lamotrigine
with repeated levels at 2 months. Both infants were nursing with supplemental formula 2 to 3 times a day. Th
levels in the neonate were a result of immature enzyme systems in the infants, specifically hepatic glucuronic
the infants (Liporace et al, 2004).
d) Serum lamotrigine levels in three women and their nursed infants were measured and the infants' intake c
None of the infants experienced adverse effects (Ohman & Vitols, 2000).

4) Drug Levels in Breastmilk
- **a)** Parent Drug
  - **1)** Percent Adult Dose in Breastmilk
    - **a)** 9% (2-20%) (Ohman & Vitols, 2000)
  - **2)** Milk to Maternal Plasma Ratio
    - **a)** 0.61 (0.5-0.77) (Ohman & Vitols, 2000)

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Acetaminophen

Carbamazepine

Desogestrel

Escitalopram

Estradiol Cypionate

Ethinyl Estradiol

Ethynodiol Diacetate

Etonogestrel

Evening Primrose

Fosphenytoin

Ginkgo

Levonorgestrel

Lopinavir

Mestranol

Methsuximide

Norethindrone

Norgestimate

Norgestrel

Oxcarbazepine

Phenobarbital

Phenytoin

Primidone

Rifampin

Risperidone

Ritonavir

Rufinamide

Sertraline

Valproic Acid

3.5.1.A Acetaminophen

1) Interaction Effect: decreased lamotrigine effectiveness

2) Summary: In a randomized study, the effect of acetaminophen on the pharmacokinetics of lamotrigine wa area under the plasma concentration-time curve of lamotrigine decreased by 15% and 20% respectively. Rer al, 1990a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor the clinical effectiveness of lamotrigine therapy. Routine increases in lamot failure occurs. An occasional dose of acetaminophen is unlikely to significantly decrease lamotrigine concent

7) Probable Mechanism: increased renal clearance

8) Literature Reports

a) Acetaminophen enhances the urinary elimination of lamotrigine after single doses of the anticonvulsa mg dose of lamotrigine followed by acetaminophen 900 mg 3 times a day resulted in a decrease in AUC compared to administration of lamotrigine with placebo. No differences in peak plasma concentration or t lamotrigine recovered in the urine was also higher when administered with acetaminophen. It was sugge lamotrigine from the circulation (Depot et al, 1990).

3.5.1.B Carbamazepine

1) Interaction Effect: reduced lamotrigine efficacy, loss of seizure control, and a potential risk of neurotoxicity

2) Summary: The clearance of lamotrigine may double during concomitant therapy with carbamazepine (Goa 1991a; Mikati et al, 1989a; Jawad et al, 1987a). In addition, increased serum concentrations of carbamazepir carbamazepine) and neurotoxicity have been reported during concomitant administration of carbamazepine a investigators have found that lamotrigine had no effect on either carbamazepine or its metabolite (Schapel et While lamotrigine has no appreciable effect on the steady-state carbamazepine concentration, carbamazepin (Prod Info Lamictal(R), 2003e).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor seizure control and follow patients for signs of neurotoxicity (nausea, vertig increase lamotrigine doses and/or reduce carbamazepine doses. It may be advantageous to monitor the seru metabolite, carbamazepine-10,11-epoxide. Increased side effects have been associated with carbamazepine When given in combination with an enzyme-inducing antiepileptic agent, the manufacturer recommends an ir two weeks for adult patients, followed by 50 mg twice daily for the third and fourth weeks, advancing by 100 r to 500 mg administered in two divided doses.

7) Probable Mechanism: hepatic induction by carbamazepine of lamotrigine metabolism; possible alteration

8) Literature Reports

a) While lamotrigine alone has a steady-state elimination half-life of between 25 to 37 hours, coadminist approximately 14 or 15 hours (Binnie et al, 1986c; Jawad et al, 1987; Peck, 1991d). Lamotrigine clearan mL/min/kg) in healthy volunteers given lamotrigine alone (Cohen et al, 1987; Posner et al, 1989; Posner therapy ranged from 0.044 to 0.084 L/h/kg (0.73 to 1.4 mL/min/kg) (Jawad et al, 1987; Mikati et al, 1989; decrease incrementally the half-life of lamotrigine by 1.7 hours for every 100 mg of carbamazepine withir

1987).
b) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially i of other anticonvulsants. The teratogenicity of these drugs is largely or wholly related to the levels of the Dyke et al, 1991b; Finnell et al, 1992b). The epoxide/parent drug ratio is generally increased when phen any other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide lamotrigine (Bianchetti et al, 1987b; Ramsay et al, 1990b; Spina et al, 1996b). Such combinations increa monotherapy and about 10-fold over background rates.
c) No pharmacokinetic interaction between carbamazepine and lamotrigine was found in children. Three generalized epilepsy who had been treated with carbamazepine for longer than one year started lamotrig lamotrigine dose was increased by 1 mg/kg/day every other week until clinical response or side effects o change significantly from baseline when lamotrigine was coadministered (29.9 mmol/L vs. 28.8 mmol/L). metabolite of carbamazepine, carbamazepine-10,11-epoxide, significantly decreased from 6.4 mmol/L to Boreus, 1997).
d) Carbamazepine reduces the plasma levels of lamotrigine. A 65-year-old male suffering from complex carbamazepine (400 mg three times daily) and lamotrigine (200 mg three times daily). Seizures occurred and a beta-agonist were used for an obstructive lung disease. A current pneumonia was being treated w was 1.7 mcmol/mL and a trough carbamazepine was 11 mcmol/mL. The patient continued to suffer from levitiracetam (1500 mg twice daily) within 4 weeks. After 4 weeks of levitiracetam therapy the patient's ca lamotrigine plasma levels were 12.1 mcmol/mL. Lamotrigine levels increased rapidly after reductions in t combination was well tolerated and seizures stopped completely after 4 weeks. A drug interaction should result in ineffective antiepileptic therapy (Koch et al, 2003).

3.5.1.C Desogestrel

1) Interaction Effect: decreased plasma lamotrigine concentrations
2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive
8) Literature Reports
a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose) and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%) contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu (95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of gluc lamotrigine and ethinyl estradiol (Christensen et al, 2007).
b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the pa patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absen concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizure discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora when oral contraceptives were discontinued. These effects were independent of whether the oral contrac norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lar combination contraceptives (Sabers et al, 2001).
c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication. used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wome those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a (p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe
d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1 clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.D Escitalopram

1) Interaction Effect: an increased risk of myoclonus

2) Summary: Myoclonus occurred in 2 patients receiving escitalopram and lamotrigine concomitantly, where escitalopram in 1 patient. There was no evidence of a metabolic enzyme interaction with lamotrigine, and the additive/synergistic effect of lamotrigine and escitalopram on the 5-HT1A receptors, or by an additive inhibitio (Rosenhagen et al, 2006). Exercise caution when using both drugs concurrently and monitor for signs and sy and jerking.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use caution if escitalopram and lamotrigine are used concurrently as this resulted i resolved after escitalopram was withdrawn (Rosenhagen et al, 2006). Monitor for signs and symptoms of myo
7) Probable Mechanism: additive inhibition of voltage-gated calcium channels; additive or synergistic effects
8) Literature Reports
a) Myoclonus occurred in 2 patients following concomitant treatment with escitalopram and lamotrigine. escitalopram 30 mg/day for depression, developed daytime and nighttime myoclonus after 8 weeks of re treatment of bipolar type II disorder. Serum levels of both drugs, measured after the onset of myoclonus, escitalopram levels remained stable compared to a baseline level drawn prior to starting lamotrigine ther continued to have myoclonus while on escitalopram and lamotrigine therapy. Further analysis revealed t CYP2C19, and CYP2D6 enzymes. The second patient, a 28-year-old woman taking lamotrigine 300 mg/ nighttime myoclonus after 2 weeks of receiving escitalopram (titrated to 20 mg/day) for generalized anxie same frequency of myoclonus while on both therapies; however, the myoclonus resolved 2 weeks after e measured at the onset and after the myoclonus resolved, did not change. Although escitalopram is meta CYP2D6, there was no evidence of a metabolic enzyme interaction with lamotrigine. It was postulated th or synergistic effect of lamotrigine and escitalopram on the 5-HT1A receptors, or by an additive inhibition (Rosenhagen et al, 2006).

3.5.1.E Estradiol Cypionate

1) Interaction Effect: decreased plasma lamotrigine concentrations
2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive
8) Literature Reports
a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose) and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%) contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu (95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of gluc lamotrigine and ethinyl estradiol (Christensen et al, 2007).
b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the p patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absen concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizure discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora when oral contraceptives were discontinued. These effects were independent of whether the oral contrac norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lar combination contraceptives (Sabers et al, 2001).
c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication. used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wome those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a (p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe
d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1 clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.F Ethinyl Estradiol

1) Interaction Effect: decreased plasma lamotrigine concentrations

2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig
Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an
the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a
lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c
contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont
maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease
use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor
system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive

8) Literature Reports

a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that
lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace
a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest
a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose)
and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%)
contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu
(95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa
seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of glu
lamotrigine and ethinyl estradiol (Christensen et al, 2007).

b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the p
patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absen
concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizure
discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s
plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora
when oral contraceptives were discontinued. These effects were independent of whether the oral contrac
norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lar
combination contraceptives (Sabers et al, 2001).

c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication.
used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wome
those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a
(p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe

d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1
clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i
concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti
serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom
lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar
containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.G Ethynodiol Diacetate

1) Interaction Effect: decreased plasma lamotrigine concentrations

2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig
Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an
the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a
lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c
contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont
maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease
use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor
system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive

8) Literature Reports

a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that
lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace
a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest
a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose)
and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%)
contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu
(95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa

seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of gluc
lamotrigine and ethinyl estradiol (Christensen et al, 2007).
b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the pa
patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absen
concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizure
discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s
plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora
when oral contraceptives were discontinued. These effects were independent of whether the oral contrac
norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lar
combination contraceptives (Sabers et al, 2001).
c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication.
used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wome
those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a
(p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe
d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1
clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i
concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti
serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom
lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar
containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.H Etonogestrel

1) Interaction Effect: decreased plasma lamotrigine concentrations
2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig
Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an
the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a
lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c
contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont
maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease
use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor
system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive
8) Literature Reports
a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that
lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace
a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest
a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose)
and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%)
contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu
(95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa
seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of gluc
lamotrigine and ethinyl estradiol (Christensen et al, 2007).
b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the pa
patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absen
concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizure
discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s
plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora
when oral contraceptives were discontinued. These effects were independent of whether the oral contrac
norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lar
combination contraceptives (Sabers et al, 2001).
c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication.
used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wome
those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a
(p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe
d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1
clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i
concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti
serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom
lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar
containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.I Evening Primrose

1) Interaction Effect: reduced anticonvulsant effectiveness
2) Summary: Theoretically, evening primrose oil may reduce the effectiveness of anticonvulsants by lowering

contraindicated in patients with epilepsy (Barber, 1998; Newall et al, 1996).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of evening primrose oil with anticonvulsants.
7) Probable Mechanism: evening primrose oil may reduce the seizure threshold

3.5.1.J Fosphenytoin
1) Interaction Effect: reduced lamotrigine efficacy
2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are Cerebyx(R), 1999). Potent hepatic enzyme-inducing drugs including phenytoin enhance the metabolic cleara steady-state elimination half-life of approximately 24 to 30 hours, coadministration of phenytoin reduces the h et al, 1986; Jawad et al, 1989; Peck, 1991).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Higher doses of lamotrigine are needed when given concurrently with enzyme-indu When given in combination with an enzyme-inducing antiepileptic agent, the manufacturer recommends an ir two weeks for adult patients, followed by 50 mg twice daily for the third and fourth weeks, advancing by 100 r to 500 mg administered in two divided doses.
7) Probable Mechanism: increased lamotrigine metabolism
8) Literature Reports
a) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially i of other anticonvulsants. The teratogenicity of these drugs is largely or wholly related to the levels of the Dyke et al, 1991; Finnell et al, 1992). The epoxide/parent drug ratio is generally increased when phenyto other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hyc lamotrigine (Bianchetti et al, 1987; Ramsay et al, 1990; Spina et al, 1996). Such combinations increase t monotherapy and about 10-fold over background rates.

3.5.1.K Ginkgo
1) Interaction Effect: decreased anticonvulsant effectiveness
2) Summary: In a case report, 2 patients with epilepsy previously well controlled by valproate sodium develo extract. Seizure control was regained after ginkgo was withdrawn (Granger, 2001a). An infant developed seiz from ingestion of ginkgo seeds (Yagi et al, 1993a). The compound 4'-O-methylpyridoxine, a neurotoxin, is fou in leaves, the ginkgo component from which commercially available extracts are derived (Arenz et al, 1996a). sufficient amounts of 4'-O-methylpyridoxine to cause seizures. However, ginkgo products are not commonly a contained in the commercial product. Of concern are those instances where, depending on the harvest seasc methylpyridoxine may be present in sufficient amounts to be problematic in vulnerable populations (eg, infant
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use of ginkgo and anticonvulsants in patients with epilepsy. If se previously controlled by anticonvulsant medication, inquire about the use of ginkgo seed or leaf extract. If pos product to ascertain if 4'-O-methylpyridoxine is present.
7) Probable Mechanism: neurotoxin 4'-O-methylpyridoxine (found in leaves and seeds of ginkgo biloba) may
8) Literature Reports
a) The serum of a 21-month-old patient with gin-nan food poisoning was assayed for 4'-O-methylpyridox micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds, decreasing to 0.05 mcg/mL at 1 methylpyridoxine content was responsible for the tonic/clonic convulsions and loss of consciousness obs particularly vulnerable (Yagi et al, 1993).
b) Four to six milligrams of the neurotoxin 4'-O-methylpyridoxine have been isolated from 2 kilograms of commercially-available products. Highest amounts were found in seeds (85 micrograms (mcg)/seed) and July and beginning of August. The albumen of the seed can contain 105.15 mcg/gram dry weight, but thi boiled. The unprocessed seed coats contain from 5.44-7.15 mcg/gram dry weight. The neurotoxin in gink detectable in homeopathic preparations. Specifically, 8.13 mcg/mL of 4'-O-methylpyridoxine was found ir mcg/mL in Kaveri Forte(R), and 7.18 mcg/mL in Gingium(R). Based on recommended daily intake, this tr methylpyridoxine of 48.78 mcg, 58.62 mcg, 11.40 mcg, and 43.08 mcg for Tebonin Forte(R), Rokan(R), the homeopathic products, Ginkgo biloba Urtinktur Hanosan(R) and Ginkgo biloba Urtinktur DHU(R) con methylpyridoxine, respectively. However, the authors note that the amount contained in medicinal extrac significance. Concern remains with the variance in 4'-O-methylpyridoxine content depending on the seas 1996).
c) Seizures recurred in 2 patients, both with epilepsy that was well controlled prior to ingesting ginkgo bi 78-year-old man) had been free of seizures for at least 18 months prior to beginning therapy with Gb 120 developed seizures within 2 weeks of beginning Gb therapy, and both remained seizure-free (without cha (Granger, 2001).

3.5.1.L Levonorgestrel
1) Interaction Effect: decreased plasma lamotrigine concentrations

2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig
Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an
the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a
lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c
contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont
maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease
use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor
system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive
8) Literature Reports
a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that
lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace
a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest
a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose)
and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%)
contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu
(95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa
seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of gluc
lamotrigine and ethinyl estradiol (Christensen et al, 2007).
b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the p
patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absen
concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizure
discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s
plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora
when oral contraceptives were discontinued. These effects were independent of whether the oral contrac
norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lar
combination contraceptives (Sabers et al, 2001).
c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication.
used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wome
those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a
(p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe
d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1
clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i
concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti
serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom
lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar
containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.M Lopinavir

1) Interaction Effect: decreased lamotrigine serum concentrations
2) Summary: Coadministration of lamotrigine and lopinavir/ritonavir in healthy subjects significantly decrease
lamotrigine clearance in an open-label, sequential, 3-period trial. The postulated mechanism of action is enha
and/or lopinavir on lamotrigine, which is metabolized by direct glucuronidation. A doubling of the lamotrigine d
lopinavir/ritonavir in this study (vanderLee et al, 2006). Monitor patients for loss of lamotrigine efficacy and ad
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Coadministration of lamotrigine and lopinavir/ritonavir in healthy subjects significant
increased lamotrigine clearance. A doubling of the lamotrigine dose was required to overcome the interaction
al, 2006). If these agents are coadministered, monitor patients for loss of lamotrigine efficacy and adjust lamo
7) Probable Mechanism: increased lamotrigine metabolism
8) Literature Reports
a) In an open-label, sequential, 3-period trial, coadministration of lamotrigine and lopinavir/ritonavir in he
exposure and half-life, and increased lamotrigine clearance; a doubling of the lamotrigine dose is require
to 65 years (n=24) received oral lamotrigine 50 mg once daily for days 1 and 2, followed by 100 mg twice
100 mg twice daily was added on day 11. Lamotrigine trough levels (Cmin) were measured between day
300 mg twice daily depending on the percentage of decrease. Among 18 patients who completed the stu
day 20 (lamotrigine plus lopinavir/ritonavir) compared to day 10 (lamotrigine alone). The median AUC, C
were not bioequivalent to those on day 10, with a geometric mean ratio (GMR) for lamotrigine AUC (day
0.54). Consequently, the lamotrigine dose was increased to 200 mg twice daily from day 23 to day 31 in
bioequivalent to that on day 10, with a GMR (day 31/day 10) of 0.91 (90% CI, 0.82 to 1.02). The median
metabolite to lamotrigine on day 20 was almost double to that on day 10 (0.57 on day 10 versus 1.12 on
induction of glucuronidation of lamotrigine by ritonavir, and possibly also due to lopinavir. The pharmacol
altered (vanderLee et al, 2006).

3.5.1.N Mestranol

1) Interaction Effect: decreased plasma lamotrigine concentrations

2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig
Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an
the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a
lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c
contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont
maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease
use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor
system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive

8) Literature Reports

a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that
lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace
a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest
a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose)
and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%)
contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu
(95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa
seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of gluc
lamotrigine and ethinyl estradiol (Christensen et al, 2007).

b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the p
patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absen
concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizure
discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s
plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora
when oral contraceptives were discontinued. These effects were independent of whether the oral contrac
norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lar
combination contraceptives (Sabers et al, 2001).

c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication.
used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wome
those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a
(p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe

d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1
clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i
concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti
serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom
lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar
containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.O Methsuximide

1) Interaction Effect: reduced lamotrigine concentrations and possible loss of seizure control

2) Summary: During a retrospective study, it was determined that methsuximide significantly decreases lamo
receiving combination therapy, lamotrigine concentrations were 69.7% lower than compared to lamotrigine m
induces lamotrigine metabolism (May et al, 1999a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor seizure control and anticipate a possible need to increase lamotrigine dose
methsuximide is withdrawn from therapy, doses of lamotrigine may need to be reduced.

