**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

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 tat
            2) Extended-release tablets must be swallowed whole with liquid, do not chew, divide, or crush (Prod Inl
   B) Oral route
      1) Tablet, Extended Release
         a) Store paliperidone extended-release tablets at 25 degrees Celsius (77 degrees Fahrenheit), with excursio

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 in intervals of at least 5 days, to a maximum of 12 mg/day. In some patients, a lower starting dose of 3 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 dose is 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 paliperidone administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacokinetic study (Vermeir et al, 2008). 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 kg) with a mean body mass index of 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 extensive CYP2D6 metabolizers. Nor was there a difference in Cmax and the genotypic expression of UGT1A1 and UGT1A6 metabolizing enzymes (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 (Prod Info INVEGA(TM) 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 administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacokinetic 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, 73.38 kg) with a mean body mass index of 25.5 kg/m(2) (range, 24 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-state 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-label 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, 73.38 kg) with a 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 infinity) between the 2 poor and 3 extensive CYP2D6 metabolizers. Nor was there a difference in AUC and the genotypic expression 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 renal function due to reduced clearance. Following a 9-mg dose of paliperidone extended-release, there was a 1.5-fold increase in drug exposure among patients with renal impairment due to reduced clearance. Following a 9-mg/m(2) dose of paliperidone extended-release, there was a 1.5-fold increase in drug exposure among patients with renal impairment (Creatinine clearance (CrCl) 50 to less than 80 milliliters/minute (mL/min)); a 2.6-fold increase among those with moderate renal impairment (CrCl 30 to less than 50 mL/min); and a 4.8-fold increase among those with severe renal impairment (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(TM) extended-release 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 INVEGA(TM) extended-release oral tablets, 2006)
      a) After administration of paliperidone extended-release 12 milligrams to healthy ambulatory individuals, a 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) extended-release 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 oral tablets, 2006).
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-release oral tablets, 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) 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 to INVEGA(TM) extended-release oral tablets, 2006).
   b) There were 4 primary metabolic pathways identified in vivo, each accounting for no more than 10% of 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, caucasian, male 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(2)).
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 pharmacokinetic 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, 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 4.55% (standard deviation, +/-1.42%) of 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 paliperidone solution administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacokinetic 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, 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 3.75% (standard deviation, +/-1.42%) of excreted in the urine as M1 metabolite. The detection of M9 was in the urine of extensive 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 single, 1-mg dose solution administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacokinetic 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, 73.38 kg) with a mean body mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m(2)). M10 was excreted in the feces (Vermeir et al, 2008).
   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 pharmacokinetic 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, 73.38 kg) with a mean body mass index of 25.5 kg/m(2) (range, 24 to 28 kg/m(2)). M11 was excreted in the feces (Vermeir et al, 2008).
solution administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacoerinetic 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, 73.38 kg/m²) (range, 24 to 28 kg/m²)). M11 was excreted in the feces (Vermeir et al, 2008).

5) M12 (Vermeir et al, 2008)
   a) The pathways for paliperidone to M12 formation was alcohol dehydrogenation and also nonenzymatic metabolism. The 1-mg dose of paliperidone solution administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacokinetic 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, 73.38 kg) with a mean body mass index of 25.5 kg/m² (range, 24 to 28 kg/m²)). A mean of 2.7% (standard 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 paliperidone administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacokinetic 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, 73.38 kg) with a mean body mass index of 25.5 kg/m² (range, 24 to 28 kg/m²)). A mean of 4.06% (standard deviation, +/-1.03%) of the dose was 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 solution administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacokinetic 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, 73.38 kg) with a mean body mass index of 25.5 kg/m² (range, 24 to 28 kg/m²)). The mean clearances (standard deviation) were as follow: a) 113 +/- 10.3 mL/min, glomerular filtration rate, 25.9 +/- 2.36 mL/min; and active renal clearance, 27.3 mL/min (Vermeir et al, 2008).

   2) Renal Excretion (%)
      a) 59% (range, 51% to 67%) unchanged (Vermeir et al, 2008; Prod Info INVEGA(TM) extended-release oral tablets, 2006).
         1) One week following administration of a single oral dose of immediate-release radioactive-paliperidone to 5 healthy volunteers, 59% (range, 51% to 67%) of the dose was excreted into the urine unchanged from 26% to 41% was recovered as metabolites, 6% to 12% of the dose was not recovered (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

   2) The mean total dose excreted in the urine was 59.4% (standard deviation +/- 7.12%) after a single, 1-mg dose of paliperidone solution administered to healthy, caucasian, male volunteers in the fasted state, in an open-label 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) with a mean body mass index of 73.38 kg (range, 24 to 28 kg/m²) with a mean body mass index of 25.5 kg/m² (range, 24 to 28 kg/m²).