7) Probable Mechanism: hepatic induction by methsuximide of lamotrigine metabolism

8) Literature Reports

a) Lamotrigine serum concentrations from 222 patients receiving lamotrigine monotherapy (n = 64) or co
evaluated. Thirteen patients were being treated with lamotrigine and methsuximide. In the lamotrigine mo
7.14 mcg/mL while the mean dose was 7.27 mg/dose/kg. The lamotrigine level-to-dose ratio (LDR) in thi
subjects receiving methsuximide in addition to lamotrigine, the plasma concentration was 3.06 mcg/mL v
lamotrigine LDR in this group was 0.31 mcg/mL/mg/kg, demonstrating the inducing properties of methsu

3.5.1.P Norethindrone

1) Interaction Effect: decreased plasma lamotrigine concentrations

2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig
Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an
the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a

lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c
contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont
maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease
use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor
system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive
8) Literature Reports
a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that
lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace
a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest
a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose)
and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%)
contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu
(95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa
seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of gluc
lamotrigine and ethinyl estradiol (Christensen et al, 2007).
b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the pa
patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absen
concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizure
discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s
plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora
when oral contraceptives were discontinued. These effects were independent of whether the oral contrac
norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lar
combination contraceptives (Sabers et al, 2001).
c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication.
used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wome
those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a
(p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe
d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1
clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i
concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti
serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom
lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar
containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.Q Norgestimate

1) Interaction Effect: decreased plasma lamotrigine concentrations
2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig
Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an
the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a
lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c
contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont
maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease
use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor
system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive
8) Literature Reports
a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that
lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace
a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest
a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose)
and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%)
contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu
(95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa
seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of gluc
lamotrigine and ethinyl estradiol (Christensen et al, 2007).
b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the pa
patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absen
concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizure
discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s

plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora
when oral contraceptives were discontinued. These effects were independent of whether the oral contrac
norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lar
combination contraceptives (Sabers et al, 2001).

c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication.
used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wome
those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a
(p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe

d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1
clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i
concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti
serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom
lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar
containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.R Norgestrel

1) Interaction Effect: decreased plasma lamotrigine concentrations

2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in sig
Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient's clinical condition an
the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et a
lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine c
contraceptives in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont
maintain clinical response (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease
use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal cor
system patch, 2008; Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive

8) Literature Reports

a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that
lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace
a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest
a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose)
and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%)
contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glu
(95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 pa
seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of gluc
lamotrigine and ethinyl estradiol (Christensen et al, 2007).

b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the pa
patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absen
concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizure
discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased s
plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when ora
when oral contraceptives were discontinued. These effects were independent of whether the oral contrac
norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lar
combination contraceptives (Sabers et al, 2001).

c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication.
used oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among wome
those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives a
(p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe

d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1
clearance of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and i
concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti
serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in wom
lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lar
containing oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 20

3.5.1.S Oxcarbazepine

1) Interaction Effect: reduced lamotrigine concentrations and possible loss of seizure control

2) Summary: Oxcarbazepine is structurally similar to carbamazepine but does not form an epoxide metabolit
effects of carbamazepine. When lamotrigine and oxcarbazepine were administered concurrently to 14 epilept
decreased 28.7% compared to lamotrigine monotherapy (May et al, 1999c). In two patients who had received
ulcers occurred several weeks after oxcarbazepine discontinuation or dose reduction. Induction of lamotrigine
the mechanism, such oxcarbazepine discontinuation or a dose reduction may have resulted in a slow increas
(O'Neill & deLeon, 2007). Concomitant use of lamotrigine and oxcarbazepine may require monitoring the pati
lamotrigine dose as necessary. Conversely, in patients receiving these agents concurrently, if oxcarbazepine

doses may need to be reduced. Additionally, the patient may need to be monitored over several weeks for sig
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor seizure control and anticipate a possible need to increase lamotrigine dose oxcarbazepine is withdrawn from therapy or if dosage is reduced, lamotrigine doses may need to be reduced weeks for symptoms of lamotrigine toxicity.
7) Probable Mechanism: hepatic induction by oxcarbazepine of lamotrigine metabolism
8) Literature Reports
a) Two patients, receiving lamotrigine and oxcarbazepine concurrently, experienced oral ulcers several reduction. In the first case, a 35-year-old woman being treated for bipolar II disorder (BD II), hypothyroidi experiencing one week of worsening depression and two days of suicidal thoughts and treated with oxca aripiprazole, quetiapine, lithium, naproxen, pantoprazole, amoxicillin, and levothyroxine. On day 2, lamot mg/day by day 6. Oxcarbazepine dose was decreased and stopped by day 5, and she was discharged o aripiprazole, escitalopram, naproxen, pantoprazole, levothyroxine, and hydroxyzine. On day 42 (41 days oxcarbazepine), she developed painful tongue ulcers. Subsequently, lamotrigine was stopped and the ul old man with BD II, hypertension, and GERD was admitted following a suicide attempt and prescribed ox venlafaxine, mirtazapine, metoprolol, and famotidine. Lamotrigine 50 mg/day was initiated on day 11 and discharged on day 14 with lamotrigine 100 mg and oxcarbazepine 1200 mg (along with other medication mg/day after discharge. On day 44 (22 days after oxcarbazepine dose decrease), he developed several lamotrigine and oxcarbazepine were discontinued and the ulcers resolved completely (O'Neill & deLeon,
b) Lamotrigine serum concentrations from 222 patients receiving lamotrigine monotherapy (n = 64) or co evaluated. Fourteen patients were being treated with lamotrigine and oxcarbazepine. In the lamotrigine r 7.14 mcg/mL while the mean dose was 7.27 mg/dose/kg. The lamotrigine level-to-dose ratio (LDR) in thi subjects receiving oxcarbazepine in addition to lamotrigine, the plasma concentration was 4.73 mcg/mL lamotrigine LDR in this group was 0.71 mcg/mL/mg/kg, demonstrating the inducing properties of oxcarba

3.5.1.T Phenobarbital
1) Interaction Effect: reduced lamotrigine efficacy, loss of seizure control
2) Summary: Potent hepatic enzyme-inducing drugs including phenobarbital enhance the metabolic clearanc state elimination half-life of approximately 24 to 30 hours, coadministration of phenobarbital reduces the half- al, 1989a; Peck, 1991a) and decreases the lamotrigine steady-state concentration by approximately 40% (Pr therapy with lamotrigine, valproic acid, and an enzyme inducer on lamotrigine metabolism does not appear to
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Higher doses of lamotrigine are needed when given concurrently with enzyme-indu given in combination with an enzyme-inducing antiepileptic agent, the manufacturer recommends an initial la weeks for adult patients, followed by 50 mg twice daily for the third and fourth weeks, advancing by 100 mg d 500 mg administered in two divided doses.
7) Probable Mechanism: hepatic induction by phenobarbital of lamotrigine metabolism
8) Literature Reports
a) In 13 patients treated with either carbamazepine or phenobarbital with lamotrigine, the half-life of lam children over the age of 2 years and young adults with epilepsy that was not controlled with a single age subjects taking lamotrigine alone has been 25.4 hours with repeated dosing (Prod Info Lamictal(R), 2003

3.5.1.U Phenytoin
1) Interaction Effect: reduced lamotrigine efficacy
2) Summary: Potent hepatic enzyme-inducing drugs including phenytoin enhance the metabolic clearance of elimination half-life of approximately 24 to 30 hours, coadministration of phenytoin reduces the half-life of lam Jawad et al, 1989b; Peck, 1991b). The addition of phenytoin decreases the lamotrigine steady-state concentr phenytoin. Lamotrigine has no significant effect on steady-state phenytoin concentrations (Prod Info Lamictal
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Higher doses of lamotrigine are needed when given concurrently with enzyme-indu When given in combination with an enzyme-inducing antiepileptic agent, the manufacturer recommends an ir two weeks for adult patients, followed by 50 mg twice daily for the third and fourth weeks, advancing by 100 r to 500 mg administered in two divided doses.
7) Probable Mechanism: increased lamotrigine metabolism
8) Literature Reports
a) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially i of other anticonvulsants. The teratogenicity of these drugs is largely or wholly related to the levels of the Dyke et al, 1991a; Finnell et al, 1992a). The epoxide/parent drug ratio is generally increased when pheny any other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide lamotrigine (Bianchetti et al, 1987a; Ramsay et al, 1990a; Spina et al, 1996a). Such combinations increa monotherapy and about 10-fold over background rates.

3.5.1.V Primidone

1) Interaction Effect: decreased lamotrigine efficacy

2) Summary: When primidone is added to lamotrigine therapy, the steady-state lamotrigine concentration de 2003).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Higher doses of lamotrigine are needed when given concurrently with enzyme-indu given in combination with an enzyme-inducing antiepileptic agent, the manufacturer recommends an initial la weeks for adult patients, followed by 50 mg twice daily for the third and fourth weeks, advancing by 100 mg d 500 mg administered in two divided doses.

7) Probable Mechanism: hepatic enzyme induction

3.5.1.W Rifampin

1) Interaction Effect: decreased lamotrigine exposure

2) Summary: Coadministration of a single 25-mg dose of lamotrigine in healthy volunteers receiving rifampin increased apparent clearance of lamotrigine (approximately 2-fold). Lamotrigine's AUC decreased by approxi chewable dispersible oral tablets, 2006). Use caution if these agents are coadministered. Monitor patients for doses accordingly.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Coadministration of lamotrigine and rifampin has led to significantly increased lamo LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006). Monitor patients for loss of lamotrigine ef

7) Probable Mechanism: increased lamotrigine clearance

3.5.1.X Risperidone

1) Interaction Effect: increased risperidone plasma concentrations and risk of adverse effects

2) Summary: Increased risperidone plasma concentrations, with signs of toxicity, developed in a patient adm regimen of risperidone and clozapine (Bienentreu & Kronmuller, 2005).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Clinicians should be aware of the increased risk of risperidone adverse effects in pa When concomitant lamotrigine is initiated, discontinued, or the dose of lamotrigine is changed, re-evaluate th

7) Probable Mechanism: unknown

8) Literature Reports

a) Increased risperidone plasma concentrations and subsequent toxicity were reported in a patient recei risperidone and clozapine. The patient, a 26-year-old woman diagnosed with schizophrenia, had sustain clozapine 550 milligrams (mg) daily and risperidone 8 mg daily. Baseline plasma concentrations of risper (ng/mL) and 800-1100 ng/mL, respectively. Lamotrigine was initiated, with the dose incrementally titrated concentrations increased to 1300 ng/mL and 263 ng/mL, respectively; no symptoms of intoxication were of 225 mg daily, after which risperidone plasma concentration increased to 412 ng/mL, accompanied by dose was reduced to 2 mg daily and completely withdrawn shortly thereafter (Bienentreu & Kronmuller, 2

3.5.1.Y Ritonavir

1) Interaction Effect: decreased lamotrigine serum concentrations

2) Summary: Coadministration of ritonavir and lamotrigine may result in decreased serum concentrations of solution, 2006). Coadministration of lamotrigine and lopinavir/ritonavir in healthy subjects significantly decrea lamotrigine clearance in an open-label, sequential, 3-period trial. The postulated mechanism of action is enha drugs that are metabolized by direct glucuronidation (vanderLee et al, 2006). If lamotrigine and ritonavir are a need to be increased (Prod Info NORVIR(R) oral capsules, solution, 2006). In one study, a doubling of the la effect (vanderLee et al, 2006). Monitor patients for loss of lamotrigine efficacy.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Coadministration of lamotrigine and ritonavir may result in decreased lamotrigine se be increased (Prod Info NORVIR(R) oral capsules, solution, 2006). In one study, a doubling of the lamotrigine (vanderLee et al, 2006). Monitor patients for loss of lamotrigine efficacy.

7) Probable Mechanism: increased lamotrigine metabolism

8) Literature Reports

a) In an open-label, sequential, 3-period trial, coadministration of lamotrigine and lopinavir/ritonavir in he exposure and half-life, and increased lamotrigine clearance; a doubling of the lamotrigine dose is require to 65 years (n=24) received oral lamotrigine 50 mg once daily for days 1 and 2, followed by 100 mg twice 100 mg twice daily was added on day 11. Lamotrigine trough levels (Cmin) were measured between day 300 mg twice daily depending on the percentage of decrease. Among 18 patients who completed the stu day 20 (lamotrigine plus lopinavir/ritonavir) compared to day 10 (lamotrigine alone). The median AUC, C were not bioequivalent to those on day 10, with a geometric mean ratio (GMR) for lamotrigine AUC (day

0.54). Consequently, the lamotrigine dose was increased to 200 mg twice daily from day 23 to day 31 in bioequivalent to that on day 10, with a GMR (day 31/day 10) of 0.91 (90% CI, 0.82 to 1.02). The median metabolite to lamotrigine on day 20 was almost double to that on day 10 (0.57 on day 10 versus 1.12 on induction of glucuronidation of lamotrigine by ritonavir, and possibly also due to lopinavir. The pharmacol altered (vanderLee et al, 2006).

3.5.1.Z Rufinamide

1) Interaction Effect: decreased lamotrigine plasma concentrations

2) Summary: Concomitant administration of lamotrigine and rufinamide may result in lamotrigine concentrati dependent on the concentration of rufinamide, so maximum changes will most likely occur in children and oth rufinamide (Prod Info BANZEL(TM) oral tablets, 2008).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Caution is advised if lamotrigine and rufinamide are coadministered as this may res Risk is increased in children and in other patients who achieve significantly higher levels of rufinamide (Prod

7) Probable Mechanism: unknown

3.5.1.AA Sertraline

1) Interaction Effect: an increased risk of lamotrigine toxicity (fatigue, sedation, confusion, decreased cogniti

2) Summary: Two case reports describe epileptic patients who experienced lamotrigine toxicity when sertrali primarily via glucuronidation, while sertraline relies on N-demethylation, hydroxylation, oxidative deamination decreases lamotrigine metabolism through competitive inhibition of glucuronidation (Kaufman & Gerner, 199

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Caution should be exercised when combining sertraline and lamotrigine therapy. La dosages adjusted accordingly.

7) Probable Mechanism: inhibition of lamotrigine glucuronidation

8) Literature Reports

a) A 39-year-old female with epilepsy was maintained on lamotrigine 200 mg daily with a baseline lamot intermittent explosive disorder, sertraline 25 mg daily was initiated. Six weeks later, the lamotrigine level confusion and cognitive impairment. Sertraline was increased to 50 mg daily while lamotrigine was decre eliminated the patient's confusion and impaired cognition, and the blood level of lamotrigine stabilized at

b) Lamotrigine 450 mg daily was not controlling seizures in a 17-year-old female with mixed epileptic dis and titrated to 75 mg daily without any side effects. Lamotrigine was also increased to 600 mg daily, and fatigue, and decreased cognition. The lamotrigine blood level was 19.3 mcg/mL at this time. The sertralir lamotrigine level was increased to 800 mg daily, resulting in a new steady-state lamotrigine level of 9.8 n decreased to approximately 50% with a 33% decrease in the sertraline daily dose, even though the lamo Gerner, 1998).

3.5.1.AB Valproic Acid

1) Interaction Effect: increased elimination half-life of lamotrigine leading to lamotrigine toxicity (fatigue, drow rashes

2) Summary: Valproic acid interferes with the metabolic clearance of lamotrigine. The normal elimination half receiving concomitant valproic acid therapy, the half-life increases to approximately 40 to 60 hours. The mecl the two drugs for hepatic metabolism (Binnie et al, 1986b; Peck, 1991c; Eriksson et al, 1996a; Sallustio & Mo disseminated intravascular coagulation, and fatal toxic necrolysis have been reported with this combination ir Page II et al, 1998a). Given the increased risk of rash in pediatric patients, careful monitoring of lamotrigine s younger than 16 years of age, for whom the indication for lamotrigine is restricted to those who have been dia syndrome. The dose of lamotrigine should be reduced when coadministered with valproate (Prod Info Depak 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Dosage reductions of lamotrigine are necessary with concurrent valproic acid thera inducing medications. The manufacturer recommends a lamotrigine dose of 25 mg every other day for the firs next two weeks, advancing to a maintenance dose of 100 mg to 400 mg daily in increments of 25 mg to 50 m only other antiepileptic medication, the usual maintenance dose of lamotrigine is 100 to 200 mg daily. Discon the rash is clearly not drug related (Prod Info lamotrigine oral tablets, 2006).

7) Probable Mechanism: decreased lamotrigine metabolism

8) Literature Reports

a) A 23-year-old woman presented to the emergency room with generalized rash, redness and swelling sore throat 3 weeks after lamotrigine was added to her anti-epilepsy regimen. Her initial regimen consist 500 mg twice daily was added 2 months and lamotrigine 50 mg twice daily was added 3 weeks prior to c erythrocyte sedimentation rate and C-reactive protein. However, serum carbamazepine and valproic acic lamotrigine concentrations were not measured. She was diagnosed with lamotrigine-induced Stevens-Jo Reactions Probability Scale score of 6 (probably drug induced). Lamotrigine was discontinued and treatn

day 18 on oral carbamazepine 400 mg twice daily and oral valproic acid 1500 mg/day. At the one month
oromucosal and skin lesions, with areas of hyperpigmentation. The patient's increased risk of developing
combination of lamotrigine and valproic acid leading to decreased metabolism of lamotrigine, or due to ir
manufacturer's recommended starting dose of 25 mg per day (Kocak et al, 2007).
b) Fever, rash, multiorgan dysfunction, and disseminated intravascular coagulation were reported in two
Both children were receiving valproic acid for treatment of seizures. Lamotrigine was added because of p
starting lamotrigine, but did not abate after lamotrigine was discontinued (Chattergoon et al, 1997).
c) A 54-year-old male presented to the hospital with a five-day history of facial swelling, intermittent feve
extremities, neck, and back. He had been taking allopurinol 100 mg daily and captopril 50 mg daily for fo
multiforme brain tumor, valproic acid and lamotrigine therapy was begun and the doses were titrated to v
50 mg twice daily approximately four weeks prior to his hospital admission. By hospital day 7, the patient
his back, face, and trunk, accounting for more than 60% of his total body surface area. He continued to d
hospital day 12. His death was attributed to toxic epidermal necrolysis probably due to lamotrigine therap
1998).
d) A study including 28 patients with intractable epilepsy was conducted to determine whether the dose
acid were inversely related to lamotrigine clearance. Valproic acid was initiated at 500 mg/day for 3 days
tolerance and response. The valproic acid dose was increased 125 to 250 mg every 3 weeks, until patien
Upon initiation of valproic acid, the dose of lamotrigine was decreased by 50%, so as to maintain lamotri
monotherapy. A 50% reduction in lamotrigine clearance was reported in these patients. The dose of lam
valproic acid therapy to maintain comparable lamotrigine Css. However, additional increases in valproic
lamotrigine to maintain stable lamotrigine Css. Seizure-free periods were significantly longer during treat
lamotrigine monotherapy, an indication that therapeutic synergism exists between lamotrigine and valpro
e) A study involving eight patients with epilepsy found a significant increase in lamotrigine area under th
with concomitant valproic acid administration. Dosages of valproic acid of up to 1,000 mg/day resulted in
fold. Even low doses of valproic acid (200 mg/day) resulted in significant increases in lamotrigine AUC (r
concentrations by inhibiting lamotrigine metabolism and increased half-life has been achieved with the us
al, 2000).
f) Lamotrigine decreased valproic acid steady-state concentrations by 25% in 18 healthy volunteers ove
lamotrigine to the existing therapy did not cause a change in plasma valproate concentrations in adult or
addition of valproate increased lamotrigine steady-state concentrations in normal volunteers by more tha
g) In a black box warning from the manufacturer, the incidence of severe rash may be higher in patients
Info Lamictal(R), 2003d).

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Therapeutic

1) Laboratory Parameters

a) A therapeutic plasma concentration range has not been established for lamotrigine. Dosing of lamotrigine
plasma concentration. Monitoring of plasma levels of lamotrigine and concomitant antiepileptic drugs may be
Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
b) Due to the possibility of increased clearance during pregnancy lamotrigine serum levels should be monito
Battino, 2007; Tran et al, 2002a). Although, therapeutic concentrations have not been established, prepregna
provide a reference concentration for comparison to concentrations during pregnancy, when concentrations d
characteristics of lamotrigine (Tomson & Battino, 2007).