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 extensive 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 clearance was reduced with decreasing estimated creatinine clearance (CrCl). Following administration of a 3-milligram dose of paliperidone extended release, there was a 32% reduction in patients with mild renal impairment (CrCl 50 to less than 80 milliliters/minute (mL/min)); a 64% reduction in patients with moderate renal impairment (CrCl 30 to less than 50 mL/min) to a 71% reduction in patients with severe renal impairment (CrCl 10 to less than 30 mL/min) (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

      b) The mean total plasma clearance was 91 +/- 15 mL/min after a single, 1-mg dose of paliperidone solution administered to healthy, caucasian, male volunteers in the fasted state, in an open-label pharmacokinetic 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, 73.38 kg) with a mean body mass index of 25.5 kg/m² (range, 24 to 28 kg/m²) (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 mean terminal elimination half-life of paliperidone is approximately 23 hours (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
      b) renal impairment, 24 hours to 51 hours
         a) The mean terminal elimination half-lives of paliperidone following administration of a 3-milligram dose administered to 24 hours, 40 hours, and 51 hours among individuals with mild (creatinine clearance 50 to less than 80 milliliters/minute (mL/min)); moderate renal impairment (CrCl 30 to less than 50 mL/min) to severe 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-related psychosis (unapproved use); increased risk of death; most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia) (Prod Info INVEGA(R) extended-release oral tablets, 2008)
   b) bradycardia; increased risk of torsade de pointes and/or sudden death (Prod Info INVEGA(R) extended-release oral tablets, 2008)
   c) cardiac arrhythmias; use should be avoided due to risk of prolonged QT interval (Prod Info INVEGA(R) extended-release oral tablets, 2008)
   d) cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (eg, dehydrations, antihypertensive medications); increased risk of orthostatic hypotension and syncope (Prod Info INVEGA(R) extended-release oral tablets, 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, chlorpromazine) 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, dehydration); may disrupt body temperature regulation (Prod Info INVEGA(R) extended-release oral tablets, 2008)
   g) congenital long QT syndrome; increased risk of torsade de pointes and/or sudden death (Prod Info INVEGA(R) extended-release oral tablets, 2008)
   h) diabetes mellitus or risk factors for diabetes mellitus; increased risk of severe hyperglycemia; monitor blood glucose (R) extended-release oral tablets, 2008)
   i) elderly patients, especially elderly women are at increased risk of tardive dyskinesia (Prod Info INVEGA(R) extended-release oral tablets, 2008)
   j) esophageal dysmotility and aspiration may occur; use cautiously in patients at risk for aspiration pneumonia (Prod Info INVEGA(R) extended-release oral tablets, 2008)
   k) gastrointestinal narrowing, severe (eg, esophageal motility disorders, small bowel inflammatory disease, short gut syndrome); increased risk of fatal intestinal perforation, peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's divertisium (Prod Info INVEGA(R) extended-release oral tablets, 2008)
   l) hyperglycemia (some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death) is a risk (Prod Info INVEGA(R) extended-release oral tablets, 2008)
   m) hypokalemia or hypomagnesemia; increased risk of torsade de pointes and/or sudden death (Prod Info INVEGA(R) extended-release oral tablets, 2008)
   n) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info INVEGA(R) extended-release oral tablets, 2008)
   o) neuroleptic malignant syndrome, potentially fatal, has been reported in association with antipsychotic drugs; immediate withdrawal of the 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 INVEGA(R) extended-release oral tablets, 2008)
   q) seizure disorder, history, or conditions that lower the seizure threshold (Prod Info INVEGA(R) extended-release oral tablets, 2008)
   r) suicide risk (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 oral tablets, 2008)

3.2 Precautions

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

B) bradycardia; increased risk of torsade de pointes and/or sudden death (Prod Info INVEGA(R) extended-release oral tablets, 2008)

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

D) cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (eg, dehydrations, antihypertensive medications); increased risk of orthostatic hypotension and syncope (Prod Info INVEGA(R) extended-release oral tablets, 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, chlorpromazine) 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, dehydration); may disrupt body temperature regulation (Prod Info INVEGA(R) extended-release oral tablets, 2008)

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

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

I) elderly patients, especially elderly women are at increased risk of tardive dyskinesia (Prod Info INVEGA(R) extended-release oral tablets, 2008)

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

K) gastrointestinal narrowing, severe (eg, esophageal motility disorders, small bowel inflammatory disease, short gut syndrome); increased risk of fatal intestinal perforation, peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's divertisium (Prod Info INVEGA(R) extended-release oral tablets, 2008)

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

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

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

O) neuroleptic malignant syndrome, potentially fatal, has been reported in association with antipsychotic drugs; immediate withdrawal of the 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 INVEGA(R) extended-release oral tablets, 2008)

Q) seizure disorder, history, or conditions that lower the seizure threshold (Prod Info INVEGA(R) extended-release oral tablets, 2008)

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 taking paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=2,720); however, causal relationship to paliperidone has not 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 was 0% (0/38) in patients receiving paliperidone extended-release (ER), compared with 0% (0/30) in patients receiving placebo. The study included 114 patients (mean age: 76 years) with 99% having moderate to severe schizophrenia, receiving either placebo or median mean dose of paliperidone ER 7.4 mg and 8.5 mg in placebo/paliperidone ER and paliperidone ER/paliperidone ER groups, respectively, during the open-label phase.

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 with paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=2,720); however, causal relationship to paliperidone has not been determined (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
3.3.3.1D **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% of patients receiving paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 1% in placebo-treated patients. The incidence of orthostatic hypotension increased with the dose, occurring particularly at the 9-mg and 12-mg doses of paliperidone 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 hypotension was 3% (3/76) in patients receiving paliperidone extended-release (ER), compared with 0% (0/38) in patients receiving placebo according to a prospective, 6-week, double-blind, randomized, placebo-controlled, optional 24-week open-label extension safety trial. In general, paliperidone ER was well tolerated in the geriatric population compared with placebo.