2) Physical Findings

a) Patients receiving lamotrigine for the treatment of epilepsy should be monitored for a therapeutic respons
of seizures(Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2
b) Patients receiving lamotrigine for the treatment of bipolar 1 disorder should be assessed for a therapeutic
episodes (eg, depression, mania, hypomania, mixed episodes) (Prod Info LAMICTAL chewable dispersible o
2009).

B) Toxic

1) Laboratory Parameters

a) Although, lamotrigine has no significant effects on the plasma levels of other antiepileptic drugs, serum lev
especially during dosage adjustments (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, or

2) Physical Findings

a) Observe patient for signs of rash or skin reaction (Prod Info LAMICTAL chewable dispersible oral tablets,

1) Discontinue lamotrigine therapy at the first sign of a rash. If the cause of rash has been clearly identif
to be discontinued (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrat

b) Evaluate patient for signs of hypersensitivity reaction, such as fever and lymphadenopathy. Hypersensitiv
multiorgan failure/dysfunction. Lamotrigine should be discontinued if other causes of the symptoms are not id
tablets, oral tablets, orally disintegrating tablets, 2009).

c) Assess patient for worsening of depressive symptoms and/or development of suicidality at the initiation of
requiring the closest monitoring for suicide risk are those with a history or presence of suicidal behavior or th
chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).

d) Data reviewed by the US Food and Drug Administration suggest an increased risk of suicidal behavior or
antiepileptic drugs (AEDs). The increased risk of suicidality was noted at 1 week after starting an AED and co
epilepsy, psychiatric disorders, or other conditions were all at an increased risk for suicidality compared to pla
emergence or worsening of depression, suicidality, and other unusual changes in behavior, which may includ
and hypomania (US Food and Drug Administration, 2008).

4.2 Patient Instructions

A) Lamotrigine (By mouth)

Lamotrigine

Treats certain types of seizures and mood disorders. Often used along with other medicines.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to lamotrigine.

How to Use This Medicine:
Tablet, Chewable Tablet, Dissolving Tablet, Long Acting Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed
you. Do not use more medicine or use it more often than your doctor tells you to.
You may take this medicine with or without food.
It is best to swallow the regular tablet whole. You may break or crush the tablet if your doctor tells you to, but
The chewable tablet may be swallowed whole, or chewed and taken with a small amount of water or diluted f
a teaspoon of water or fruit juice and swallow the mixture after 1 minute.
If you are using the disintegrating tablet, make sure your hands are dry before you handle the tablet. Do not o
are ready to take it. Remove the tablet from the blister pack by peeling back the foil, then taking the tablet out
in your mouth. It should melt quickly. After the tablet has melted, swallow or take a drink of water.
Swallow the extended-release tablet whole. Do not crush, break, or chew it.
Use only the brand of this medicine that your doctor prescribed. Different brands may not work the same way
This medicine can be used with other seizure medicines. Keep using all of your seizure medicines unless you
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d
pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some forms to
This medicine comes with patient instructions. Read and follow these instructions carefully. Ask your doctor o

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next o
missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after
throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a
Make sure your doctor knows if you are using any other medicine to control seizures (such as carbamazepine
primidone, valproic acid, valproate, Depakene®, Depakote®, Dilantin®, Mysoline®, or Tegretol®). Make sure
(Rimactane®, Rifadin®). Tell your doctor if you are also using birth control pills, or if you are also using hormo
Ask your doctor before you start or stop using any medicines, including birth control pills and hormone replac
Make sure your doctor knows if you are receiving methotrexate (Rheumatrex®, Trexall®) or pemetrexed (Alim

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have kidney problems, liver prob
problems, or depression.
It is important to tell your doctor if you become pregnant while using this medicine. Your doctor may want you

seizure medicine.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your
If you have a skin rash while using this medicine, call your doctor right away. Sometimes a rash is a sign of a
This medicine may cause serious allergic reactions affecting multiple body organs (e.g., liver or kidney). Che
symptoms: fever, dark urine, headache, hives, muscle pain or stiffness, stomach pain, unusual tiredness, or y
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your do
start to feel more depressed and have thoughts about hurting yourselves. Report any unusual thoughts or be
are new or get worse quickly. Make sure the doctor knows if you or your child have trouble sleeping, get upse
reckless. Also tell the doctor if you or your child have sudden or strong feelings, such as feeling nervous, ang
you, your child, or anyone in your family has bipolar disorder (manic-depressive) or has tried to commit suicid
This medicine lowers the number of some types of blood cells in your body. Because of this, you may bleed d
problems, avoid being near people who are sick or have infections. Wash your hands often. Stay away from p
bruised, cut, or injured. Brush and floss your teeth gently. Be careful when using sharp objects, including razo
If your symptoms do not improve or if they get worse, call your doctor.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, d
Blistering, peeling, or red skin rash.
Bloody stools.
Blurred or double vision.
Changes in your menstrual cycle (period).
Chest pain.
Extreme weakness, dizziness, or fainting.
Feeling unusually sleepy, sad, grouchy, moody, or nervous.
Fever, chills, cough, sore throat, and body aches.
Nosebleed.
Pain, soreness, or itching in your vagina.
Painful sores in your mouth or around your eyes.
Painful urination or a change in how much or how often you urinate.
Problems with balance or walking.
Swelling in your face, hands, ankles, or feet.
Swollen, painful, or tender lymph glands in your neck, armpit, or groin.
Thoughts of killing yourself.
Tremors.
Unusual bleeding, bruising, or weakness.
Wheezing or troubled breathing.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Dry mouth.
Eye twitching or eye movements you cannot control.
Headache, neck pain, back pain, or joint pain.
Increased sexual desire.
Loss of appetite, or weight loss.
Mild rash.
Nausea, vomiting, diarrhea, stomach upset or pain, or passing gas.
Runny or stuffy nose, or nose irritation.
Unable to concentrate or remember things.
Unable to sleep, or sleeping too much.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Bipolar I Disorder

1) Lamotrigine is indicated as maintenance treatment of Bipolar I Disorder to delay the time to occurrence of moc
acute mood episodes (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tab

B) Seizure

1) Extended-release lamotrigine is indicated as adjunctive therapy for partial onset seizures with or without secor
(Prod Info LAMICTAL XR oral extended-release tablets, 2009). Chewable dispersible or orally disintegrating lamo
seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary tonic-clonic seizures in adults and p
indicated as monotherapy in the treatment of epilepsy in patients 16 years or older who are being converted from
valproic acid as the single antiepileptic agent (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets,
efficacy in controlling partial and tonic-clonic seizures, primarily generalized seizures (absence and myoclonic), ju
syndrome (Trevathan et al, 2006)

2) Lamotrigine is an anticonvulsant with excellent potential in the management of various types of seizures. Its ar

carbamazepine; however, it is associated with less sedative effects and other neurotoxicity than many existing an
lamotrigine, including its rapid and complete oral absorption, long elimination half-life, relatively low protein bindin
lack of active or toxic metabolites, makes it desirable as an anticonvulsant.
3) The major drawback to the use of lamotrigine is that Stevens-Johnson syndrome occurs in approximately 1/10
4) Initiating lamotrigine at conservative doses and titrating lamotrigine slowly when added to concomitant valproic
(Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) The exact mechanism of action of lamotrigine has not been fully elucidated. It is thought to act by inhibiting rel
inhibition of voltage-sensitive sodium channels (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablet
1987a; Meldrum, 1991; O'Donohoe, 1991; Porter, 1989; Reynolds, 1993; Perucca, 1993). In animals, plasma con
(mcg/mL) are of similar protective efficacy as therapeutic concentrations of phenytoin and carbamazepine in the m
tests. It also reduces or abolishes the afterdischarge induced by focal stimulation of the cortex or hippocampus in
not block or reduce the rate of development of kindling, it does decrease the number of kindled responses and the
Lamotrigine is not effective in threshold tests (Jawad et al, 1989c; Leach et al, 1991; Peck, 1991e).
2) Further evidence that lamotrigine inhibits glutamate release is exhibited in the rat model, in which kainic acid n
inhibited, whereas quinolinic acid and ibotenic acid neurotoxicity, mediated by N-methyl-D-aspartate (NMDA) rece
3) The pharmacological profile of lamotrigine is similar to that of phenytoin. In vitro animal studies have shown it t
release in brain tissue, with no effect on potassium-induced amino acid release. This suggests that the drug acts a
neuronal membranes and inhibit neurotransmitter release, namely glutamate (Leach et al, 1986).
4) Single doses of lamotrigine cause an acute reduction in or abolition of photosensitivity in patients with epilepsy
hallmarks of epileptic activity (Binnie et al, 1986d; Jawad et al, 1986).

4.5 Therapeutic Uses

Absence seizure; Adjunct

Bipolar disorder, depressed phase

Bipolar I disorder

Brain injury

Cancer pain

Convulsions in the newborn, Intractable

Dementia of frontal lobe type

Depersonalization disorder

Depression, Treatment-resistant; Adjunct

Epilepsy, Refractory

Epileptic psychosis

Infantile neuronal ceroid lipofuscinosis

Juvenile myoclonic epilepsy

Lennox-Gastaut syndrome; Adjunct

Migraine

Mood swings

Neuropathic pain

Obesity

Pain

Palatal myoclonus

Parkinson's disease, Idiopathic

Paroxysmal choreoathetosis, Paroxysmal

Partial seizure, Adjunct or monotherapy

Reflex epilepsy

Rett's disorder

Schizophrenia, Refractory

Sexual dysfunction

Shortlasting, unilateral, neuralgiform pain with conjunctival injection and tearing syndrome

Status epilepticus

Tinnitus

Tonic-clonic seizure, Primary generalized; Adjunct

Trigeminal neuralgia

West syndrome

4.5.A Absence seizure; Adjunct

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Preliminary results for add-on therapy in resistant cases and for initial monotherapy are encouraging (Bu

3) Pediatric:

a) In a pediatric case series, patients meeting strict diagnostic criteria for isolated typical absence epilepsy in age: 7 years) whose absence seizures were refractory to standard therapy received add-on lamotrigine and e dosage of 2.9 milligrams/kilogram/day (mg/kg/day) for a median follow-up of 3.1 years. Five of eight children months (median) and remain seizure-free on lamotrigine alone, with only one relapse necessitating resumptic treated with lamotrigine monotherapy after initial diagnosis also attained complete seizure control at a mediar years. One child had to discontinue lamotrigine due to rash. Electroencephalographic abnormalities resolved

4.5.B Bipolar disorder, depressed phase

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

In an 8-week open-label study (n=20) of lamotrigine in adolescents ages 12 to 17 years (mean age 15.8; depressive episode, lamotrigine was effective, whether as adjunctive or monotherapy, in decreasing dep

3) Pediatric:

a) In an 8-week open-label study (n=20) of lamotrigine in adolescents ages 12 to 17 years (mean age 15.8; 7 depressive episode, lamotrigine was effective, whether as adjunctive or monotherapy, in decreasing depress lamotrigine with a mean final dose of 132 +/- 31 milligrams (mg)/day. Seven patients had the diagnosis of bip patients had bipolar disorder not otherwise specified. The primary measure for response was a "1" or "2" on t secondary measure for response was at least a 50% decrease in the Children's Depression Rating Scale-Re were 19 evaluable patients with 16 (84%) considered responders by primary criteria and 12 (63%) considered of 28 or less on the CDRS-R and a CGI Severity scale (CGI-S) score of 1 or 2) was attained by 11 of 19 (58% R scores from baseline to study end (mean change -30.1 +/- 11.9; p less than 0.001). Patients with a baseline than 20 were less likely to be responders by secondary criteria (p=0.04), but YMRS scores did decrease sign on adjunctive medication (n=7) showed no significant differences in CADRES scores compared with those or week 8 (p=0.35). Patients on adjunctive medication did not have a better response than those on monotherap Modified also improved from baseline to week 8 with decreases in total aggression (48.9 +/- 50.2 to 16.7 +/- 2 +/- 2.5; p less than 0.001), and suicide (1.56 +/- 2.1 to 0.26 +/- 0.65; p=0.02). There was no significant weight (kg); p=0.34). Adverse events reported were headache (84%), fatigue (58%), nausea (53%), sweating (47%) reported rash, but on further investigation, it was concluded that they experienced skin irritations, not true ras events, and no patients had any significant laboratory abnormalities during the study (Chang et al, 2006).

4.5.C Bipolar I disorder

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated for the maintenance therapy of bipolar 1 disorder to delay the time to occurrence of mood episo standard therapy (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegratin Effective in refractory bipolar disorder in case reports and open studies (Robillard & Conn, 2002; Calabre Some patients with rapid-cycling bipolar disorder succeeded on lamotrigine maintenance monotherapy (

3) Adult:

a) The results of a small, open label study indicate that adjunctive lamotrigine therapy may be effective in the this uncontrolled study, five hospitalized, geriatric patients (ages 65 to 85 years) with bipolar disorder in the d milligrams (mg) at bedtime, titrated weekly in 12.5 mg/day increments to a total dose of 75 or 100 mg) in addi receiving both lithium and valproate therapy for at least 4 months prior to beginning the study and were nonre selective serotonin reuptake inhibitor or a tricyclic antidepressant. Following six weeks of treatment, at least a Rating Scale scores of 3 patients. All three patients had rapid- cycling bipolar disorder. Nonresponsive patien bipolar disorder. Lamotrigine was well tolerated, however one patient developed coarse hand tremor that imp randomized studies are needed to confirm these findings (Robillard & Conn, 2002).

b) Oral lamotrigine as maintenance monotherapy was effective prophylactic treatment for some patients with placebo-controlled trial (n=180). Prior to the double-blind phase of the study, patients entered an open-label p 8 weeks to a target of 200 milligrams (mg)/day (weeks 1 and 2: 25 mg/day; weeks 3 and 4: 50 mg/day; week up to 300 mg/day); after 4 to 8 weeks of lamotrigine, all other psychotropic medications were tapered off. The to vary; after the preliminary phase, mean daily dose was 287.9 mg/day. Randomization placed patients on p proportion of patients who were able to maintain on placebo or lamotrigine without requiring added pharmacc the difference was not significant (p=0.177). Median survival time without added treatment was 18 weeks and patients, respectively. The percentage of patients able to complete 6 months of the randomized phase withou group (41% versus 26%, p=0.03), and especially among those with bipolar II subtype. Most adverse events w most common side effects (Calabrese et al, 2000).

c) Data from a 48-week open-label trial lend support to lamotrigine's effectiveness as add-on (n=60) or monc other therapies for bipolar I or II disorder. Of 40 evaluable subjects with depressive symptoms, 48% and 20% respectively, with a mean 42% decrease in Hamilton Depression Scale scores. Of 31 evaluable subjects with marked and moderate improvement, respectively, with a mean 74% decrease in Mania Rating Scale scores. Adverse effects included dizziness (29%), tremor (23%), somnolence (21%), headache (19%), nausea (15%) rate was 51%. Controlled trials are in progress (Calabrese et al, 1999).

d) Lamotrigine appeared to have some mood-stabilizing and antidepressant effects in 5 rapid-cycling bipolar lamotrigine at an average dose of 185 milligrams/day. Three scales were used to measure improvement with improvement after therapy as compared to before therapy (p less than 0.006). The other scales did not show less than 0.289) and Young Mania Rating Scale (p less than 0.552). Further randomized studies are needed

e) In an open trial of lamotrigine therapy in 7 patients with treatment-refractory mood disorder, mixed results used with 2 patients showing marked improvement, 2 had a moderate response, 2 had no response and 1 dis Sternbach, 1997).

f) In a 41-year-old female with longstanding bipolar disorder, add-on lamotrigine effectively substituted for lit high-dose steroid therapy. Prednisone was necessary to treat lithium-induced interstitial nephritis. Lamotrigin increased to 200 mg every 12 hours within 9 days. Despite escalating prednisone doses to 120 mg/day, her r concurrent medications included perphenazine, temazepam, clonazepam, and nifedipine (Preda et al, 1999).

g) A 48-year-old man with treatment-refractory bipolar disorder had a good response to lamotrigine titrated t psychotic mania and depression and responded to a combination of lamotrigine, paroxetine and levothyroxin

4.5.D Brain injury

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Provided improvement in a series of patients with severe brain injury (Chatham Showalter & Kimmel, 20

3) Adult:

a) Lamotrigine therapy in a case series of 13 patients with severe brain injury brought better than expected s retrospective chart review . Use of lamotrigine was triggered by significant unexpected improvement in 1 case and an allergic reaction to phenytoin. The patient was on day 268 after a subarachnoid hemorrhage (SAH); s oriented and animated, his short-term memory improved, his conversation became coherent, and his ability t discharged to his home. On the Rancho Los Amigos Cognitive Scale, he improved from level III to level VIII. the cohort of 13 patients, all were severely impaired (due to SAH (5), motor vehicle accidents (4), falls from 1 resection (1)); the Rancho level was II to III for all; 3 had a Glasgow Coma Scale score of 3. Mean starting da been on an anticonvulsant prior to lamotrigine. Mean lamotrigine final daily dose was 250 milligrams (range 1 showed more cognitive improvement than expected; 4 improved at an expected modest rate. After mean 72 1 to a son's home, and 1 to a community residential program; after rehabilitation of mean 117 days, 3 were di Kimmel, 2000).

4.5.E Cancer pain

See Drug Consult reference: MANAGEMENT OF CANCER-RELATED PAIN IN ADULT PATIENTS

4.5.F Convulsions in the newborn, Intractable

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIa
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

May be effective as adjunct therapy in decreasing the number of infantile spasms (Mikati et al, 2002)

3) Pediatric:

a) In part of an open-label, prospective study, adjunctive lamotrigine therapy decreased the daily number of seizures per day (p=0.028) in patients diagnosed with intractable seizures. Enrolled infants had to have been the 13 patients were diagnosed with infantile spasms, 1 was diagnosed with both infantile spasms and partial partial seizures. In this study, one infant had no response and no infants became seizure free. Doses were ba neonates who were taking enzyme-inducing agents, doses up to 10 milligrams per kilogram per day (mg/kg/d months of age, who were taking enzyme- inducing agents, final doses ranged between 10 to 20 mg/kg/day. I valproate and enzyme inducers, were dosed between 5 to 10 mg/kg/day. In infants between 1 and 12 months final dose. One case of skin rash, which subsided after a day, and one case of elevated liver enzymes, which reported. Eleven of the 13 infants had no observed adverse effects (Mikati et al, 2002).

4.5.G Dementia of frontal lobe type

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Lamotrigine successfully treated severely aggressive behavior resulting from frontal lobe dementia in a s

3) Adult:

a) A 65-year-old female psychiatric inpatient with frontal lobe dementia (presenile condition) and resultant ag psychotropic medications greatly benefited from add-on lamotrigine. With dosing of 12.5 milligrams/day (mg/d showed "dramatic" improvement in all symptoms, with no further aggressive episodes through 6 months of fo

4.5.H Depersonalization disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Lamotrigine did not show any benefit in the treatment of depersonalization disorder (Sierra et al, 2003)

3) Adult:

a) In a pilot, double-blinded, randomized, placebo- controlled, crossover study, lamotrigine did not show any
Fourteen men and women were randomized to one arm of lamotrigine then placebo or another arm of placeb
two-week wash out period before crossing over to the other arm. Lamotrigine was dose escalated over sever
Each month patients were assessed using the Present State Examination and the Cambridge Depersonaliza
study due to nonadherence to the study protocol. One other patient dropped out due to developing neutroper
These individuals were not included in the statistical analyses. Analysis of the administered scale scores reve
endpoint scores in both arms. Mild nausea, dizziness, and muscle aches were reported with lamotrigine use

4.5.I Depression, Treatment-resistant; Adjunct

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Treatment with add-on oral lamotrigine led to similar efficacy results as lithium augmentation in patients v
label, randomized, prospective study (n=34) (Schindler & Anghelescu, 2007)
Results of a retrospective chart review (n=37) showed that adjunctive lamotrigine was efficacious and we
refractory, unipolar depression in adults (Barbee & Jamhour, 2002)

3) Adult:

a) General Information

1) Treatment with oral lamotrigine used as an add-on to antidepressant therapy was safe and demonstra
treatment-refractory, unipolar depression (Schindler & Anghelescu, 2007; Barbee & Jamhour, 2002; Roc
prospective study (n=34), lamotrigine, initiated at 25 milligrams (mg) per day and titrated up to 250 mg/da
augmentation (Schindler & Anghelescu, 2007). Two other retrospective chart reviews found similar impro
mg/day (Barbee & Jamhour, 2002; Rocha & Hara, 2003). Notably, responses in both reviews were base
scores, which were culled retrospectively from chart notes. Patients included in the open-label study as v
anxiety comorbidity and had received a variety of prior antidepressant and/or combination augmentation
studies and there were no instances of skin rash or other dermatological toxicity.

b) Clinical Trials

1) In an open-label, randomized, prospective study (n=34), treatment with add-on oral lamotrigine was v
augmentation in patients with treatment-resistant, unipolar depression. Patients who had experienced a
according to the DSM-IV (Text Revised), with a minimum score of 17 points on the Hamilton Rating Scal
study purposes, treatment-resistant depression was defined as non-response (less than 50% reduction o
classes of antidepressants for at least 6 weeks. Patients were randomized to receive augmentation with
lithium (n=17; mean age, 50.3 years) orally for 8 weeks. Lamotrigine was initiated at 25 milligrams (mg) o
week 3) and 50 mg (at weeks 5 and 6) to a target daily dosage of 150 mg. In cases of non-response or p
Lithium was titrated over several days to a blood level of 0.6 to 0.8 millimoles/liter. Prior antidepressant t
augmentation strategies were discontinued. Based on clinical need, concomitant use of benzodiazepines
(n=27) were treated as inpatients during this study. Weekly assessments were conducted using the HRS
Prior to study initiation, most patients had received treatment with a variety of augmentation or combinati
therapy (n=20), atypical antipsychotics (n=27), and right unilateral electroconvulsive therapy (n=5), and 4
axis I or II disorder. At baseline, the mean duration of current depressive episode (lamotrigine, 6.9 month
prior episodes (lamotrigine, 2.94; lithium, 2.76; p=0.84) was similar between the groups. An intention-to-t
in HRSD scores in both groups. The mean +/- standard deviation (SD) HRSD score decreased from 22.7
group and from 21.5 +/- 3.8 at baseline to 13.3 +/- 5.7 in the lithium group (p=0.11 between groups at we
regards to the time point of onset of symptom resolution. The mean +/- SD CGI scores decreased from 6
(mildly ill) in the lamotrigine group and from 6.24 +/- 0.66 (severely ill) at baseline to 4.12 +/- 1.22 (moder
score of 7 points or less) occurred in 23% (n=4) and 18% (n=3) of lamotrigine- and lithium-treated patien
treated patients versus 41% (n=7) of lithium-treated patients responded (ie, 50% or greater reduction in i
(ie, 25%-49% reduction in HRSD score) occurred in 47% (n=8) and 35% (n=6) of lamotrigine- and lithium
side effects were dry mouth, blurred vision, headache, tremor, weight gain, vertigo, constipation, and dia
tremor (lamotrigine, n=2; lithium, n=5), frequencies for all effects were similar in both groups. Dermatolog
study (Schindler & Anghelescu, 2007).

2) A retrospective chart review (n=37) revealed that add-on treatment with lamotrigine was efficacious a
depression. Charts of patients (mean age 50.22 years; range, 18-75 years) with a diagnosis of major dep
who had received lamotrigine augmentation following failure of at least two adequate trials (minimum of
antidepressants were reviewed. Patients with current psychotic symptoms, or hypomania/mania were ex
at bedtime for 2 weeks and then increased to 50 mg/day for 2 weeks; further dosage increases were ma
improved or the patient was no longer able to tolerate further dosage increases. Patients included in the
continued on treatment with their primary antidepressant or concomitant augmentation medications with
those agents; one patient discontinued all antidepressant therapy prior to initiation of lamotrigine treatme
generalized anxiety disorder (n=16), panic disorder (n=5), social or specific phobia (n=5, n=2), posttraum
disorder (n=3), and anxiety not otherwise specified (n=1). With the exception of two patients, none of the
initiation of lamotrigine, study patients had received a mean of 13.27 (range, 2-29) antidepressant trials a

medications during lamotrigine therapy. The mean duration of lamotrigine treatment was 35.41 weeks (ra
Functioning (GAF) scores were recorded at the time of each visit. Prior to initiation of lamotrigine, the me
+/- 8.27. There was a statistically significant improvement in GAF scores following lamotrigine therapy (d
Rating Scale (CGI) scores were evaluated retrospectively based on extensive, detailed progress notes re
augmentation, intent-to-treat analysis found that 15 (40.5%) patients were rated as much or very much ir
as unchanged. The mean +/- SD lamotrigine dose among responders was 113.33 +/- 93.48 mg, which d
of current depressive episode, number of prior antidepressant trials, stage of treatment resistance, and C
CGI rating scores in the intent-to-treat analysis. The most commonly reported treatment-emergent side e
nausea (n=5), and tremor (n=4). There were no instances of skin rash during this study (Barbee & Jamh

4.5.J Epilepsy, Refractory

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective as add-on therapy in treatment-resistant focal and generalized epilepsy (Huber et al, 1998)
May be useful in the treatment of intractable childhood epilepsy (Lerman-Sagie & Lerman, 1998)

3) Adult:

a) In an observational study, lamotrigine was useful as add-on therapy in a group of 125 multi-handicapped, epilepsy . Although most effects were only partial, 28.8% of patients had a reduction of 50% or more in seizu epilepsies, 26.7% with generalized epilepsies, and 22.4% with both. A mean lamotrigine dose of 391 milligra combination of valproic acid and lamotrigine was particularly effective(Huber et al, 1998).

b) Lamotrigine was reported to be useful in treating 10 adult patients (23 to 44 years old) with intractable abs started in childhood and persisted into adulthood . Lamotrigine was initially started at 0.2 milligrams/kilogram maximum of 5 mg/kg. All patients were receiving valproic acid. Except for valproic acid, all other antiepileptic optimal lamotrigine dose. Valproic acid doses ranged from 600 to 2000 mg/day and lamotrigine doses were 1 tonic-clonic seizures was achieved in all patients; 7 patients achieved cessation of absence seizures with 3 p Sagie & Lerman, 1998).

4) Pediatric:

a) In an open-label, long-term study (n=41), add-on lamotrigine therapy proved successful in 44% of study su years of age; mean 12 years) with refractory severe partial epilepsy (mean seizure frequency 3.6/day). All en major antiepileptic drugs. Eighteen patients (44%) remained on lamotrigine after 12 to 48 months of follow-up occurred in 15 patients (34%) (p less than 0.00006), with 6 of these subjects remaining seizure-free. Three of marked improvement in behavior, although seizure frequency was unchanged. Higher response rates were o symptomatic of cerebral malformation. Seizure worsening occurred in 9 patients; transient rash developed in starting daily dose was 0.2 to 2.5 milligrams/kilogram (mg/kg) titrated over 2 to 4 weeks to an initial maintena subsequently adjusted based on clinical response up to a maximum of 1.8 to 15 mg/kg/day; mean dose was valproate, median dose was 4.8 mg/kg/day; for those on enzyme-inducing drugs except valproate, median do

b) In an open trial, 16 out of 63 children had a complete response to lamotrigine add-on treatment for their re types with a mean of 1.72 seizure types per child. Seizure types included infantile spasms, simple partial seiz seizures, myoclonic seizures, typical absence seizures, and atypical absence seizures. A complete response achieved a 50% to 90% decrease in seizures (Buoni et al, 1998).

c) In an open, prospective trial, 30 of 56 children with generalized epilepsies were improved with lamotrigine than 18 years old and suffered from Lennox-Gastaut syndrome (15), childhood absence (4), severe myocloni symptomatic generalized (24) and other epilepsies (5). An improvement of greater than 50% was observed ir in 11 of 24 children with other symptomatic generalized epilepsy (p less than 0.09). Rash occurred in 4 patier was discontinued and lamotrigine was restarted without recurrence of rash (Farrell et al, 1997).

d) In an open trial, lamotrigine was useful as add-on therapy in about one-third of patients (2 to 22 years old) lamotrigine 5 to 15 milligrams/kilogram/day (lower doses for patients receiving concomitant valproic acid). Aft seizure frequency of more than 50% and 8 of these patients became seizure-free. Lamotrigine was most effe absences, and atonic seizures (Coppola & Pascotto, 1997).

e) Fourteen children suffering from refractory epilepsy received lamotrigine as add-on therapy. A decrease ir lamotrigine was observed in 6 of the 7 patients who completed the study. The median total seizure frequency study, seizure frequency had decreased by more than 50% in 2 patients, by more than 75% in 2 patients, and seizure frequency was unchanged (Battino et al, 1996)(Battino et al, 1995b).

f) In one series, 8 of 10 children with various seizure disorders had decreased total seizure count when lamo used in increasing doses up to 2 milligrams/kilogram/day (mg/kg/day) in patients taking valproic acid, and in c phenytoin, phenobarbital, or carbamazepine. After 3 months, the dose was increased by 50%. The median to 21 to 916) to 46/month (range 6 to 644) after 6 months. Patients with atypical absence and complex partial se patients, respectively, experiencing greater than 50% reduction in seizure frequency. Myoclonic seizures dec remission; however, 4 patients had an increased frequency of myoclonic seizures. Tonic-clonic seizures decr significant adverse effect noted was drowsiness in 3 patients; however, this did not require dosage reduction

g) In 161 patients remaining on lamotrigine during a 2-year follow-up, 21 of the first 55 patients evaluated ha free. Best response was in generalized epilepsy, particularly absence seizures. Rash was the most commonl valproate (Yuen, 1992).

h) Twelve children with severe or life-threatening epilepsy received lamotrigine (250 to 900 milligrams/day). S
for 12 to 61 months with 4 on monotherapy. No patient was hospitalized for status epilepticus. No adverse ef

4.5.K Epileptic psychosis

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in 2 case reports (DeLeon & Furmaga, 1999)

3) Adult:

a) Two cases were presented describing patients with epilepsy-related psychosis that was resistant to antips
lamotrigine. The first was a 39-year-old woman with seizures and psychosis that included thought broadcasti
clonazepam, phenytoin and gabapentin without improvement in seizure control or decrease in psychotic sym
closed head injury, seizures, delusions of persecution, and aggressive behavior. His treatment consisted of c
improvement in seizure control and relief from psychotic symptoms occurred with the addition of lamotrigine t
twice daily and the man was titrated to 450 mg daily. Also in both cases risperidone was tapered and disconti
the need for antipsychotic therapy (DeLeon & Furmaga, 1999).

4.5.L Infantile neuronal ceroid lipofuscinosis

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

In 1 study, lamotrigine was useful as adjunctive therapy for seizures associated with infantile neuronal ce

3) Pediatric:

a) Lamotrigine was useful in treating seizures associated with infantile neuronal ceroid lipofuscinosis . Lamot
16 children (2.5 to 12 years old) at a dose of 0.5 milligrams/kilogram and increased every 2 weeks as needed
10 patients seizure frequency decreased by more than 50%. In 4 children seizures decreased by 100%. Mon
successful (Aberg et al, 1997).

4.5.M Juvenile myoclonic epilepsy

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective; Pediatric, Ineffective
Recommendation: Adult, Class III; Pediatric, Class III
Strength of Evidence: Adult, Category C; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Exacerbation of myoclonus reported in juvenile myoclonic epileptic patients treated with lamotrigine (Bira

3) Adult:

a) A group of 7 patients 16 to 32 years of age with juvenile myoclonic epilepsy (JME) experienced immediate
of the cohort had previously used valproic acid. Three patients began lamotrigine as add-on therapy to valpro
therapy. In either instance, JME deteriorated, with worsening of myoclonus in all 7 patients and appearance o
the patients were switched back to valproic acid or to topiramate without further adverse sequelae. Dosing of
given as monotherapy and 150 to 200 mg/day when combined with valproate (Biraben et al, 2000).

4) Pediatric:

a) A group of 7 patients 16 to 32 years of age with juvenile myoclonic epilepsy (JME) experienced immediate
of the cohort had previously used valproic acid. Three patients began lamotrigine as add-on therapy to valpro
therapy. In either instance, JME deteriorated, with worsening of myoclonus in all 7 patients and appearance o
the patients were switched back to valproic acid or to topiramate without further adverse sequelae. Dosing of
given as monotherapy and 150 to 200 mg/day when combined with valproate (Biraben et al, 2000).

4.5.N Lennox-Gastaut syndrome; Adjunct

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (2 years and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated as adjunctive therapy for the generalized seizures of Lennox-Gastaut syndrome (Prod Info LAM

orally disintegrating tablets, 2009)

3) Adult:

a) In a double-blind, placebo-controlled study, lamotrigine as add-on therapy was effective for seizures asso
years old) received placebo (n=90) or lamotrigine (n=79) with a maximum dose of 100 to 200 milligrams for p
milligrams for other patients. For all seizure types, the median frequency changed from 16.4 and 13.5 per we
to 9.9 and 14.2 per week after 16 weeks of treatment, respectively (p less than 0.002). Reduction of seizure f
lamotrigine group and in 16% of the placebo group (p less than 0.01). The results were similar for drop attack
absence seizures did not significantly change. Two patients on lamotrigine and valproic acid developed rash

b) Thirteen patients with Lennox-Gastaut syndrome (age 5.5 to 27 years) received lamotrigine 100 to 400 mi
seizure-free after 2 months to 2 years of treatment. Eight of 13 achieved control of at least 1 seizure type. Six
1991).

4) Pediatric:

a) In a double-blind, placebo-controlled study, lamotrigine as add-on therapy was effective for seizures asso
years old) received placebo (n=90) or lamotrigine (n=79) with a maximum dose of 100 to 200 milligrams for p
milligrams for other patients. For all seizure types, the median frequency changed from 16.4 and 13.5 per we
to 9.9 and 14.2 per week after 16 weeks of treatment, respectively (p less than 0.002). Reduction of seizure f
lamotrigine group and in 16% of the placebo group (p less than 0.01). The results were similar for drop attack
absence seizures did not significantly change. Two patients on lamotrigine and valproic acid developed rash

b) As part of a larger open, prospective trial, 11 of 15 children with Lennox-Gastaut syndrome were improved
milligrams/kilogram/day (Farrell et al, 1997).

c) Thirteen patients with Lennox-Gastaut syndrome (age 5.5 to 27 years) received lamotrigine 100 to 400 mi
seizure-free after 2 months to 2 years of treatment. Eight of 13 achieved control of at least 1 seizure type. Six
1991).

4.5.O Migraine

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Appears to be effective only in patients with an aura before their migraine (Lampl et al, 1999)

3) Adult:

a) Lamotrigine appears to act specifically on the aura mechanism in relieving migraine headaches and appe
headache (D'Andrea et al, 1999)(Lampl et al, 1999). In one study, 21 patients receiving lamotrigine 100 millig
their attacks from 6.1/month at baseline to 0.7/month after 3 months (p less than 0.0001). In 13 patients the a
reduced. In 5 patients with migraine without aura, there was no change (D'Andrea et al, 1999). Similarly, in 1
migraine, lamotrigine 25 to 100 mg daily produced a significant decrease in aura episodes after 4 months (p l
months from 23 minutes at baseline to 3 minutes (p less than 0.001) (Lampl et al, 1999). In the treatment of g
than placebo in 77 patients (Steiner et al, 1997).

4.5.P Mood swings

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Lamotrigine was beneficial in post-stroke pathological laughing and crying in 1 case study (Ramasubbu,

3) Adult:

a) In a single case report, lamotrigine improved symptoms of pathological laughing and crying in a 60-year-o
affecting the left frontal and temporal lobes. The patient had developed symptoms 3 to 4 weeks after the strol
and inappropriate to the stimuli or felt emotion. Twelve months after the onset of symptoms, lamotrigine was
increased to 75 mg during weeks 3 and 4, and to 100 mg during weeks 5 and 6. Laughing spells gradually de
no spells after week 4 of therapy. Crying spells gradually decreased from 7 to 8 spells per day, lasting for 3 to
therapy. After 8 weeks of follow-up, clinical improvements were still maintained. The patient did not report any
(Ramasubbu, 2003).

4.5.Q Neuropathic pain

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Ineffective for the treatment of chemotherapy-induced peripheral neuropathy in a randomized, placebo-c
Mixed results observed in neuropathic pain due to diabetes (Eisenberg et al, 2001) and HIV (Simpson et
controlled trials
No appreciable effect seen with lamotrigine for intractable neuropathic pain (McCleane, 1999) or neurop
2002) in randomized, double-blind, placebo-controlled trials, although lamotrigine was promising for a sm
(Finnerup et al, 2002)

3) Adult:

a) Lamotrigine was not effective for relieving neuropathic pain symptoms in 125 patients with chemotherapy-
phase 3 randomized, placebo-controlled study. Patients with symptomatic CIPN with pain scores of either gre
Group (ECOG) neuropathy scale (ENS), or greater than 3 on a 0 to 10 Numerical Rating Scale (NRS) were e
numbers correspond to greater severity of symptoms. Participants were randomized to treatment with lamotri
mg/day over 10 weeks; n=63) or placebo (n=62). The primary efficacy measure, patient-reported "average" d
ENS, was assessed weekly. Secondary efficacy measures, such as the World Health Organization (WHO) cl
decreased tendon reflexes, 2 = severe paresthesias and/or mild weakness, 3 = intolerable paresthesias and/
evaluate changes in CIPN symptoms related to, but distinct from, pain. At the time of enrollment, the proporti
chemotherapy was 38% and 45% (p=0.47) for the lamotrigine and placebo arms, respectively, with the remai
arm was similar with regard to demographic factors and chemotherapy drugs responsible for CIPN at baselin
and 3.6 (p=0.22), and symptoms using ENS were 2 and 1.9 (p=0.31) for lamotrigine and placebo, respectivel
severity decreased in both groups without significant differences between them. According to the NRS, the m
units (p=0.56) and symptom severity (by ENS) decreased by 0.4 and 0.3 units (p=0.36) in treatment and plac
least pain scores by NRS (-0.2 and 0.1), and by WHO pain scales (-0.2 and -0.1) were similar between treatm
differences were noted between the 2 groups with regard to some of the secondary endpoints, these were nc
according to those patients still receiving chemotherapy and those who had completed chemotherapy, neithe
compared with placebo. Adverse events were similar for both groups, although patients receiving lamotrigine
adverse events compared to placebo (33% vs 18% respectively, p=0.06). The most common toxicities (grade
placebo groups, respectively, included ataxia (24% vs 16%), rash (6% vs 5%), constipation (0% vs 2%), arthr
vomiting (0% vs 2%), pruritis (2% vs 0%), fatigue (2% each), and headache (0% vs 4%) (Rao et al, 2008).