3.3.3.1E **Prolonged QT interval**

1) Incidence: 3% to 7% (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 placebo-treated patients (Prod Info INVEGA(TM) extended-release oral tablets, 2006). Among ECG measurements taken during these trials, a change in QTc interval exceeding 60 milliseconds occurred only in 1 subject in the 12-mg group. Overall, none of the subjects had a QTc interval exceeding 50 milliseconds at the 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 electrocardiographic prolongation of QTc interval 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, optional open-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 compared to 3% in placebo. Numbers from measurements taken during these trials, a change in QTc interval exceeding 60 milliseconds occurred only in 1 subject in the 12-mg group. Overall, none of the subjects had a QTc interval exceeding 50 milliseconds at the time point (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3.3.3.1F **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 patients receiving paliperidone extended-release (ER), compared with 0% (0/38) in patients receiving placebo according to a prospective, 6-week, double-blind, randomized, placebo-controlled, optional 24-week open-label extension safety trial. Tachyarrhythmia occurred only in 2 subjects in the 12-mg group. Overall, none of the subjects had a tachyarrhythmia.

3) Geriatric

   a) During the double-blind phase of a safety trial in 114 geriatric patients, the incidence of tachyarrhythmia was 7% (5/76) in patients receiving paliperidone extended-release (ER), compared with 0% (0/38) in patients receiving placebo. The study included 114 patients (mean age of 70 years), with 99% having moderate to severe schizophrenia, receiving either placebo or median mean dose of paliperidone ER 8.4 milligrams/day (mg/day) during the double-blind phase and median mean doses of 7.4 mg and 8.5 mg in the placebo/paliperidone ER and paliperidone ER/paliperidone ER groups, respectively, during the open-label phase (Tzimos et al, 2008).

3.3.3.1G **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 was 13% (4/30) in patients receiving placebo, and was 16% in patients continuing with paliperidone ER treatment from the double-blind phase. During the open-label phase, the incidence of tachycardia was 10% (6/58) in patients continuing with paliperidone ER treatment from the double-blind phase. Prolonged QTcB prolongation of 500 milliseconds or greater led to discontinuation of paliperidone ER. In general, paliperidone ER was well tolerated in the geriatric population compared with placebo.

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 childbearing potential, postmenopausal women, and men, respectively, in an open-label, clinical trial of patients treated with first-generation antipsychotics (ie, chlorpromazine, droperidol, flupenthixol, fluphenazine, 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 hyperprolactinemia following treatment with higher doses of these antipsychotics. Hyperprolactinemia may potentially result in sexual dysfunction, bone mineral density (ie, osteopenia and osteoporosis), and breast and pituitary tumors (Tzimos et al, 2008).

3) Geriatric
   a) During the double-blind phase of a safety trial in 114 geriatric patients, the incidence of increased prolactin levels in male patients and 49% in female patients receiving paliperidone extended-release (ER), according to a double-blind, randomized, placebo-controlled, optional 24-week open-label extension safety trial. The mean dose was 75.3 +/- 10.8 nanograms/mL in females and 27.2 +/- 8.7 nanograms/mL in males. During the open-label phase, prolactin levels increased in patients switched to paliperidone ER from placebo, and was stable for patients continuing ER treatment from the double-blind phase. In general, paliperidone ER was well tolerated in the geriatric population. 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 mg/day during the double-blind phase. The incidence of weight gain increased with the dose, particularly at the 9-mg and 12-mg doses of 7.4 mg and 8.5 mg in the placebo/paliperidone ER and paliperidone ER/paliperidone ER groups, respectively (Tzimos et al, 2008).

4) Management
   a) Appropriate drug selection, monitoring and management are all important when prescribing antipsychotic agents to prevent hyperprolactinemia. Prior to treatment with an antipsychotic, question patients regarding the potential for inducing hyperprolactinemia. Female patients should be assessed for menstrual abnormalities and male patients, for galactorrhea. Female patients should be informed of the potential for sexual dysfunction with antipsychotic use. Several weeks after an antipsychotic is started, obtain a prolactin level measurement. In cases where the patient experiences troublesome adverse effects, discontinuing the antipsychotic is not an option, treatment with a dopamine agonist (eg, 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 was observed in 9% of patients treated with paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 1% in placebo-treated patients (n=355). The incidence of weight gain increased with the dose, particularly at the 9-mg and 12-mg doses (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