b) Lamotrigine effectively improved numerical pain scores in patients with diabetic neuropathy but failed to p
indices in a randomized, double-blind, placebo-controlled clinical trial conducted in Israel. Patients (n=53) wit
neuropathy of at least 6 months duration, and pain scores of at least 4 on a scale of 0 (no pain) to 10 (worst i
analgesics for 3 days prior to starting a diary during the baseline period. Patients were randomized to an 8-w
daily for 2 weeks, then 50 mg daily for 2 weeks, and then 100 mg, 200 mg, 300 mg, and 400 mg daily for one
placebo (n=26; mean age, 57.8 +/- 1.7 years). Doses were administered as once daily for the first 2 weeks ar
primary endpoint was a patient-recorded pain intensity score, using the same 0 to 10 numerical pain scale ac
the morning and evening, and patients were instructed not to take any rescue medication for at least 2 hours
characteristics were similar between groups except patients in the lamotrigine group had a significantly longe
patients in the placebo group (9.6 +/- 1.1 years; p=0.04). Distal symmetric pain in the legs (stocking-like distri
abnormal neurologic examinations that indicated peripheral neuropathy. Patients in the lamotrigine group exp
6.4 +/- 0.1 to 4.2 +/- 0.1, while patients in the placebo group had an overall decline of 6.5 +/- 0.1 to 5.3 +/- 0.1
pain intensity scores were observed at lamotrigine doses of 200, 300, and 400 mg compared to placebo. Dur
pain was seen in 12 patients receiving lamotrigine and 5 patients receiving placebo (p=0.05), while the overa
arm compared to 20% in the placebo arm. Of 7 patients in the lamotrigine group who required rescue analge
their use during the last 4 weeks of treatment compared to no changes in analgesic requirements in the 3 pat
No significant differences were found between groups in the McGill Pain Questionnaire, the Beck Depression
assessment of efficacy and tolerability, which were completed at baseline and at week 8. Rash occurred in 2
7th weeks of treatment, although both cases resolved upon discontinuation of lamotrigine (Eisenberg et al, 20

c) Results from a randomized, double-blind, placebo-controlled study demonstrated lamotrigine was well-tole
in patients receiving neurotoxic antiretroviral therapy (ART). Two groups of patients were randomized to plac
those not receiving ART (n=135). The study included a 7-week dose escalation phase followed by a 4-week m
to induce the metabolism of lamotrigine started the dose escalation phase at 25 milligrams (mg) every other d
known to induce metabolism of lamotrigine started at a dose of 25 mg daily. During the 4-week maintenance
for patients not receiving enzyme-inducing drugs and 600 mg/day for patients receiving enzyme-inducing dru
Scale did not differ between lamotrigine and placebo for either group at the end of the maintenance phase. H
Scale reflected greater improvement with lamotrigine than with placebo in the group receiving ART (p=0.004)
also showed greater improvement on the Visual Analogue Scale for Pain Intensity and the McGill Pain Asses
of global impression of change in pain (p less than or equal to 0.02). The incidence of adverse events was sir
2003).

d) In a randomized, double-blind, placebo-controlled crossover trial, lamotrigine treatment had no effect on th
(n=22) of patients with spinal cord injury (SCI) but did reduce pain in a subset of the sample, which was chara
with or without motor function, preserved below the lesion level and including sacral segments S4-S5). Patien
were given lamotrigine, beginning with 25 milligrams (mg) and increasing to a target dose of 400 mg/day, or p
period, crossed over to the other treatment for 9 weeks. The dose of lamotrigine was limited by individual tole
dose of 300 mg/day, and 5 had a final dose of 200 mg/day. Among the 12 patients with incomplete SCI lesion
an 11-point pain scale) to lamotrigine. Three patients also responded to placebo. The median difference in pa
in the group with incomplete lesions. All patients who had evoked pain (brush allodynia or wind-up-like pain) v
evoked pain was a responder (p less than 0.001), suggesting that the presence of evoked pain may be a pre
et al, 2002).

e) In a randomized, placebo-controlled, double-blind trial of 100 adults with intractable neuropathic pain, lam

mg/day exhibited no appreciable analgesic efficacy. Subjects completed daily diaries with visual analog score into weekly scores. With mean scores from week 8 compared to week 1, there were no statistically significant analgesic consumption, overall pain, burning pain, numbness, "pins and needles," shooting pain, skin sensitivity points out that this study does not rule out lamotrigine's efficacy using a different dosing scheme or in other n

4.5.R Obesity

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

In a single center, double-blind, placebo-controlled, randomized study (n=40) of healthy adult volunteers greater or equal to 30 but less than 40), while there was no statistically significant mean change in body subjects who took placebo, lamotrigine showed a statistically significant difference in mean change in BM (Merideth, 2006).

3) Adult:

a) In a single center, double-blind, placebo-controlled, randomized study (n=40) of healthy adult volunteers v greater or equal to 30 but less than 40), while there was no statistically significant mean change in body weig subjects who took placebo, lamotrigine showed a statistically significant difference in mean change in BMI an were randomized to receive lamotrigine 200 milligrams (mg)/day (n=20) or placebo (n=20) for 26 weeks. Initia weeks until the maintenance dose of 150 to 200 mg/day was reached. All patients were titrated to lamotrigine mg/day and was discontinued early from the study. Of those subjects randomly assigned, 28 completed the 2 placebo). Subjects completed the Impact of Weight on Quality of Life (IWQOL) scale at baseline and endpoin difference in baseline body weight between the 2 groups (lamotrigine mean +/- standard deviation (SD) equa equal 225 +/- 32.7 lb; p=0.0588). The primary study outcome of change in body weight from baseline to endp lamotrigine and placebo, respectively (p=0.0623). There was a statistically significant difference in mean cha and -0.1 +/- 1.05 for lamotrigine and placebo, respectively (p=0.0421). A greater change in quality of life satis lamotrigine group (p=0.0065). Other secondary outcomes showed no significant differences. No serious adve in the placebo group discontinued treatment due to edema. No lamotrigine subjects discontinued treatment d the most frequently reported adverse event with a 15% incidence across the study group (Merideth, 2006).

4.5.S Pain

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Possibly effective for different pain syndromes (Eisenberg et al, 2003; Vestergaard et al, 2001; Cianchett
Lamotrigine provided moderate analgesia for central post-stroke pain (Vestergaard et al, 2001)
Open-label data suggest possible benefit in treating resistant paroxysmal limb pain and painful tonic spa 1999)
Possibly effective in treating sciatica (Eisenberg et al, 2003)

3) Adult:

a) Multiple Sclerosis-Related Pain

1) Open-label add-on lamotrigine 25 milligrams/day (mg/day) titrated slowly to a maximum dose of 400 Multiple sclerosis-related pain syndromes refractory to multiple other medications. Improvement in parox eight of 21 (38%) patients, with five of 21 (24%) experiencing improvement in painful tonic spasms. The year in some cases. These results require confirmation in a placebo-controlled trial (Cianchetti et al, 199

b) Postoperative Pain

1) Lamotrigine may be effective in reducing postoperative pain In a double-blind, placebo-controlled stu either lamotrigine 200 milligrams or placebo 1 hour before receiving spinal anesthesia for transurethral p were lower in the lamotrigine group than in the placebo group at 2 hours (p equal to 0.04), 4 hours (p les (Bonicalzi et al, 1997).

c) Post-stroke Pain

1) In a double-blind, randomized, crossover trial (n=30), patients with central post-stroke pain experienc milligrams/day. Subjects were randomized to 8-week courses of lamotrigine and placebo, separated by a lamotrigine was titrated at 2-week intervals from 25 milligrams (mg)/day to 50 mg/day, 100 mg/day, and pain score over the last week of treatment from 7 to 5 (p=0.01 compared with placebo). Twelve of 27 sub defined as a pain score 2 or more points lower than their score using placebo. No significant analgesia o secondary end points, including global physical pain score over last 4 weeks and pain stimulated by a co lamotrigine (p=0.02 and p=0.01, respectively); the trend favored lamotrigine on other secondary end poir events occurred at similar rates in the 2 periods. Mild rash was associated with lamotrigine use in 2 patie during the lamotrigine period due to mild rash, severe headache, and severe pain (Vestergaard et al, 20

d) Sciatica

1) An open-label, non-comparative study involving 14 patients suggests that lamotrigine may be effectiv radiculopathy for 12 to 36 months. They underwent a 1 week washout period from previous analgesics a was initiated at 25 milligrams (mg) once daily and was doubled weekly up to the maintenance dose of 40 dose for 4 weeks. Of the 14 patients, only 7 completed the full 11 weeks. Diarrhea, dizziness and person discontinuation. In patients who received at least 1 week of lamotrigine and in whom drug plasma concer numerical pain scale scores for spontaneous pain decreased from 7.6 to 4.5 at the end of 11 weeks (p le spontaneous pain also decreased from 7.9 to 4.1 (p less than 0.05). Scores from the Short Form of the M less than 0.05). A linear correlation was found between lamotrigine concentrations and the mean weekly analog measurements (both p=0.001). Due to high dropout rates and the open-label design of the study, (Eisenberg et al, 2003).

4.5.T Palatal myoclonus

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Eliminated ear clicks associated with palatal myoclonus in one case (Nasr & Brown, 2002)

3) Adult:

a) Ear-clicking associated with palatal myoclonus (PM) was stopped by lamotrigine treatment in a 37-year-ol admitted to psychiatric services because of an acute psychotic episode associated with excessive alcohol co After alcohol detoxification and antipsychotic treatment (thioridazine 100 milligrams (mg) 3 times daily), he wa patient reported gradual improvement, with disappearance of ear-clicking and slowing of the frequency of pal clinical examination. After discharge, the man began again to drink alcohol and stopped taking lamotrigine, re Brown, 2002).

4.5.U Parkinson's disease, Idiopathic

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

No beneficial effect (Shinotoh et al, 1997)

3) Adult:

a) Lamotrigine had no beneficial effects on patients with Parkinson's disease treated either during a single d (n=12) (Shinotoh et al, 1997).

4.5.V Paroxysmal choreoathetosis, Paroxysmal

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in 3 children with paroxysmal kinesigenic choreoathetosis (Uberall & Wenzel, 2000)

3) Pediatric:

a) Low-dose lamotrigine was safe and effective in 3 children with idiopathic paroxysmal kinesigenic choreoat year-old girl, and a 10-year-old boy. The first boy was started on lamotrigine 5 milligrams (mg)/day, with titrati mg/kilogram (kg); titration from 5 to 10 to 25 to 50 mg). On that dosage, his attacks were significantly decreas was attack-free. The girl received increasing doses, starting from 5 mg/day ranging up to 100 mg/day (4.7 mg dose, she was attack-free also. The second boy began taking lamotrigine 10 mg/day, with titration biweekly t point his dystonic attacks ceased. In all cases, lamotrigine was well tolerated. Previous medications which ha carbamazepine, phenobarbital, and flunarizine. The patients had used lamotrigine for 16, 19, and 27 months,

4.5.W Partial seizure, Adjunct or monotherapy

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (13 years and older, extended-release only; 2 years and older, only)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category A; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Extended-release formulation is indicated as adjunctive therapy for partial onset seizures with or without older (Prod Info LAMICTAL XR oral extended-release tablets, 2009)

Indicated as adjunctive therapy in the treatment of partial seizures in adults and pediatric patients with ep tablets, oral tablets, orally disintegrating tablets, 2009)

Indicated for conversion to monotherapy in patients receiving treatment with a single enzyme-inducing a chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

Beneficial in patients with seizures resistant to various combinations of carbamazepine, phenobarbital, p

3) Adult:

a) Extended-release formulation is indicated as adjunctive therapy for partial onset seizures with or without s older (Prod Info LAMICTAL XR oral extended-release tablets, 2009).

b) Of the 527 patients enrolled in a 6-year, open-label, continuation study examining the use of lamotrigine n partial seizures, the clinical status of 58% of patients were judged to have improved from baseline and the lor incidence of adverse effects. Patients were recruited from 5 primary clinical studies of adjunctive lamotrigine. milligrams per day (range 100 to 730 mg per day). Forty-three percent (n=229) of patients completed the stuc 37% of patients, miscellaneous reasons (7%), adverse events (5%) and administrative reasons (5%; eg, prot Overall clinical status was judged on a 7 point scale by the investigators. Mild, moderate, and marked improv the time of discontinuation when compared to pre-lamotrigine clinical status. No change was seen in 30% of and marked deterioration) was seen in 12% of patients. Adverse events were noted in 98% of patients. The n diplopia, ataxia, headache, somnolence, nausea, amblyopia and accidental injury. Serious adverse events w a serious adverse event by 0.4% of patients. No patients developed Stevens-Johnson syndrome (Faught et a

c) As an add-on treatment, lamotrigine (LTG) was effective in the treatment of epileptic drop attacks (EDA) ir patients being treated with antiepileptic drugs but still experiencing at least one EDA per month and at least 4 were observed for 3 months (baseline), given LTG over a 4-month period during which the dose was increase months while taking the maintenance dose. Prior medications were continued throughout the study. In patien milligrams/day (mg/day), which was increased incrementally every 2 weeks to a final dose of 150 mg/day. In was 25 mg/day, which was increased to 300 mg/day. In the last month of the titration period, if necessary, do tolerated dose. Of the 12 patients who completed the study, all had more than a 50% reduction in their total s 75% decrease in seizure frequency. EDA disappeared in 6 patients, improved by 80% in 3 patients and by 50 improvement in EDA frequency. The average maximum LTG dosages were 200 mg/day with valproic acid an al, 2001).

d) Monotherapy with lamotrigine was successful in most patients with partial seizures converted from adjunc double-blind trial, 156 patients who had experienced at least 4 seizures during each of 2 consecutive 4-week monotherapy were randomized to receive adjunct therapy with either valproate 1000 milligrams (mg)/day or l week period with patients then converted to monotherapy with lamotrigine or valproate over the next 4 weeks had: doubling of average monthly seizure count, doubling of highest consecutive 2-day seizure frequency, en prolongation of generalized tonic-clonic seizures. Percentage of patients failing monotherapy in the lamotrigir was 69%. A low dose of valproate was used to demonstrate the efficacy of lamotrigine and provide some pro demonstrate lamotrigine superiority or equivalence.(Gilliam et al, 1998)

e) Double-blind, placebo-controlled add-on trials demonstrated that lamotrigine is efficacious in treating refra produced a 26% or greater reduction in seizure frequency in 48% of patients and 50% or greater reduction in (n=216), observed median reductions in seizures relative to baseline were 8%, 20%, and 36% in patients rec and lamotrigine 500 mg/d, respectively (Matsuo et al, 1993b). In addition, preliminary data indicate that lamot generalized seizures (Binnie et al, 1989); (Sander et al, 1990; Pers Comm, 1993). In one trial, 15 of 19 adult reduction in seizure frequency; some patients were able to withdraw one or more anticonvulsants while maint 1992).

f) In a long-term study, 38% of 16 adult patients with refractory epilepsy had a reduction of seizure frequency year. Further follow-up indicates some decline in efficacy, since the percentage of improved patients droppec al, 1994a).

g) Ten of the 27 patients with refractory complex partial, secondarily generalized tonic clonic, atypical absen 12 months due to lack of efficacy . Patients were studied over a 2-year period with 11 of the remaining patien frequency. Only 3 patients with atypical absence and atonic seizures showed a significant response.

h) In 104 patients remaining in an 11-month, open-label study evaluating add-on lamotrigine for severe refra reduction in seizure frequency (Sander et al, 1990). Nineteen patients withdrew from the study due to advers drowsiness, and rash or due to an increase in seizure frequency (Pisani et al, 1991).

i) In a double-blind, placebo-controlled trial of add-on lamotrigine therapy, 15 of 23 adult patients with refract experienced a 50% or greater reduction in seizure frequency. The blood levels of concomitantly administered adverse effects were noted (Loiseau et al, 1990).

j) Lamotrigine is useful in controlling simple and complex partial seizures and secondarily generalized tonic c crossover trial, 21 patients refractory to multiple anticonvulsants including phenobarbital, phenytoin, primidon 100 milligrams/day (dosage adjusted to produce trough plasma concentrations of 1.5 to 2 micrograms/millilite showed improvement with lamotrigine treatment; the mean reduction in seizure frequency was 59% (confider improvement in simple and complex partial seizures; 8 of 15 showed improvement in secondarily generalizec common adverse reactions included fatigue, diplopia, drowsiness, ataxia, and headache. These were not cor

4) Pediatric:

a) Extended-release formulation is indicated as adjunctive therapy for partial onset seizures with or without s older (Prod Info LAMICTAL XR oral extended-release tablets, 2009).

b) In part of an open-label, prospective study, adjunctive lamotrigine therapy decreased the daily number of

per day (p=0.027) in patients diagnosed with intractable seizures. Enrolled infants had to have been previous
patients were diagnosed with partial seizures, 1 was diagnosed with both infantile spasms and partial seizure
spasms. In this study, one infant had no response and no infants became seizure free. Doses were based up
neonates who were taking enzyme-inducing agents, doses up to 10 milligrams per kilogram per day (mg/kg/d
months of age, who were taking enzyme-inducing agents, final doses ranged between 10 to 20 mg/kg/day. In
and enzyme inducers, were dosed between 5 to 10 mg/kg/day. In infants between 1 and 12 months of age, ta
One case of skin rash, which subsided after a day, and one case of elevated liver enzymes, which subsided
Eleven of the 15 infants had no observed adverse effects (Mikati et al, 2003).

c) In an open-label, long-term study (n=41), add-on lamotrigine therapy proved successful in 44% of study s
years of age; mean 12 years) with refractory severe partial epilepsy (mean seizure frequency 3.6/day). All en
major antiepileptic drugs. Eighteen patients (44%) remained on lamotrigine after 12 to 48 months of follow-up
occurred in 15 patients (34%) (p less than 0.00006), with 6 of these subjects remaining seizure-free. Three of
marked improvement in behavior, although seizure frequency was unchanged. Higher response rates were o
symptomatic of cerebral malformation. Seizure worsening occurred in 9 patients; transient rash developed in
starting daily dose was 0.2 to 2.5 milligrams/kilogram (mg/kg) titrated over 2 to 4 weeks to an initial maintena
subsequently adjusted based on clinical response up to a maximum of 1.8 to 15 mg/kg/day; mean dose was
valproate, median dose was 4.8 mg/kg/day; for those on enzyme-inducing drugs except valproate, median do

d) The efficacy and safety of add-on lamotrigine for treatment of partial seizures in children were demonstrat
entered an 8-week baseline phase to confirm the presence of intractable seizures with their current antiepilep
dose escalation phase and a 12-week maintenance phase. The median reductions in seizure frequency durin
were 36% and 6.7% in lamotrigine and placebo recipients, respectively (p=0.008). Secondarily generalized s
respectively (p=0.003). A decline in seizure frequency of at least 50% occurred in 42% and 16% of the lamot
0.001). Dizziness, tremor, nausea and ataxia were significantly more common with lamotrigine than with plac

4.5.X Reflex epilepsy

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Pilot data from a small case series suggest possible efficacy in startle/noise-induced reflex epilepsy (Fau

3) Adult:

a) Four adults with debilitating, refractory startle-induced seizure disorders gained relief from add-on lamotrig
eliminated "drop attacks" brought on by sudden noise, yet one patient had to discontinue lamotrigine after 10
drop attacks resumed. The other patients maintained excellent seizure control with no adverse effects noted

4.5.Y Rett's disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Lamotrigine controlled seizures and modulated symptoms of Rett syndrome in 2 case reports (Kumanda

3) Pediatric:

a) Two young girls (4.5 and 2.5 years of age) diagnosed with Rett syndrome showed marked improvement o
therapy. In the 4.5-year-old girl, myoclonic seizures were present, along with microcephaly, mental retardatio
unsteadiness, hypertonia, hyperactive deep tendon reflexes, and stereotypical wringing hand movements. La
lamotrigine 3 milligrams/kilogram (mg/kg) daily. At 6 months, she was seizure-free. Hand movements and au
respiratory function was improved. The younger girl exhibited tonic-clonic seizures, hypotonia, hyperactive de
movements. Phenobarbital and valproic acid were given, but did not control the seizures. With lamotrigine 3 m
the girl became seizure-free. Her abnormal hand movements, though continuing, were appreciably decreased
pyruvate in cerebrospinal fluid (CSF) were all normal. The authors suggested that the remedial effects of lam
release (glutamate concentrations in CSF were reported to be elevated in Rett syndrome) (Kumandas et al, 2

4.5.Z Schizophrenia, Refractory

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Adjunctive lamotrigine improved positive symptoms scores but did not improve total symptom scores in a
schizophrenia (Tiihonen et al, 2003)

When added to clozapine treatment, improved psychiatric symptoms in 3 patients (Saba et al, 2002)

3) Adult:

a) In a randomized, double-blinded, placebo-controlled, crossover trial, adjunctive lamotrigine improved the p total symptom scores in patients resistant to clozapine therapy. Patients (n=34) were diagnosed with schizop with no epilepsy or current anticonvulsant or lithium therapy and who had an unsatisfactory response with clo period lasted 14 weeks and started with a 1-week placebo lead-in. Lamotrigine was initiated at 25 milligrams/ followed by 100 mg/d for 2 weeks, 150 mg/d for 2 weeks and then 200 mg/d for 4 weeks. Doses were then ta Negative Syndrome Scale (PANSS) scores changed from 68.55 to 64.31 in the lamotrigine arm and from 69. analysis). PANSS negative symptoms scores changed from 19.97 to 18.69 in the lamotrigine arm and 19.8 to However, PANSS positive symptom scores improved from 17.24 to 16.24 the lamotrigine arm compared to a intent to treat) and general psychopathological symptoms scores changed from 31.34 to 29.38 in the lamotrig (p=0.03, intent to treat) (Tiihonen et al, 2003).

b) In 3 patients who had responded poorly to 6 months of treatment with clozapine, addition of lamotrigine fo and 28% decrease in BPRS (Brief Psychiatric Rating Scale) scores). Patient 1: clozapine dosage 700 mg/day 50 mg/day), 43 on day 56 (lamotrigine 100 mg/day), 30 on day 84 (lamotrigine 150 mg/day). His degree of im hospitalization. Steady-state concentrations of clozapine, norclozapine, and lamotrigine in plasma were 235 r micrograms/mL (mcg/mL), respectively, on day 83. Patient 2: clozapine 500 mg/day. BPRS score 66 on day (with lamotrigine dose increasing to 75 mg/day. Steady state plasma concentrations for clozapine, norclozapir 0.57 mcg/mL, respectively, at day 56. Patient 3: clozapine dosage 700 mg/day. BPRS score 43 on day 0, 35 (lamotrigine 75 mg/day), and 31 on day 84 (lamotrigine 200 mg/day). Steady-state concentrations of clozapin ng/mL, 420 ng/mL, and 1.28 mcg/mL, respectively, on day 85. No marked side effects, rash, or hematologica 2002).

4.5.AA Sexual dysfunction

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

In three case reports, substitution of lamotrigine for gabapentin resolved impotence in men with epilepsy

3) Adult:

a) Three men who developed impotence while being treated with multiple anticonvulsants for long-standing e on lamotrigine. In each case, lamotrigine was initiated and escalated while gabapentin was tapered and witho frequency in these individuals (Husain et al, 2000).

4.5.AB Shortlasting, unilateral, neuralgiform pain with conjunctival injection and tearing syndrome

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Lamotrigine appeared to be curative in case reports of SUNCT syndrome (short-lasting unilateral neuralg tearing syndrome) (Malik et al, 2002)

3) Adult:

a) Symptoms of SUNCT syndrome resolved following lamotrigine treatment in one female patient. An 80-yea pain with episodes occurring every 15 to 20 minutes failed to respond to treatment with carbamazepine, gaba hydrocodone/acetaminophen. Lamotrigine therapy was initiated at 25 milligrams (mg)/day for 1 week and titra The intensity of her attacks shrunk by half within 1 week of beginning lamotrigine. Her episodes were comple year of follow-up (Malik et al, 2002).

b) A 66-year-old female with SUNCT SYNDROME of 6 months duration with recent worsening (up to 15 atta therapy. SUNCT syndrome was resistant to aspirin and other nonsteroidal agents and carbamazepine. After sudden exacerbation of attacks occurred, which then abated completely following lamotrigine dose escalation 3-month course of therapy, with no further episodes through 15 months of follow-up (D'Andrea et al, 1999).

4.5.AC Status epilepticus

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Successful control of status epilepticus has been reported in one case refractory to intravenous diazepar More data are needed to ascertain the role of lamotrigine in the therapy of status epilepticus (Pisani et al

3) Pediatric:

a) Lamotrigine may be an important adjunct to other drugs in the treatment of status epilepticus. In one case carbamazepine 1200 milligrams/day (mg) and phenobarbital 200 mg/day experienced an unexplained increas generalized convulsive status epilepticus refractory to multiple boluses and continuous infusion of diazepam. followed by 200 mg twice a day, with prompt resolution of status epilepticus and a resulting decrease in seizu discharged on lamotrigine, phenobarbital 100 mg twice a day, and carbamazepine 400 mg 3 times a day (Pis

4.5.AD Tinnitus

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Lamotrigine's effects on chronic tinnitus were equivocal in a placebo-controlled, crossover trial (Simpson

3) Adult:

a) Lamotrigine did not clearly demonstrate efficacy in ameliorating chronic tinnitus in a randomized, double-b patient received lamotrigine in an escalating regimen (25 to 100 milligrams/day) and placebo in two different Patients assessed the loudness, annoyance and awareness of tinnitus on visual analog scales (VAS) at base observed between lamotrigine and placebo in terms of VAS scores or audiometry. According to patient quest (35%) and 6 (19%) patients while on lamotrigine and placebo, respectively. The majority reported "no change correlate with response to lamotrigine (Simpson et al, 1999).

4.5.AE Tonic-clonic seizure, Primary generalized; Adjunct

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (2 years and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated as adjunctive therapy for primary generalized tonic-clonic seizures in adults and pediatric patie chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

The efficacy of lamotrigine as adjunctive therapy for primary generalized tonic-clonic seizures was demo involving 117 adult and pediatric patients (Prod Info LAMICTAL chewable dispersible oral tablets, oral ta

3) Adult:

a) The efficacy of lamotrigine as adjunctive therapy for primary generalized tonic-clonic seizures was demon involving 117 adult and pediatric (at least 2 years of age) patients. The study included an 8-week baseline ph generalized tonic-clonic seizures during the baseline phase were randomized to oral lamotrigine therapy (n=5 their existing antiepileptic drug (AED) regimen of up to 2 drugs. The adult target dose of lamotrigine ranged fr concomitant antiepileptic therapy. Efficacy was based on the percent change from baseline in primary genera primary generalized tonic-clonic seizures in the intent-to-treat population, which included both adult and pedia lamotrigine and placebo, respectively (p=0.006) (Prod Info LAMICTAL chewable dispersible oral tablets, oral

4) Pediatric:

a) The efficacy of lamotrigine as adjunctive therapy for primary generalized tonic-clonic (PGTC) seizures wa trial involving a total of 117 adult and pediatric (aged 2 to 19 years; mean age, 11 years) patients with PGTC drugs (AED). The study included an 8-week baseline phase after which patients who had at least 3 primary g phase were randomized. The pediatric subgroup was randomized to oral lamotrigine therapy (n=21) or placel study consisted of an escalation phase (12 weeks for patients 2 to 12 years and 7 weeks for patients greater with a pediatric target dose of lamotrigine ranging from 3 milligrams/kilogram/day (mg/kg/day) to 12 mg/kg/da The most common concomitant antiepileptic drug was valproate which was used in 67% of the lamotrigine gr reduction in PGTC seizures from baseline (primary efficacy measure) was 77% and 40% in patients receiving median percent decrease in PGTC seizures during the escalation phase was 72% and 30% in the lamotrigine decrease during the maintenance phase was 83% and 42%, respectively (p=0.058). The overall median PGT group and 2.5 in the placebo group (p=0.007) (Trevathan et al, 2006; Prod Info LAMICTAL chewable dispers 2009).

4.5.AF Trigeminal neuralgia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective for essential and symptomatic trigeminal neuralgia (Zakrzewska et al, 1997; Lunardi et al, 1997

3) Adult:

a) Lamotrigine demonstrated antineuralgic properties in 13 patients with trigeminal neuralgia . In a double-bli compared to placebo in patients receiving steady doses of carbamazepine or phenytoin. Each drug was give therapies. Lamotrigine was superior to placebo (p less than 0.011) on a composite efficacy index score which scores, and global evaluations. Interestingly, during the second phase of the trial, those receiving placebo aft improvement observed during lamotrigine therapy. The authors speculated that lamotrigine may have produc drug, or this could have occurred randomly since there were relatively small patient numbers. More studies a (Zakrzewska et al, 1997).

b) In an open, prospective trial, lamotrigine showed impressive results in the treatment of 20 patients with tri to 75 years old) with an "essential" form of trigeminal neuralgia while the second group consisted of 5 patient associated with multiple sclerosis. In the first group, 11 patients had a complete remission with 1 patient attai with 150 to 250 mg/day and 2 patients requiring 400 mg/day. Four patients continued to have pain at the 400 group had full relief of pain with lamotrigine 150 to 200 mg/day. Patients with relief continued to be pain-free a

4.5.AG West syndrome

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Spasms resolved in three infants following treatment with low-dose lamotrigine (Cianchetti et al, 2002).

3) Pediatric:

a) Symptoms of West syndrome in three infants resolved following treatment with low-dose lamotrigine. Spas following the initiation of lamotrigine therapy (1.25 milligrams (mg) one to three times daily) after unsuccessfu ACTH). The infants remained seizure-free at maintenance doses of lamotrigine 1.25 mg/day to 2.5 mg twice

4.6 Comparative Efficacy / Evaluation With Other Therapies

Carbamazepine

Gabapentin

Lithium

Topiramate

4.6.A Carbamazepine

4.6.A.1 Seizure

a) Carbamazepine and lamotrigine are equally effective as monotherapy in patients with newly diagnosed ep randomly assigned to a fixed dosage titration of either carbamazepine or lamotrigine. After four weeks, all pa lamotrigine or 600 mg/day of carbamazepine; for the next 24 weeks, doses were adjusted according to effica patients who were seizure-free for the last 6 months of the study were 39% and 38% for lamotrigine and carb was better tolerated, and more patients were able to complete the study period than patients treated with carb common with carbamazepine than lamotrigine (22% versus 12%, respectively) (Brodie et al, 1995).

b) As initial monotherapy in elderly patients newly diagnosed with epilepsy, lamotrigine demonstrated a supe carbamazepine. Subjects (n=150) were randomized in a double-blinded 2:1 ratio to lamotrigine 25 milligrams medications were titrated slowly upward over 6 weeks to 50 mg twice daily and 200 mg twice daily, respectiv duration. The median doses of lamotrigine and carbamazepine in study completers were 100 mg/day and 40 concentrations at week 24 were 2.3 mg/liter (L) and 6.9 mg/L, respectively. Somnolence (29% versus 12%) a often in the carbamazepine versus lamotrigine groups, respectively. The corresponding withdrawal rates wer 42% and 18% of discontinuations, respectively. The hazard ratio for withdrawal with carbamazepine compare to 4). Efficacy measures were considered secondary endpoints in this trial. While no between-group differenc significantly more lamotrigine recipients remained seizure-free over the last 16 weeks of the study (39% vers

4.6.B Gabapentin

4.6.B.1 Mood disorder

a) Preliminary results from a cross-over study (randomized, double- blinded) suggest that LAMOTRIGINE m the improvement of refractory mood disorders (n=31) (Frye et al, 2000). Study subjects included bipolar I (11 23 were rapid-cycling); all had tried other mood stabilizing agents previously. Percentages of those who had for gabapentin, and 23% for placebo based on the Clinical Global Impression (CGI) scale modified for bipolar

responders were defined as those who were much or very much improved on the CGI scale. Both agents we
developed a rash caused by lamotrigine; the rash progressed to toxic epidermal necrolysis, requiring treatme
trend showed that subjects tended to lose weight on lamotrigine relative to the weight gained on gabapentin.
(mg) daily in week 1, titrated to 50 mg/day in week 2, 50 to 100 mg/day in week 3, 150 to 300 mg for weeks 4
was given at an initial daily dose of 900 mg, titrated to 1500 mg by the end of week 1, 2700 mg by the end of
and 4800 mg by week 5 to 6. Mean daily doses as of week 6 were 274 mg for lamotrigine and 3987 mg for ga

4.6.B.2 Adverse Effects

a) In healthy volunteers, cognitive difficulties were associated with topiramate while gabapentin and lamotrig
Healthy young adults (n=17) were randomized to receive topiramate 5.7 milligrams/kilogram (mg/kg), lamotrig
titrated up over 4 weeks. Neurobehavioral performances were then compared at baseline, 2 weeks, and 4 we
group made significantly more errors during week 2 (p less than 0.02) and during week 4 (p less than 0.004)
symbol digits modalities test, the topiramate group performed poorer than the lamotrigine and gabapentin at
lamotrigine group at week 4 (p less than 0.04). On memory tests at week 2 the topiramate group was worse t
lamotrigine group was below that of the gabapentin group but above the topiramate group. At week 4 the gro
more symptoms of depressed mood at week 4 compared to the lamotrigine and gabapentin groups (p less th
the lamotrigine group at week 4 (p less than 0.02). Further long-term drug effects should be evaluated.

4.6.C Lithium

4.6.C.1 Bipolar disorder

a) In a double-blinded study (GW606), lamotrigine and lithium were both statistically superior to placebo in th
mood episode in recently (within 60 days) MANIC or HYPOMANIC patients with bipolar I disorder. During an
lamotrigine therapy while other psychotropic drugs were discontinued. Patients who tolerated the open-label
lithium (n=46) or placebo (n=70) as the sole agent for maintenance therapy for 18 months. Lamotrigine doses
was titrated to serum levels of 0.8 to 1.1 mEq/L. The median time to intervention due to a mood episode was
in the lithium arm (p=0.46) and 85 days in the placebo arm (p=0.02). The difference in the median time to inte
placebo as well as between lithium and placebo (p=0.003). Of the mood events, 20 lamotrigine patients, 8 lith
This difference was statistically significant between the lithium and placebo arms (p=0.006). Of the mood eve
placebo patients developed depression. This was statistically different between the lamotrigine and placebo a
of depression were not statistically different between lamotrigine and lithium (p=0.09 and 0.36, respectively).
discontinue therapy early due to adverse events compared to placebo and lamotrigine (p=0.01 and 0.003, res
the number of patients enrolled was lower than projected and patients randomized into each study arm had r
could bias results (Bowden et al, 2003).

b) In a double-blinded study (GW605), both lamotrigine and lithium were statistically superior to placebo in th
mood episode in recently (within 60 days) DEPRESSED PATIENTS with bipolar I disorder. During an 8- to 16
therapy while other psychotropic drugs were discontinued. Patients who tolerated lamotrigine were then rand
or placebo (n=121) as the sole agent for maintenance therapy for up to 18 months. Lamotrigine doses range
evaluations were performed in patients who received 200 to 400 mg daily (n=169). Lithium was titrated to ser
intervention due to a mood episode was 200 days in the lamotrigine arm compared to 170 days in the lithium
(p=0.029). The difference in the median time to intervention was significant between lamotrigine and placebo
Interventions for emerging depression occurred nearly 3 times more often than interventions for manic sympt
symptoms of mania after 1 year compared to 86% of lithium patients and 72% of placebo patients. This differ
and placebo arms (p=0.026). Of the lamotrigine patients, 57% did not develop symptoms of depression after
placebo patients. This was statistically different between the lamotrigine and placebo arms (p=0.047). Develo
not statistically different between lamotrigine and lithium (p=0.125 and 0.434, respectively). Results should be
each study arm had responded to lamotrigine in the open-label phase which could bias results (Calabrese et

4.6.D Topiramate

1) Adverse Effects

a) In healthy volunteers, cognitive difficulties were associated with topiramate while gabapentin and lamotrig
Healthy young adults (n=17) were randomized to receive topiramate 5.7 milligrams/kilogram (mg/kg), lamotrig
titrated up over 4 weeks. Neurobehavioral performances were then compared at baseline, 2 weeks, and 4 we
group made significantly more errors during week 2 (p less than 0.02) and during week 4 (p less than 0.004)
symbol digits modalities test, the topiramate group performed poorer than the lamotrigine and gabapentin at
lamotrigine group at week 4 (p less than 0.04). On memory tests at week 2 the topiramate group was worse t
lamotrigine group was below that of the gabapentin group but above the topiramate group. At week 4 the gro
more symptoms of depressed mood at week 4 compared to the lamotrigine and gabapentin groups (p less th
the lamotrigine group at week 4 (p less than 0.02). Further long-term drug effects should be evaluated.

6.0 References

1. Aberg L, Heiskala H, Vanhanen S-L, et al: Lamotrigine therapy in infantile neuronal ceroid lipofuscinosis (INCL). Ne
2. Anon: Lamotrigine pregnancy registry interim report 1September 1992 through March 2005. GlaxoSmithKline, Cha
2176, July 2005.
3. Arenz A, Klein M, Fiehe K, et al: Occurrence of neurotoxic 4'-0-methylpyridoxine in Ginkgo biloba leaves, Ginkgo m
1996; 62:548-51.
4. Arenz A, Klein M, Fiehe K, et al: Occurrence of neurotoxic 4'-0-methylpyridoxine in Ginkgo biloba leaves, Ginkgo m