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% of patients treated with paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 1% in placebo-treated patients (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 treated with paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 1% in placebo-treated patients (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 treated with paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=2,720); however, causal relationship to paliperidone has not 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 treated with paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=2,720); however, causal relationship to paliperidone has not been 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 treated with paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 4% in placebo-treated patients. The incidence of akathisia increased with the dose, occurring particularly at the 9-mg and 12-mg doses (Prod Info INVEGA(TM) 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. In a prospective, 6-week, double-blind, randomized, placebo-controlled, optional 24-week open-label extension of the open-label phase, the incidence of dizziness was 3% (1/30) of patients switched to paliperidone ER from placebo, compared to 10% (6/58) in patients continuing with paliperidone ER treatment from the double-blind phase. In general, dizziness was well tolerated in the geriatric population compared with placebo. The study included 114 patients (mean age 99 years) having moderate to severe schizophrenia, receiving either placebo or median mean dose of paliperidone 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-label phase (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 treated with paliperidone doses ranging from 3 mg to 12 mg orally once daily (n=850) compared to 1% in placebo-treated patients. 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, 2008b). 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 may occur with a greater severity with high potency and at higher doses of first generation antipsychotic medications. Younger age groups appear to be at greater risk for developing acute dystonia (Prod Info INVEGA(R) extended-release oral tablets, 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, dystonia, bradykinesia, cogwheel rigidity, drooling, and
involved bradykinesia, cogwheel rigidity, drooling, hypertonia, muscle rigidity, and musculoskeletal
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 patients
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 patients
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 pl
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 paliperidon 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
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 year
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/pal
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<
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 antipsychotics associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (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 t
with the use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared with antipsychotic medications. The analysis excluded patients with cancer and included only new users of antipsychotic medications. The primary study outcome was 180-day all-cause mortality. A set of potential confounders was measured by utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patient and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in the group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio 1.39 to 1.56). In the multi-variable analysis which controlled for potential confounders, the mortality ratio for the risk of death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.19 to 1.40). With doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression 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-release oral tablets, 2006).
   a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential risk to the fetus justifies the potential risk to the mother.

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. When generation antipsychotic drugs during the last trimester of pregnancy has been linked to extrapyramidal symptoms, it is unknown whether paliperidone could lead to similar neonatal effects. Until further data are available, it is recommended that paliperidone be used during pregnancy only if the potential benefits to the mother justifies the potential risk to the fetus.

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 with breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug to breastfeeding women.

2) Literature Reports
   a) Lactation studies with paliperidone have not been conducted in humans. In animal studies, paliperidone was excreted into human milk. Therefore, paliperidone recommended that women receiving paliperidone should not breast-feed infants (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Acecainide
Ajmaline
Amiodarone
Arsenic Trioxide
Azimilide
Bretyllium
Carbamazepine
Chlorpromazine
Disopyramide
Dofetilide
Gatifloxacin
Hydroquinidined
Ibutilide
Iloperidone
Lapatinib
Levodopa
Mesoridazine
Methadone
Moxifloxacin
Nilotinib
Paroxetine
Pirmenol
Prajmaline
Procainamide
Prochlorperazine
Ranolazine
Sematilide
Sotalol
Tedisamil
Tetrabenazine
Thioridazine
Trifluoperazine

3.5.1.A Aceainide
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 ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info Solotab tablets, 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) extended-release oral 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 should result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
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, haloperidone, quetiapine, risperidone, serindole, sulprofide, ziprasidone, and zotepine (Prod Info FANAPT(TM) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003). Due to the risk of additive QTc prolongation, 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 recommended (Prod Info Solian(R), 1999b; O'Brien et al, 1999b; Prod Info INVEGA(TM) extended-release oral tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of antipsychotics with a drug from this class is not recommended (TM oral tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and Class IA antiarrhythmics, the concurrent administration of antipsychotics with a drug from this class is not recommended (TM oral tablets, 2009; Prod Info Quinaglute(R), 1999).
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), iloperidone therapy 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 therapy (Norgren et al, 1997).
   c. The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Tc 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) were unchanged, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for these 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 ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info Solotab tablets, 2005). 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 should result in additive QTc interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
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 fibrillation, and torsades de pointes and should not be administered with other drugs that may prolong the QT interval. Several antipsychotics have demonstrated QT prolongation including amisulpride (O'Brien et al, 1999), haloperidol (O'Brien et al, 1999), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006; Prod Info CORDARONE(R) oral tablets, 2006; Prod Info Sola...
8) Literature Reports
   a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes
   or sudden heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL
   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 trioxide
   returned to baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluation, men experienced more pronounced QT prolongation than men, and there was no correlation with age (Prod

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 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, 2006).
   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 ventricul
   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, 2006).
   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 (Cmax) under the concentration-time curve (AUC) values of paliperidone by 37%. Coadministration with carbamazepine, could increase paliperidone renal clearance by 35%. The dose of paliperidone should be evaluated concurrently with carbamazepine. If therapy with carbamazepine is discontinued, the dose of paliperidone should be decreased if 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 paliperidone. 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(TM) extended-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 35% 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 Ctr 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), sulthiame (Lande et al, 1998), (Prod Info GEDON(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 phenothiazines, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.J 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, haloperidol, perphenazine, quetiapine, risperidone, sertindole, sulpiride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009a; Prod Info Quetiapine Oral Tablet, 2009b; Prod Info Sertindole Oral Tablet, 2009b; Prod Info Ziprasidone Oral Tablet, 2009b; Prod Info Zotepine Oral Tablet, 2009b). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info INVEGA(TM) extended-release oral tablets, 2006). Therefore, the concurrent administration of gatifloxacin and paliperidone should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006). Due to the risk of additive QTc prolongation, the concurrent administration of paliperidone and class III antiarrhythmic agents should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
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), iloperidone significantly increased the QTc interval (Prod Info FANAPT(TM) oral tablets, 2009).

3.5.1.K 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 ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info Sotalol Tablets, 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) extended-release oral 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 should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006). Therefore, the concurrent administration of gatifloxacin and paliperidone should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
7) Probable Mechanism: additive 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, haloperidol, perphenazine, quetiapine, risperidone, sertindole, sulpiride, ziprasidone, and zotepine (Prod Info FANAPT(TM) extended-release oral tablets, 2009). 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 1.7 ng/mL to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were unchanged, thereby suggesting that the authors that a tissue binding mechanism is more likely responsible for changes than an elimination alteration (Young et al, 1993).
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 inji
2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incr
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. It
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 f
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;
ventricular fibrillation, and torsades de pointes (Prod Info CORDARONE(R) oral tablets, 2006; Prod Info total
2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) t
ables, 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, 2006).
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 poir
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) li
iloperidone in patients with persistent QTc measurements greater than 500 msec (Prod Info FANAPT(TM) on
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 si
cardiovascular illness, eg, cardiac arrhythmia, QT prolongation, recent acute myocardial infarction, and unco
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 poir
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) li
TYKERB oral tablets, 2008). Thirteen patients had either QTcF (corrected QT by the Friedericia method) gre
an increase in QTcF of greater than 60 msec in an uncontrolled, open-label, dose escalation study in advan
(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
Onset: unspecified
Substantiation: theoretical
Clinical Management: Concomitant use of lapatinib and drugs that prolong the QT interval may result in an increased risk of torsade de pointes. Therefore, caution should be used when these agents are used concomitantly. Consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte levels (Prod Info TYKERB oral tablets, 2008).

Probable Mechanism: additive effects on the QT interval

3.5.1.P Levodopa
Interaction Effect: loss of levodopa efficacy
Summary: Because paliperidone is an antagonist with a high affinity for dopamine type 2 receptors, it is expected that paliperidone will have an additive effect to levodopa, which can result in loss of levodopa efficacy. Monitor patients for loss of levodopa efficacy.
Severity: moderate
Onset: unspecified
Substantiation: theoretical
Clinical Management: Concurrent use with paliperidone is expected to antagonize the effects of levodopa due to pharmacologic antagonism (Prod Info INVEGA(TM) extended-release oral tablets, 2006). Use caution if paliperidone is used concurrently in patients receiving levodopa.
Probable Mechanism: pharmacologic antagonism

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

3.5.1.R Methadone
Interaction Effect: an increased risk of QT interval prolongation
Summary: Cases of QT interval prolongation and serious arrhythmias, including torsade de pointes, have been associated with methadone use (Prod Info DOLOPHINE(R) HYDROCHLORIDE oral tablets, 2006). Treatment with paliperidone associated with QTc prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2006a). The coadministration of paliperidone and other drugs known to prolong the QTc interval, including methadone, should be avoided due to the risk of additive QT interval prolongation (Prod Info INVEGA(TM) extended-release oral tablets, 2006a).
Severity: major
Onset: unspecified
Substantiation: theoretical
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).
Probable Mechanism: additive effects on QT interval prolongation

3.5.1.S Moxifloxacin
Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
Summary: Moxifloxacin has been shown to prolong the QTc interval in some patients (Prod Info AVELOX(R) oral tablets, 2005). Modest increases in the QTc interval have been noted with paliperidone use (Prod Info INVEGA(TM) extended-release oral tablets, 2006a). Although pharmacokinetic studies between moxifloxacin and paliperidone have not excluded an additive effect, caution is advised. Therefore, the concurrent administration of moxifloxacin and paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006a) should be avoided due to the potential for additive effects on the QT interval.
Severity: major
Onset: unspecified
Substantiation: theoretical
Clinical Management: The concurrent administration of moxifloxacin and paliperidone should be avoided due to the potential for additive effects on the QT interval (Prod Info INVEGA(TM) extended-release oral tablets, 2006a).
Probable Mechanism: additive effects on QT prolongation

3.5.1.T Nilotinib
Interaction Effect: an increased risk of QT interval prolongation
Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes with nilotinib, consideration should be given to avoiding concomitant use of nilotinib with drugs that prolong the QT interval. 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 avoided for additive effects on the QT interval and increased risk of torsade de pointes. However, if concurrent therapy is necessary, patient closely monitored 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 concentrations. Paliperidone (9-hydroxyrisperidone) is the major active metabolite of risperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2007). Concomitant use of paroxetine and risperidone has resulted in increased plasma concentrations of paliperidone, particularly at higher (40 mg) paroxetine doses (Saito et al, 2005; Spina et al, 2007). Paliperidone and paroxetine are used concomitantly. Consider monitoring for increased paliperidone side effects, including 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 increase paliperidone plasma concentrations (Prod Info INVEGA(TM) extended-release oral tablets, 2007). Consider monitoring for increased paliperidone side effects, including neuroleptic malignant syndrome, QTc prolongation, or tardive dyskinesia.
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, 1.6 to 16.5) average in CYP2D6 extensive metabolizers who were treated concomitantly with a single dose of paliperidone 20 mg/day. Studies with higher paroxetine doses have not been conducted. The clinical relevance of these findings is unknown (Prod Info INVEGA(TM) extended-release oral tablets, 2007).

b) Paroxetine, a potent inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, primiparous women may have decreased plasma concentrations of risperidone (9-OH-risperidone) or other pathways of risperidone biotransformation. In a study in which patients were stabilized on risperidone and received adjunctive paroxetine 20 mg/day to treat negative symptoms, concomitant depression, or both, plasma concentrations of risperidone were significantly 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 both. Plasma concentrations of risperidone, 9-OH-risperidone, and total risperidone were increased by 13% (95% CI, 6.7 to 22), 17% (95% CI, 7.3 to 31.4), and 16% (95% CI, 5.6 to 31), respectively. The clinical relevance of these findings is unknown (Prod Info INVEGA(TM) extended-release oral tablets, 2007).