1996a; 62:548-551.
5. Australian Drug Evaluation Committee: Prescribing medicines in pregnancy: An Australian categorisation of risk of
Administration. Australian Capital Territory, Australia. 1999. Available from URL: http://www.tga.gov.au/docs/html/m
6. Barbee JG & Jamhour NJ: Lamotrigine as an augmentation agent in treatment-resistant depression. J Clin Psychia
7. Barber AJ: Evening primrose oil: a panacea?. Pharm J 1998; (June 4):723-725.
8. Bartoli A, Guerrini R, Belmonte A, et al: The influence of dosage, age, and comedication on steady state plasma la
prospective study with preliminary assessment of correlations with clinical response. Ther Drug Monit 1997; 19(3):2
9. Battaglia D, Iuvone L, Stefanini MC, et al: Reversible aphasic disorder induced by lamotrigine in atypical benign chi
10. Battino D, Croci D, Granata T, et al: Lamotrigine plasma concentrations in children and adults: influence of age and
627.
11. Battino D, Estienne M, & Avanzini G: Clinical pharmacokinetics of antiepileptic drugs in paediatric patients. Part II. I
vigabatrin, oxcarbazepine and felbamate. Clin Pharmacokinet 1995; 29:341-69.
12. Battino D, Estienne M, & Avanzini G: Clinical pharmacokinetics of antiepileptic drugs in paediatric patients. Part II. I
vigabatrin, oxcarbazepine and felbamate. Clin Pharmacokinet 1995a; 29:341-69.
13. Battino D, Estienne M, & Avanzini G: Clinical pharmacokinetics of antiepileptic drugs in paediatric patients. Part II. I
vigabatrin, oxcarbazepine and felbamate. Clin Pharmacokinet 1995b; 29:341-69.
14. Besag F, McShane T, Neville B, et al: Factors associated with serious skin reactions in children aged 12 years and
41:67-69.
15. Betts T, Goodwin G, Withers RM, et al: Human safety of lamotrigine. Epilepsia 1991; 32(suppl 2):S17-S21.
16. Bianchetti G, Padovani P, Thenot JP, et al: Pharmacokinetic interactions of progabide with other antiepileptic drugs
17. Bianchetti G, Padovani P, Thenot JP, et al: Pharmacokinetic interactions of progabide with other antiepileptic drugs
18. Bianchetti G, Padovani P, Thenot JP, et al: Pharmacokinetic interactions of progabide with other antiepileptic drugs
19. Bienentreu SD & Kronmuller K-T H: Increase in risperidone plasma level with lamotrigine. Am J Psychiatry 2005; 1
20. Binnie CD, Debets RMC, Engelsman M, et al: Double-blind crossover trial of lamotrigine (Lamictal) as add-on thera
229.
21. Binnie CD, van Emde Boas W, Kasteleijn-Nolste-Trenite DGA, et al: Acute effects of lamotrigine (BW430C) in pers
22. Binnie CD, van Emde Boas W, Kasteleijn-Nolste-Trenite DGA, et al: Acute effects of lamotrigine (BW430C) in pers
23. Binnie CD, van Emde Boas W, Kasteleijn-Nolste-Trenite DGA, et al: Acute effects of lamotrigine (BW430C) in pers
24. Binnie CD, van Emde Boas W, Kasteleijn-Nolste-Trenite DGA, et al: Acute effects of lamotrigine (BW430C) in pers
25. Binnie CD, van Emde Boas W, Kasteleijn-Nolste-Trenite DGA, et al: Acute effects of lamotrigine (BW430C) in pers
26. Biraben A, Allain H, Scarabin JM, et al: Exacerbation of juvenile myoclonic epilepsy with lamotrigine. Neurology 20
27. Birnbaum AK, Kriel RL, Im Y, et al: Relative bioavailability of lamotrigine chewable dispersible tablets administered
28. Bonicalzi V, Canavero S, Cerutti F, et al: Lamotrigine reduces total postoperative analgesic requirement: a randomi
Surgery 1997; 122:567-570.
29. Boot B: Recurrent lamotrigine-induced aseptic meningitis. Epilepsia 2009; 50(4):968-969.
30. Bowden C, Calabrese J, Sachs G, et al: A placebo-controlled 18-month trial of lamotrigine and lithium maintenance
bipolar I disorder. Arch Gen Psychiatry 2003; 60:392-400.
31. Brodie MJ, Overstall PW, Giorgi L, et al: Multicentre, double-blind, randomised comparison between lamotrigine an
diagnosed epilepsy. Epilepsy Res 1999; 37:81-87.
32. Brodie MJ, Richens A, Yuen AWC, et al: Double-blind comparison of lamotrigine and carbamazepine in newly diag
33. Brodie MJ: Lamotrigine.. Lancet 1992; 339:1397-1400.
34. Brown TS, Appel JE, Kasteler JS, et al: Hypersensitivity reaction in a child due to lamotrigine. Pediatr Dermatol 19
35. Buehler BA, Delimont D, Van Waes M, et al: Prenatal prediction of risk of the fetal hydantoin syndrome. N Engl J M
36. Buehler BA, Delimont D, Van Waes M, et al: Prenatal prediction of risk of the fetal hydantoin syndrome. N Engl J M
37. Buehler BA, Delimont D, Van Waes M, et al: Prenatal prediction of risk of the fetal hydantoin syndrome. N Engl J M
38. Buoni S, Grosso S, & Fois A: Lamotrigine in typical absence epilepsy. Brain Dev 1999; 21:303-306.
39. Buoni S, Grosso S, & Fois A: Lamotrigine treatment in childhood drug resistant epilepsy. J Child Neurol 1998; 13:1
40. Burstein AH: Lamotrigine.. Pharmacotherapy 1995a; 15(2):129-43.
41. Burstein AH: Lamotrigine.. Pharmacotherapy 1995; 15(2):129-43.
42. Buzan RD & Dubovsky SL: Recurrence of lamotrigine-associated rash with rechallenge (letter). J Clin Psychiatry 19
43. Calabrese J, Bowden C, Sachs G, et al: A placebo-controlled 18-month trial of lamotrigine and lithium maintenance
disorder. J Clin Psychiatry 2003; 64:1013-1024.
44. Calabrese JR, Bowden CL, McElroy SL, et al: Spectrum of activity of lamotrigine in treatment-refractory bipolar disc
45. Calabrese JR, Suppes T, Bowden CL, et al: A double-blind, placebo-controlled, prophylaxis study of lamotrigine in
Study Group. J Clin Psychiatry 2000; 61:841-850.
46. Chaffin JJ & Davis SM: Suspected lamotrigine-induced toxic epidermal necrolysis. Ann Pharmacother 1997; 31:72
47. Chang K, Saxena K, & Howe M: An open-label study of lamotrigine adjunct or monotherapy for the treatment of ad
Adolesc Psychiatry 2006; 45(3):298-304.
48. Chatham Showalter PE & Kimmel DN: Stimulating consciousness and cognition following severe brain injury: a nev
(11):997-1001.
49. Chattergoon DS, McGuigan MA, Koren G, et al: Multiorgan dysfunction and disseminated intravascular coagulation
Neurology 1997; 19:1442-1444.
50. Chattergoon DS, McGuigan MA, Koren G, et al: Multiorgan dysfunction and disseminated intravascular coagulation
Neurology 1997a; 19:1442-1444.
51. Chattergoon DS, McGuigan MA, Koren G, et al: Multiorgan dysfunction and disseminated intravascular coagulation
Neurology 1997b; 19:1442-1444.
52. Chen C, Casale EJ, Duncan B, et al: Pharmacokinetics of lamotrigine in children in the absence of other antiepilept
53. Christensen J, Petrenaite V, Atterman J, et al: Oral contraceptives induce lamotrigine metabolism: evidence from a

48(3):484-489.
54. Cianchetti C, Pruna D, Coppola G, et al: Low-dose lamotrigine in West syndrome. Epilepsy Res 2002; 51:199-200.
55. Cianchetti C, Zuddas A, Randazzo AP, et al: Lamotrigine adjunctive therapy in painful phenomena in MS: prelimina
56. Cocito L, Maffini M, & Loeb C: Long-term observations on the clinical use of lamotrigine as add-on drug in patients
57. Cocito L, Maffini M, & Loeb C: Long-term observations on the clinical use of lamotrigine as add-on drug in patients
58. Cohen AF, Land GS, Breimer DD, et al: Lamotrigine, a new anticonvulsant: pharmacokinetics in normal humans. C
59. Cohen AF, Land GS, Breimer DD, et al: Lamotrigine, a new anticonvulsant: pharmacokinetics in normal humans. C
60. Cohen AF, Land GS, Breimer DD, et al: Lamotrigine, a new anticonvulsant: pharmacokinetics in normal humans. C
61. Coppola G & Pascotto A: Lamotrigine as add-on drug in children and adolescents with refractory epilepsy and men
62. Das P, Ramaswamy S, Arora M, et al: Lamotrigine-induced neutropenia in a woman with schizoaffective disorder. I psychiatry 2007; 9(6):471-472.
63. DeLeon OA & Furmaga KM: Effect of lamotrigine treatment in epileptic psychosis. J Clin Psychopharmacol 1999; 1
64. Deleu D & Hanssens Y: Loss of aura in lamotrigine-treated epilepsy. Lancet 1997; 350(9093):1751-1752.
65. Depot M, Powell JR, Messenheimer JA Jr, et al: Kinetic effects of multiple oral doses of acetaminophen on a single 48:346-355.
66. Depot M, Powell JR, Messenheimer JA Jr, et al: Kinetic effects of multiple oral doses of acetaminophen on a single 48:346-355.
67. Devarajan S & Dursun SM: Aggression in dementia with lamotrigine treatment (letter). Am J Psychiatry 2000; 157:1
68. Devinsky O, Vuong A, Hammer A, et al: Stable weight during lamotrigine therapy: a review of 32 studies. Neurology
69. Dolk H, Jentink J, Loane M, et al: Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other m
70. Dooley J, Camfield P, Gordon K, et al: Lamotrigine-induced rash in children. Neurology 1996; 46:240-242.
71. Duchowny M, Pellock JM, Graf WD, et al: A placebo-controlled trial of lamotrigine add-on therapy for partial seizure
72. Eisenberg E, Damunni G, Hoffer E, et al: Lamotrigine for intractable sciatica: correlation between dose, plasma cor
73. Eisenberg E, Lurie Y, Braker C, et al: Lamotrigine reduces painful diabetic neuropathy: a randomized, controlled st
74. Eriksson AS & Boreus LO: No increase in carbamazepine-10,11-epoxide during addition of lamotrigine treatment ir
75. Eriksson AS & Boreus LO: No increase in carbamazepine-10,11-epoxide during addition of lamotrigine treatment ir
76. Eriksson AS, Hoppu K, Nergardh A, et al: Pharmacokinetic interactions between lamotrigine and other antiepileptic 1996; 37:769-773.
77. Eriksson AS, Hoppu K, Nergardh A, et al: Pharmacokinetic interactions between lamotrigine and other antiepileptic 1996a; 37:769-773.
78. Esfahani FE & Dasheiff RM: Anemia associated with lamotrigine. Neurology 1997; 49:306-307.
79. Farrell K, Connolly MB, Munn R, et al: Prospective, open-label, add-on study of lamotrigine in 56 children with intra 16:201-205.
80. Fatemi SH, Rapport DJ, Calabrese JR, et al: Lamotrigine in rapid-cycling bipolar disorder. J Clin Psychiatry 1997; 5
81. Faught E, Matsuo F, Schachter S, et al: Long-term tolerability of lamotrigine: data from a 6-year continuation study.
82. Faught E: Lamotrigine for startle-induced seizures. Seizure 1999; 8:361-363.
83. Fervenza FC, Kanakiriya S, Kunau RT, et al: Acute granulomatous interstitial nephritis and colitis in anticonvulsant treatment. Am J Kidney Dis 2000; 36(5):1034-1040.
84. Fillastre JP, Taburet AM, Failaire A, et al: Pharmacokinetics of lamotrigine in patients with renal impairment-influen 32.
85. Fillastre JP, Taburet AM, Fialaire A, et al: Pharmacokinetics of lamotrigine in patients with renal impairment: Influer (1):25-32.
86. Finnell RH, Buehler BA, Kerr BM, et al: Clinical and experimental studies linking oxidative metabolism to phenytoin 5):25-31.
87. Finnell RH, Buehler BA, Kerr BM, et al: Clinical and experimental studies linking oxidative metabolism to phenytoin 5):25-31.
88. Finnell RH, Buehler BA, Kerr BM, et al: Clinical and experimental studies linking oxidative metabolism to phenytoin 5):25-31.
89. Finnerup NB, Sindrup SH, Bach FW, et al: Lamotrigine in spinal cord injury pain: a randomized controlled trial. Pair
90. Fogelson DL & Sternbach H: Lamotrigine treatment of refractory bipolar disorder (letter). J Clin Psychiatry 1997; 58
91. Frye MA, Ketter TA, Kimbrell TA, et al: A placebo-controlled study of lamotrigine and gabapentin monotherapy in re 20(6):607-614.
92. Garnett WR: Lamotrigine: pharmacokinetics. J Child Neurol 1997; 12(suppl 1):S10-S15.
93. Gelisse P, Kissani N, Crespel A, et al: Is there a lamotrigine withdrawal?. Acta Neurol Scand 2002; 105(3):232-234
94. Gibbs J, Appleton RE, Rosenbloom L, et al: Lamotrigine for intractable childhood epilepsy: a preliminary communic
95. Gibbs J, Appleton RE, Rosenbloom L, et al: Lamotrigine for intractable childhood epilepsy: a preliminary communic
96. Gilliam F, Vasquez B, Sackellares JC, et al: An active-control trial of lamotrigine monotherapy for partial seizures. N
97. Gilman JT: Lamotrigine: an antiepileptic agent for the treatment of partial seizures.. Ann Pharmacother 1995; 29:14
98. Goa KL, Ross SR, & Chrisp P: Lamotrigine. A review of its pharmacological properties and clinical efficacy in epilep
99. Goa KL, Ross SR, & Chrisp P: Lamotrigine. A review of its pharmacological properties and clinical efficacy in epilep
100. Goa KL, Ross SR, & Chrisp P: Lamotrigine: a review of its pharmacological properties and clinical efficacy in epilep
101. Granger AS: Ginkgo biloba precipitating epileptic seizures. Age Ageing 2001; 30(6):523-525.
102. Granger AS: Ginkgo biloba precipitating epileptic seizures. Age Ageing 2001a; 30(6):523-525.
103. Graves NM & Leppik IE: Antiepileptic medications in development. DICP 1991; 25:978-986.
104. Green MA, Abraham MN, Horn AJ, et al: Lamotrigine-induced aseptic meningitis: a case report. Int Clin Psychopha
105. Guerrini R, Belmonte A, Parmeggiani L, et al: Myoclonic status epilepticus following high-dosage lamotrigine therap
106. Haedicke C, Angrick B, & Hauswaldt C: Lamotrigine versus carbamazepine in epilepsy [letter].. Lancet 1995; 345:1
107. Hennessy MJ & Wiles CM: Lamotrigine encephalopathy (letter). Lancet 1996; 347:974-975.

108. Hennessy MJ, Koutroumanidis M, & Elwes RDC: Neuralgic amyotrophy associated with hypersensitivity to lamotrig
109. Hosking G: Lamotrigine as add-on therapy in pediatric patients with treatment-resistant epilepsy: an overview (abst
110. Hsiao CJ, Lee JYY, Wong TW, et al: Extensive fixed drug eruption due to lamotrigine (letter). Br J Dermatol 2001; 1
111. Huber B, May T, & Seidel M: Lamotrigine in multihandicapped therapy-resistant epileptic patients. Clin Drug Invest
112. Husain AM, Carwile ST, Miller PP, et al: Improved sexual function in three men taking lamotrigine for epilepsy. Sou
113. Hvas C, Henriksen T, Ostergaard J, et al: Epilepsy and pregnancy: effect of antileptic drugs and lifestyle on birthwe
114. Institute for Safe Medication Practices: ISMP's list of confused drug names. Institute for Safe Medication Practices.
http://ismp.org/Tools/confuseddrugnames.pdf.
115. Institute for Safe Medication Practices: Medication safety alert!(R). Institute for Safe Medication Practices. Huntingc
http://ismp.org/Newsletters/ambulatory/archives/200707.asp.
116. Janszky J, Rasonyi G, Halasz P, et al: Disabling erratic myoclonus during lamotrigine therapy with high serum leve
(2):86-89.
117. Jawad S, Oxley J, Yuen WC, et al: The effect of lamotrigne, a novel anticonvulsant, on interictal spikes in patients v
118. Jawad S, Richens A, Goodwin G, et al: Controlled trial of lamotrigine (Lamictal) for refractory partial seizures. Epile
119. Jawad S, Richens A, Goodwin G, et al: Controlled trial of lamotrigine (Lamictal) for refractory partial seizures. Epile
120. Jawad S, Richens A, Goodwin G, et al: Controlled trial of lamotrigine (Lamictal) for refractory partial seizures. Epile
121. Jawad S, Richens A, Goodwin G, et al: Controlled trial of lamotrigine (Lamictal) for refractory partial seizures. Epile
122. Jawad S, Richens A, Goodwin G, et al: Controlled trial of lamotrigine (Lamictal) for refractory partial seizures. Epile
123. Jawad S, Richens A, Goodwin G, et al: Controlled trial of lamotrigine (Lamictal) for refractory partial seizures. Epile
124. Jawad S, Yuen WC, Peck AW, et al: Lamotrigine: single-dose pharmacokinetics and initial 1 week experience in re
125. Jawad S, Yuen WC, Peck AW, et al: Lamotrigine: single-dose pharmacokinetics and initial 1 week experience in re
126. Kanner A & Frey M: Adding valproate to lamotrigine: a study of their pharmacokinetic interaction. Neurology 2000;
127. Kaufman KR & Gerner R: Lamotrigine toxicity secondary to sertraline. Seizure 1998; 7:163-165.
128. Kaufman KR & Gerner R: Lamotrigine toxicity secondary to sertraline. Seizure 1998a; 7:163-165.
129. Kocak S, Girisgin SA, Gul M, et al: Stevens-Johnson syndrome due to concomitant use of lamotrigine and valproic
130. Koch H, Szecsey A, & Vogel: Clinically relevant reductionof lamotrigine concentrations by carbamazepine. Europea
131. Kraus de Camargo OA & Bode H: Agranulocytosis associated with lamotrigine. BMJ 1999; 318:1179.
132. Kumandas S, Caksen H, Ciftci A, et al: Lamotrigine in two cases of Rett syndrome. Brain Dev 2001; 23:240-242.
133. Labbate LA & Rubey RN: Lamotrigine for treatment-refractory bipolar disorder (letter). Am J Psychiatry 1997; 154(9
134. Laengler A & Meusers M: Thrombozytopenie und Exanthem unter "add-on" Therapie Lamotrigin und Valproat bei e
Syndrom. Aktuell Neurol 1995; 22:66-67.
135. Lamictal package insert (Burroughs Wellcome—US). Rev Rec 2/6/95., 12/94.
136. Lamictal package insert (GlaxoWellcome—US). Rev Rec 12/21/98., 12/98.
137. Lamictal product monograph.. Burroughs Wellcome—Canada., Rev 12/15/94, Rec 4/18/95.
138. Lampl C, Buzath A, Klinger D, et al: Lamotrigine in the prophylactic treatment of migraine aura - a pilot study. Ceph
139. Leach MJ, Baxter MG, & Critchley MAE: Neurochemical and behavioral aspects of lamotrigine. Epilepsia 1991; 32(
140. Leach MJ, Marden CM, & Miller AA: Pharmacological studies on lamotrigine, a novel potential antiepileptic drug: II.
Epilepsia 1986; 27:490-497.
141. Lerman-Sagie T & Lerman P: Dramatic effect of lamotrigine in young adults suffering from intractable absences an
Epilepsy 1998; 11:148-151.
142. Liporace J, Kao A, & D'Abreu A: Concerns regarding lamotrigine and breast-feeding. Epilepsy Behav 2004; 5(1):10
143. Loiseau P, Yuen AWC, Duche B, et al: A randomised double-blind placebo-controlled crossover add-on trial of lam
seizures. Epilepsy Res 1990; 7:136-145.
144. Lombroso CT: Lamotrigine-induced tourettism. Neurology 1999; 52:1191-1194.
145. Lorberg B, Youssef NA, & Bhagwagar Z: Lamotrigine-associated rash: to rechallenge or not to rechallenge?. intern
scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP) 2009; 12(2):257-265.
146. Lunardi G, Leandri M, Albano C, et al: Clinical effectiveness of lamotrigine and plasma levels in essential and symp
1717.
147. Malik K, Rizvi S, & Vaillancourt PD: The SUNCT syndrome: successfully treated with lamotrigine. Am Acad Pain M
148. Martin R, Kuzniecky R, Ho S, et al: Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young ac
149. Martin R, Kuzniecky R, Ho S, et al: Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young ac
150. Matsuo F, Bergen D, Faught E, et al: Placebo-controlled study of the efficacy and safety of lamotrigine in patients w
151. Matsuo F, Bergen D, Faught E, et al: Placebo-controlled study of the efficacy and safety of lamotrigine in patients w
152. Matsuo F, Bergen D, Faught E, et al: Placebo-controlled study of the efficacy and safety of lamotrigine in patients w
153. Mattson RH: Medical management of epilepsy in adults. Neurology 1998; 51(suppl 4):S15-S20.
154. May TW, Rambeck B, & Jurgens U: Influence of oxcarbazepine and methsuximide on lamotrigine concentrations in
comedication: results of a retrospective study. Ther Drug Monit 1999; 21:175-181.
155. May TW, Rambeck B, & Jurgens U: Influence of oxcarbazepine and methsuximide on lamotrigine concentrations in
comedication: results of a retrospective study. Ther Drug Monit 1999a; 21:175-181.
156. May TW, Rambeck B, & Jurgens U: Influence of oxcarbazepine and methsuximide on lamotrigine concentrations in
comedication: results of a retrospective study. Ther Drug Monit 1999b; 21:175-181.
157. May TW, Rambeck B, & Jurgens U: Influence of oxcarbazepine and methsuximide on lamotrigine concentrations in
comedication: results of a retrospective study. Ther Drug Monit 1999c; 21:175-181.
158. McCleane G: 200 mg daily of lamotrigine has no analgesic effect in neuropathic pain: a randomised, double-blind,
159. McGeer EG & Zhu SG: Lamotrigine protects against kainate but not ibotenate lesions in rat striatum. Neurosci Lett
160. Meldrum BS: Excitatory amino acid transmitters in epilepsy. Epilepsia 1991; 32(suppl 2):S1-S3.
161. Merideth CH: A single-center, double-blind, placebo-controlled evaluation of lamotrigine in the treatment of obesity
162. Messenheimer J, Mullens EL, Giorgi L, et al: Safety review of adult clinical trial experience with lamotrigine. Drug S