3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when paliperidone and paroxetine are used concomitantly as this may increase paliperidone plasma concentrations (Prod Info INVEGA(TM) extended-release oral tablets, 2007). Consider monitoring for increased paliperidone side effects, including neuroleptic malignant syndrome, QTc prolongation, or tardive dyskinesia.
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, 1.6 to 16.5) average in CYP2D6 extensive metabolizers who were treated concomitantly with a single dose of paliperidone 20 mg/day. Studies with higher paroxetine doses have not been conducted. The clinical relevance of these findings is unknown (Prod Info INVEGA(TM) extended-release oral tablets, 2007).

b) Paroxetine, a potent inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, primiparous women may have decreased plasma concentrations of risperidone (9-OH-risperidone) or other pathways of risperidone biotransformation. In a study in which patients were stabilized on risperidone and received adjunctive paroxetine 20 mg/day to treat negative symptoms, concomitant depression, or both, plasma concentrations of risperidone were significantly 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 both. Plasma concentrations of risperidone, 9-OH-risperidone, and total risperidone were increased by 13% (95% CI, 6.7 to 22), 17% (95% CI, 7.3 to 31.4), and 16% (95% CI, 5.6 to 31), respectively. The clinical relevance of these findings is unknown (Prod Info INVEGA(TM) extended-release oral tablets, 2007).

3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when paliperidone and paroxetine are used concomitantly as this may increase paliperidone plasma concentrations (Prod Info INVEGA(TM) extended-release oral tablets, 2007). Consider monitoring for increased paliperidone side effects, including neuroleptic malignant syndrome, QTc prolongation, or tardive dyskinesia.
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, 1.6 to 16.5) average in CYP2D6 extensive metabolizers who were treated concomitantly with a single dose of paliperidone 20 mg/day. Studies with higher paroxetine doses have not been conducted. The clinical relevance of these findings is unknown (Prod Info INVEGA(TM) extended-release oral tablets, 2007).

b) Paroxetine, a potent inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, primiparous women may have decreased plasma concentrations of risperidone (9-OH-risperidone) or other pathways of risperidone biotransformation. In a study in which patients were stabilized on risperidone and received adjunctive paroxetine 20 mg/day to treat negative symptoms, concomitant depression, or both, plasma concentrations of risperidone were significantly 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 both. Plasma concentrations of risperidone, 9-OH-risperidone, and total risperidone were increased by 13% (95% CI, 6.7 to 22), 17% (95% CI, 7.3 to 31.4), and 16% (95% CI, 5.6 to 31), respectively. The clinical relevance of these findings is unknown (Prod Info INVEGA(TM) extended-release oral tablets, 2007).
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. Ti
      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 f
      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, halopi
   paliperidone, quetiapine, risperidone, sertindole, sulotropride, 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-Laite et al, 1999b; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular inji
   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. Ti
      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 f
      changes than an elimination alteration (Young et al, 1993).

3.5.1.X Procaainamide
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, halopi
   paliperidone, quetiapine, risperidone, sertindole, sulotropride, 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-Laite et al, 1999b; Agelink et al, 2001b; Lande et al, 1992b; Prod Info GEODON(R) intramuscular inji
   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. Ti
      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 f
      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 QT interval; use caution when paliperidone is coadministered with ranolazine.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents 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 dose-related manner. If concomitant administration is unavoidable, use caution when paliperidone is coadministered with ranolazine for additive effects on QT interval prolongation.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Paliperidone causes an increase of QTc interval and ranolazine prolongs the QTc interval in a dose-related manner. If concomitant administration is unavoidable, use caution when paliperidone is coadministered with ranolazine for additive effects on QT interval prolongation.
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 ventricular fibrillation, and torsades de pointes. Antipsychotics, is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info CORDARONE(R), 2006; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive effects on QT interval 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 ventricular fibrillation, and torsades de pointes. Antipsychotics, is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info CORDARONE(R), 2006; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents should be avoided.
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 ventricular fibrillation, and torsades de pointes. Antipsychotics, is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info CORDARONE(R), 2006; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of paliperidone and class III antiarrhythmic agents should be avoided.
7) Probable Mechanism: additive QT prolongation

Additional text:

- 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 for additive changes than an elimination alteration (Young et al, 1993).

- Concomitant use of paliperidone and class III antiarrhythmic agents should be avoided. This may result in additive QT prolongation.

- Several antipsychotics have demonstrated QT prolongation, including amisulpride, paliperidone, sertindole, sulodipride, and zotepine.

- Due to the risk of additive QT prolongation, the concurrent administration of paliperidone and class III antiarrhythmic agents should be avoided.
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 should be avoided (Prod Info INVEGA(TM) extended-release oral tablets, 2006).

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 pointes of tetrabenazine with drugs that prolong the QT interval, the concurrent administration should be avoided. However, if concomitant use is required, close monitoring for QT interval prolongation and torsade de pointes is recommended. A double-blind, placebo-controlled crossover study of healthy subjects showed that a single 25 mg or 50 mg dose of tetrabenazine caused a mean increase of 10 ms in QT interval compared to baseline (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 closely monitored for QT prolongation (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 no data is available, the manufacturer states that concomitant use with other QT-prolonging agents is contraindicated (Prod Info Mellaril(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap), quetiapine (Owens, 2001), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (O'Brien et al, 1999), sertraline (Agelink et al, 2001), sertindole (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of thioridazine with other QT-prolonging agents is contraindicated. Several antipsychotics have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertraline (Agelink et al, 2001), sertindole (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
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 QT interval. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info C coproduct). Other phenothiazines may have similar effects, including amisulpride (Prod Info Solian(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info haloperidol (O'Brien et al, 1999), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999), sertraline (Agelink et al, 2001), sertindole (Lande et al, 1992), ziprasidone (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 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, such as improved communication, decreased hallucinations and delusions, improved socialization, and decreased attention to activities of daily living should also be monitored.

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 (Prod Info INVEGA release oral tablets, 2006)
      b) Neuroleptic malignant syndrome has been reported and patients should be monitored for the signs and symptoms of hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability (Prod Info INVEGA extended-release oral tablets, 2006).
      c) Orthostatic vital sign monitoring in patients susceptible to hypotension (Prod Info INVEGA(TM) extended-release oral tablets, 2006).
      d) QT prolongation has been reported with paliperidone, a baseline EKG may be considered (Prod Info INVEGA(TM) extended-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)
   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 tells you.
   Swallow the extended-release tablet whole. Do not crush, break, or chew it. Swallow the tablet with a liquid, which may pass into your stools. This is normal. Do not worry about it.

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 dose, 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.
   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, and
   Make sure your doctor knows if you are using medicines for heart rhythm problems (such as amiodarone, quinidine, Betapace®, Cordarone®, Procanbid®) or a diuretic, also called a "water pill" (such as furosemide, hydralazine, Aldactazide®, Aldactone®, Lasix®, Maxzide®).
   Tell your doctor if you are using levodopa (Dopar®, Larodopa®), any medicine for mental illness (such as chlorpromazine, Thorazine®, Mellaril®), or certain antibiotic medicines (such as gatifloxacin, moxifloxacin, Tequin). Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and cough medicines, 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. ‘
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 ofen.
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, twi
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
prescription and had 1 outpatient visit in each of the 2 preceding years. Sudden cardiac death was defined as oc
related to ventricular tachyarrhythmia. Current use was defined as the interval between the time the prescription was f
day’s supply. Low and high doses was defined as comparable to less than 100 milligrams (mg) of chlorpromazine, c
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 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
pter the effects of confounding of the study results, there was a secondary analysis performed in a cohoe
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 block dopamine Type 2 (D(2)) and serotonin Type 2 (SHT(2A)) receptors, and has antagonistic effects on the alpha-1 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 in 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 SCHIZOPHRENIA

**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 (SHT(2A)) receptors. It also has antagonist 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**

<table>
<thead>
<tr>
<th>FDA Labeled Indication</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1)</strong> Overview</td>
<td></td>
</tr>
<tr>
<td>FDA Approval: Adult, yes; Pediatric, no</td>
<td></td>
</tr>
<tr>
<td>Efficacy: Adult, Effective</td>
<td></td>
</tr>
<tr>
<td>Recommendation: Adult, Class IIa</td>
<td></td>
</tr>
<tr>
<td>Strength of Evidence: Adult, Category B</td>
<td></td>
</tr>
</tbody>
</table>

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) demc daily paliperidone (6 milligrams (mg), 9 mg, and 12 mg) extended-release (ER) was effective in signific schizoaffective symptoms, personal functioning, and social functioning (Kane et al, 2007).

In a randomized, double-blind, placebo-controlled study (n=113), paliperidone extended-release (ER) tat 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 ni efficacy or safety and tolerability, clinical improvements were seen, according to a prospective, 6-week 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 demonstrates 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 according to the Diagnostic of Mental Disorders Fourth Edition (DSM-IV) for at least 1 year. After discontinuation of previous medical antiparkinsonian drugs, beta-blockers or other psychotrophic agents) for three days prior to randomization group (n=628) received either paliperidone ER 6 mg (n=123), paliperidone ER 9 mg (n=122), paliperidol olanzapine 10 mg (n=128), or placebo (n=126) once daily for 6 weeks. The primary efficacy variable was PANS score from baseline to 6 weeks for each dose of paliperidone ER compared to placebo. The mean deviation (SD) decrease in PANS 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 15 placebo and olanzapine groups, respectively. All doses of paliperidone ER resulted in statistically significant placebo (p less than 0.001) in all PANS Marder factor scores. Clinical response (defined as a greater than decrease in PANS 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 23% at 6 weeks, paliperidone ER 9 mg: 57.3% at baseline vs 23% at 6 weeks, p less than 0.001 for all doses vs placebo). The number
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:
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, suicidal
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 tenn
significant efficacy was established; 14 patients (25%) in the paliperidone ER group experienced a recur
29 patients (53%) in the placebo group. In the final analysis (n=205), paliperidone ER significantly dels
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 adverse
reported for the placebo group than for the paliperidone ER group; most related to the underlying psych
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
eficacy 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 treatment
Clinical Global Impressions Severity (CGI-S) scale, Personal and Social Performance Scale, and the Scd
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/pali
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 palip
(ER) produced significantly improved Positive and Negative Syndrome Scale (PANSS) total scores compar
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 enrolment. 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
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
ose 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:
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