163. Messenheimer J, Ramsay RE, Willmore LJ, et al: Lamotrigine therapy for partial seizures: a multicenter, placebo-co 35(1):113-21.
164. Messenheimer JA, Giorgi L, & Risner ME: The tolerability of lamotrigine in children. Drug Saf 2000; 22(4):303-312.
165. Mewasingh L, Aylett S, Kirkham F, et al: Hyponatraemia associated with lamotrigine in cranial diabetes insipidus (le
166. Miaskowski, C: Guideline for the Management of Cancer Pain in Adults and Children. American Pain Society. Glen http://www.guideline.gov/summary/pdf.aspx?doc_id=7297&stat=1&string=.
167. Mikati MA, Fayad M, Koleilat M, et al: Efficacy, tolerability, and kinetics of lamotrigine in infants. J Pediatr 2002; 141
168. Mikati MA, Schachter SC, Schomer DL, et al: Long-term tolerability, pharmacokinetic and preliminary efficacy study Clin Neuropharmacol 1989; 12:312-321.
169. Mikati MA, Schachter SC, Schomer DL, et al: Long-term tolerability, pharmacokinetic and preliminary efficacy study Clin Neuropharmacol 1989a; 12:312-321.
170. Mikati MA, Schachter SC, Schomer DL, et al: Long-term tolerability, pharmacokinetic and preliminary efficacy study Clin Neuropharmacol 1989b; 12:312-321.
171. Mims J: Compassionate plea use of lamotrigine in children with incapacitating and/or life-threatening epilepsy (Abst
172. Moeller KE, Wei L, Jewell AD, et al: Acute hepatotoxicity associated with lamotrigine. Am J Psychiatry 2008; 165(4)
173. Morrell MJ: The new antiepileptic drugs and women: efficacy, reproductive health, pregnancy and fetal outcome. Ep
174. Morris R, Black A, Lam E, et al: Clinical study of lamotrigine and valproic acid in patients with epilepsy: using a drug 22:656-660.
175. Motte J, Trevathan E, Arvidsson JFV, et al: Lamotrigine for generalized seizures associated with the Lennox-Gasta
176. Nasr A & Brown N: Palatal myoclonus responding to lamotrigine. Seizure 2002; 11:136-137.
177. National Comprehensive Cancer Network: Adult Cancer Pain V.1.2008. National Comprehensive Cancer Network. http://www.nccn.org/professionals/physician_gls/PDF/pain.pdf.
178. Newall CA, Anderson LA, & Phillipson JDNewall CA, Anderson LA, & Phillipson JD (Eds): Herbal Medicines: A Gui Press, London, England, 1996.
179. Newport DJ, Pennell PB, Calamaras MR, et al: Lamotrigine in breast milk and nursing infants: determination of exp
180. Nicholson RJ, Kelly KP, & Grant IS: Leukopenia associated with lamotrigine. Br Med J 1995; 310:504.
181. O'Donnell RA & Miller AA: The effect of lamotrigine upon development of cortical kindled seizures in the rat. Neurop
182. O'Donohoe NV: Use of antiepileptic drugs in childhood epilepsy. Arch Dis Child 1991; 66:1173-1179.
183. O'Neill A & deLeon J: Two case reports of oral ulcers with lamotrigine several weeks after oxcarbazepine withdrawa
184. Ohman I & Vitols S: Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactatic
185. Oller LFV: Lamotrigine in the Lennox-Gastaut Syndrome (Abstract). Epilepsia 1991; 32(suppl 1):58.
186. Overstreet K, Costanza C, Behling C, et al: Fatal progessive hepatic necrosis associated with lamotrigine treatmen 47(9):1921-1925.
187. Page II RL, O'Neil MG, Yarbrough III DR, et al: Fatal toxic epidermal necrolysis related to lamotrigine administration
188. Page II RL, O'Neil MG, Yarbrough III DR, et al: Fatal toxic epidermal necrolysis related to lamotrigine administration
189. Page RL II, O'Neil MG, Yarbrough DR III, et al: Fatal toxic epidermal necrolysis related to lamotrigine administration
190. Page-Sharp M, Kristensen JH, Hackett LP, et al: Transfer of lamotrigine into breast milk. Ann Pharmacother 2006;
191. Parmeggiani L, Belmonte A, Ferrari AR, et al: Add-on lamotrigine treatment in children and young adults with sever study. J Child Neurol 2000; 15:671-674.
192. Pathak P & McLachlan RS: Drug-induced pseudolymphoma secondary to lamotrigine. Neurology 1998; 50:1509-15
193. Peck AW: Clinical pharmacology of lamotrigine. Epilepsia 1991; 32(suppl 2):S9-S12.
194. Peck AW: Clinical pharmacology of lamotrigine. Epilepsia 1991a; 32(suppl 2):S9-S12.
195. Peck AW: Clinical pharmacology of lamotrigine. Epilepsia 1991b; 32(suppl 2):S9-S12.
196. Peck AW: Clinical pharmacology of lamotrigine. Epilepsia 1991c; 32(suppl 2):S9-S12.
197. Peck AW: Clinical pharmacology of lamotrigine. Epilepsia 1991d; 32(suppl 2):S9-S12.
198. Peck AW: Clinical pharmacology of lamotrigine. Epilepsia 1991e; 32(suppl 2):S9-S12.
199. Perucca E: The clinical pharmacology of the new antiepileptic drugs. Pharmacol Res 1993; 28:89-106.
200. Pisani F, Gallitto G, & Di Perri R: Could lamotrigine be useful in status epilepticus? A case report (letter). J Neurol,
201. Pisani F, Xiao B, Faxio A, et al: Single dose pharmacokinetics of carbamazepine-10,11-epoxide in patients on lamo
202. Pons G: Pharmacokinetics of lamotrigine in young epileptic children (abstract). Epilepsia 1993; 34(suppl 2):168.
203. Porter RJ: Mechanisms of action of new antiepileptic drugs. Epilepsia 1989; 30(suppl 1):S29-S34.
204. Posner J, Cohen AF, Land G, et al: The pharmacokinetics of lamotrigine (BW430C) in healthy subjects with unconj Clin Pharmacol 1989a; 28:117-120.
205. Posner J, Cohen AF, Land G, et al: The pharmacokinetics of lamotrigine (BW430C) in healthy subjects with unconj Clin Pharmacol 1989; 28:117-120.
206. Posner J, Holdich T, & Crome P: Comparison of lamotrigine pharmacokinetics in young and elderly healthy volunte
207. Posner J, Holdich T, & Crome P: Comparison of lamotrigine pharmacokinetics in young and elderly healthy volunte
208. Preda A, Fazeli A, McKay BG, et al: Lamotrigine as prophylaxis against steroid-induced mania. J Clin Psychiatry 19
209. Product Information: BANZEL(TM) oral tablets, rufinamide oral tablets. Novartis Pharma AG, Woodcliff Lake, NJ, 2
210. Product Information: Cerebyx(R), fosphenytoin sodium injection. Parke-Davis, Division of Warner-Lambert, Morris P
211. Product Information: Depakote(R) ER, divalproex sodium extended-release tablets. Abbott Laboratories, North Chi
212. Product Information: LAMICTAL XR oral extended-release tablets, lamotrigine oral extended-release tablets. Glaxo
213. Product Information: LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, lamotrig disintegrating tablets. GlaxoSmithKline, Research Triangle Park, NC, 2009.
214. Product Information: LAMICTAL(R) chewable dispersible oral tablets, oral tablets, lamotrigine chewable dispersible Triangle Park, NC, 2009.
215. Product Information: LAMICTAL(R) oral tablets, lamotrigine oral tablets. GlaxoSmithKline, Research Triangle Park,
216. Product Information: LAMICTAL(R) oral tablets, chewable dispersible oral tablets, lamotrigine oral tablets chewable

Triangle Park, NC, 2006.
217. Product Information: LAMICTAL(R) oral tablets, chewable dispersible oral tablets, lamotrigine oral tablets chewable Triangle Park, NC, 2007.
218. Product Information: Lamictal(R), lamotrigine. Glaxo Wellcome Inc., Research Triangle Park, NC, 2003a.
219. Product Information: Lamictal(R), lamotrigine. GlaxoSmithKline, Research Triangle Park, NC, 2003.
220. Product Information: Lamictal(R), lamotrigine. GlaxoSmithKline, Research Triangle Park, NC, 2003b.
221. Product Information: Lamictal(R), lamotrigine. GlaxoSmithKline, Research Triangle Park, NC, 2003c.
222. Product Information: Lamictal(R), lamotrigine. GlaxoSmithKline, Research Triangle Park, NC, 2003d.
223. Product Information: Lamictal(R), lamotrigine. GlaxoSmithKline, Research Triangle Park, NC, 2003f.
224. Product Information: Lamictal(R), lamotrigine. GlaxoSmithKline, Research Triangle Park, NC, 2003g.
225. Product Information: Lamictal(R), lamotrigine. GlaxoSmithKline, Research Triangle Park, NC, 2004.
226. Product Information: Lamictal(R), lamotrigine. GlaxoSmithKline., Research Triangle Park, NC, 2003e.
227. Product Information: Lamictal. Burroughs Wellcome, Canada, 94.
228. Product Information: Lamictal. GlaxoWellcome, Canada, 97.
229. Product Information: NORVIR(R) oral capsules, solution, ritonavir oral capsules, solution. Abbott Laboratories, Nort
230. Product Information: ORTHO EVRA(R) transdermal system patch, norelgestromin/ethinyl estradiol transdermal sys Inc., Raritan, NJ, 2008.
231. Product Information: lamotrigine oral tablets, lamotrigine oral tablets. Teva Pharmaceuticals USA, Sellersville, PA,
232. Pulik M, Lionnet F, & Genet P: Successful treatment of lamotrigine-induced erythroblastopenic crisis with folinic aci
233. Ramasubbu R: Lamotrigine treatment for post-stroke pathological laughing and crying. Clin Neuropharmacol 2003;
234. Rambeck B & Wolf P: Lamotrigine clinical pharmacokinetics. Clin Pharmacokinet 1993; 25:433-443.
235. Rambeck B & Wolf P: Lamotrigine clinical pharmacokinetics.. Clin Pharmacokinet 1993a; 25(6):433-43.
236. Ramsay RE, McManus DQ, Guterman A, et al: Carbamazepine metabolism in humans: effect of concurrent anticor
237. Ramsay RE, McManus DQ, Guterman A, et al: Carbamazepine metabolism in humans: effect of concurrent anticor
238. Ramsay RE, McManus DQ, Guterman A, et al: Carbamazepine metabolism in humans: effect of concurrent anticor
239. Ramsay RE, Pellock JM, Garnett WR, et al: Pharmacokinetics and safety of lamotrigine (Lamictal) in patients with e
240. Ramsay RE, Pellock JM, Garnett WR, et al: Pharmacokinetics and safety of lamotrigine (Lamictal) in patients with e
241. Rao RD, Flynn PJ, Sloan JA, et al: Efficacy of lamotrigine in the management of chemotherapy-induced peripheral placebo-controlled trial, N01C3. Cancer 2008; 112(12):2802-2808.
242. Reutens DC, Duncan JS, & Patsalos PN: Disabling tremor after lamotrigine with sodium valproate. Lancet 1993; 34
243. Reviewer comment, 11/22/95.
244. Reviewer responses to Panel Review of 7/95.. ., .
245. Reynolds JEF (ed): Martindale: The Extra Pharmacopoeia (electronic version). Micromedex, Inc. Denver, CO. 1993
246. Robillard M & Conn DK: Lamotrigine use in geriatric patients with bipolar depression. Can J Psychiatry 2002; 47(8)
247. Rocha FL & Hara C: Lamotrigine augmentation in unipolar depression. Int Clin Psychopharmacol 2003; 18(2):97-99
248. Rosenhagen MC, Schmidt U, Weber F, et al: Combination therapy of lamotrigine and escitalopram may cause myo
249. Rzany B, Correia O, Kelly JP, et al: Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first v Lancet 1999; 353:2190-2194.
250. Saba G, Dumortier G, Kalalou K, et al: Lamotrigine-clozapine combination in refractory schizophrenia: three cases
251. Sabers A, Buchholt J, Uldall P, et al: Lamotrigine plasma levels reduced by oral contraceptives. Epilepsy Res 2001
252. Sabers A, Ohman I, Christensen J, et al: Oral contraceptives reduce lamotrigine plasma levels. Neurology 2003; 61
253. Sachs B, Ronnau AC, Ruzicka T, et al: Lamotrigine and toxic epidermal necrolysis (letter). Lancet 1996; 348:1597.
254. Sallustio BC & Morris RG: High-performance liquid chromatography quantitation of plasma lamotrigine concentratic patients with epilepsy. Ther Drug Monit 1997; 19:688-693.
255. Sarris BM & Wong JG: Multisystem hypersensitivity reaction to lamotrigine. Neurology 1999; 53:1367.
256. Sauve G, Bresson-Hadni S, Prost P, et al: Acute hepatitis after lamotrigine administration. Dig Dis Sci 2000; 45(9):1
257. Schapel GJ, Dollman W, Beran RG, et al: No effect of lamotrigine on carbamazepine and carbamazepine-epoxide 1):58.
258. Schaub JEM, Williamson PJ, & Barnes EW: Multisystem adverse reaction to lamotrigine. Lancet 1994; 344:481.
259. Schindler F & Anghelescu IG: Lithium versus lamotrigine augmentation in treatment resistant unipolar depression: Psychopharmacol 2007; 22(3):179-182.
260. Schlienger RG, Knowles SR, & Shear NH: Lamotrigine-associated anticonvulsant hypersensitivity syndrome. Neuro
261. Shinotoh H, Vingerhoets FJG, Lee CS, et al: Lamotrigine trial in idiopathic parkinsonism: a double-blind, placebo-co 1285.
262. Sierra M, Phillips M, Ivin G, et al: A placebo-controlled, cross-over trial of lamotrigine in depersonalization disorder.
263. Simpson DM, McArthur JC, Olney R, et al: Lamotrigene for HIV-associated painful sensory neuropathies. Neurolog
264. Simpson JJ, Gilbert AM, Weiner GM, et al: The assessment of lamotrigine, an antiepileptic drug, in the treatment of
265. Spina E, Pisani F, & Perucca E: Clinically significant pharmacokinetic drug interactions with carbamazepine: An up
266. Spina E, Pisani F, & Perucca E: Clinically significant pharmacokinetic drug interactions with carbamazepine: An up
267. Spina E, Pisani F, & Perucca E: Clinically significant pharmacokinetic drug interactions with carbamazepine: An up
268. Steiner TJ, Findley LJ, & Yuen AWC: Lamotrigine versus placebo in the prophylaxis of migraine with and without au
269. Tiihonen J, Hallikainen T, & Ryynanen O: Lamotrigine in treatment-resistant schizophrenia: a randomized placebo- 54:1241-1248.
270. Tomson T & Battino D: Pharmacokinetics and therapeutic drug monitoring of newer antiepileptic drugs during pregr (3):209-219.
271. Tran TA, Leppik IE, Blesi K, et al: Lamotrigine clearance during pregnancy. Neurology 2002; 59:251-255.
272. Tran TA, Leppik IE, Blesi K, et al: Lamotrigine clearance during pregnancy. Neurology 2002a; 59:251-255.
273. Trevathan E, Kerls SP, Hammer AE, et al: Lamotrigine adjunctive therapy among children and adolescents with pri

118(2):e371-e378.
274. US Food and Drug Administration: Information for Healthcare Professionals: lamotrigine (marketed as LAMICTAL(R
2006. Available from URL: http://www.fda.gov/cder/drug/InfoSheets/HCP/lamotrigineHCP.htm.
275. US Food and Drug Administration: Information for healthcare professionals suicidality and antiepileptic drugs. US F
Available from URL: http://www.fda.gov/cder/drug/InfoSheets/HCP/antiepilepticsHCP.htm.
276. Uberall MA & Wenzel D: Effectiveness of lamotrigine in children with paroxysmal kinesigenic choreoathetosis. Dev
277. Uher R & Jones HM: Hallucinations during lamotrigine treatment of bipolar disorder. Am J Psychiatry 2006; 163(4):
278. Van Dyke DC, Berg MJ, & Olson CH: Differences in phenytoin biotransformation and susceptibility to congenital ma
25:987-992.
279. Van Dyke DC, Berg MJ, & Olson CH: Differences in phenytoin biotransformation and susceptibility to congenital ma
25:987-992.
280. Van Dyke DC, Berg MJ, & Olson CH: Differences in phenytoin biotransformation and susceptibility to congenital ma
25:987-992.
281. Verma A, Miller P, Carwile ST, et al: Lamotrigine-induced blepharospasm. Pharmacotherapy 1999; 19(7):877-880.
282. Vestergaard K, Andersen G, Gottrup H, et al: Lamotrigine for central poststroke pain; a randomized controlled trial.
283. Vukelic D, Bozinovic D, Tesovic G, et al: Lamotrigine and toxic epidermal necrolysis. Dermatology 1997; 195:307.
284. Wadelius M, Karlsson T, Wadelius C, et al: Lamotrigine and toxic epidermal necrolysis. Lancet 1996; 348:1041.
285. Warner T, Patsalos PN, Prevett M, et al: Lamotrigine-induced carbamazepine toxicity: an interaction with carbamaz
286. Wheatley PL & Miller AA: Effects of lamotrigine on electrically induced afterdischarge duration in anaesthetised rat,
287. Wilton LV, Pearce GL, Martin RM, et al: The outcomes of pregnancy in women exposed to newly marketed drugs ir
1998; 105:882-889.
288. Wolf P: Lamotrigine: preliminary clinical observations on pharmacokinetics and interactions with traditional antiepile
289. Wong ICK, Mawer GE, & Sander JW: Factors influencing the incidence of lamotrigine-related skin rash. Ann Pharm
290. Wootton R, Soul-Lawton J, Rolan PE, et al: Comparison of the pharmacokinetics of lamotrigine in patients with chro
Pharmacol 1997; 43:23-27.
291. Yagi M, Wada K, Sakata M, et al: Studies on the constituents of edible and medicinal plants. IV. Determination of 4
nan food poisoning. Yakugaku Zasshi 1993; 113:596-99.
292. Yagi M, Wada K, Sakata M, et al: Studies on the constituents of edible and medicinal plants. IV. Determination of 4
nan food poisoning. Yakugaku Zasshi 1993a; 113:596-599.
293. Yuen AWC: Lamotrigine (Lamictal) as add-on therapy in pediatric patients with treatment-resistant epilepsy: an ove
294. Zakrzewska JM, Chaudhry Z, Nurmikko TJ, et al: Lamotrigine (Lamictal) in refractory trigeminal neuralgia: results fr
Pain 1997; 73:223-230.
295. vanderLee MJ, Dawood L, terHofstede HJ, et al: Lopinavir/ritonavir reduces lamotrigine plasma concentrations in h
168.

Last Modified: June 25, 2009