http://www.thomsonhc.com/hcs/librarian/PFDefaultActionId/pf.PrintReady

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7/1/2009
patients in the paliperidone ER arm had significantly improved PANSS total score, PANSS scale negative symptoms, PANSS scale disorganized thoughts scores, PANSS scale uncontrolled hostility/excitement scores, and CGI-C compared with patients in the quetiapine and placebo arms at day 14 and at the end of 6 weeks of treatment (day 42). Improvements in the paliperidone ER arm compared with the quetiapine and placebo arms at day 14 and paliperidone ER arm compared with placebo at day 42 (Table 1). Serious adverse events were reported in 2.5% of patients in the paliperidone ER, quetiapine, and placebo arms, respectively. Extrapyramidal symptoms were significantly (p less than 0.001) higher in the paliperidone ER arm following the 14-day monotherapy phase compared with quetiapine using the Simpson-Angus Rating Scale (total score). The incidence of movement disorders at day 14 significantly different between the 3 arms using the Barnes Akathisia Rating Scale and the Abnormal Involuntary Movement Scale.

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Day 14</th>
<th>Day 42</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PANSS score Mean (SE)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>-6.3* (1.8)</td>
<td>-8.4* (2.2)</td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>-1.6* (0.6)</td>
<td>-2.1* (0.7)</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>-1.3* (0.5)</td>
<td>-2.2* (0.6)</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td>-0.5 (0.3)</td>
<td>-0.6 (0.4)</td>
</tr>
<tr>
<td>Disorganized thoughts</td>
<td>-1.3* (0.4)</td>
<td>-2.1* (0.5)</td>
</tr>
<tr>
<td>Uncontrolled hostility/excitement</td>
<td>-1.5* (0.4)</td>
<td>-1.6* (0.5)</td>
</tr>
<tr>
<td><strong>CGI-S (Mean SE)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>-0.3* (0.1)</td>
<td>-0.4* (0.1)</td>
</tr>
<tr>
<td><strong>CGI-C (Mean SE)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>-0.4* (0.1)</td>
<td>-0.5* (0.1)</td>
</tr>
</tbody>
</table>

*p less than 0.05

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

### 6.0 References

49. Product Information: CORDARONE(R) oral tablets, amiodarone hcl oral tablets. Wyeth Pharmaceuticals,Inc, Philac
52. Product Information: FANAPT(TM) oral tablets, iloperidone oral tablets. Vanda Pharmaceuticals, Rockville, MD, 20
54. Product Information: INVEGA(R) extended-release oral tablets, paliperidone extended-release oral tablets. Alza Cc
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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.
71. Product Information: TASIGNA(R) oral capsules, nilotinib oral capsules. Novartis Pharmaceuticals Corporation, East
72. Product Information: TEQUIN(R) tablets, injection, gatifloxacin tablets, injection, gatifloxacin in 5% dextrose injectio
76. Product Information: XENAZINE(R) oral tablets, tetrabenazine oral tablets. Prestwick Pharmaceuticals,Inc, Washin

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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 chewable disintegrating tablets, 2009)
      2) safety and efficacy as initial monotherapy, for conversion to monotherapy from a non-enzyme-inducing antiepileptic drug regimen to lamotrigine to 200 mg/day (Prod Info LAMICTAL chewable disintegrating tablets, 2009)
      3) conversion to monotherapy from 2 or more concomitant antiepileptic drugs has not been established (Prod Info LAMICTAL chewable disintegrating tablets, 2009)

b) Bipolar I disorder
   1) (patients not taking enzyme-inducing drugs or valproic acid) 25 mg/day orally for 2 weeks, then 50 mg/day for 2 weeks, then 200 mg/day; usual maintenance dose of lamotrigine in patients not taking enzyme-inducing drugs or valproic acid is 100 mg/day (Prod Info LAMICTAL chewable 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 weeks, then 50 mg/day for 2 weeks, then 100 mg/day for 1 week (in divided doses), then 300 mg/day for 1 week (in divided doses), then may increase to 500 mg/day (in divided doses) (Prod Info LAMICTAL chewable disintegrating tablets, 2009)

b) Lennox-Gastaut syndrome; Adjunct
   1) (added to antiepileptic drug regimen with valproic acid) 25 mg/day ORALLY every OTHER day for 2 weeks, then 50 mg/day ORALLY every 1 to 2 weeks to the usual maintenance dose of 100 to 400 mg of patients 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 acid) 25 mg/day ORALLY every 2 weeks; may increase dosage by 50 mg/day every 1 to 2 weeks to the usual maintenance dose of 225 mg/day (Prod Info LAMICTAL chewable 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 dose of lamotrigine (Prod Info LAMICTAL chewable disintegrating tablets, 2009)

b) Partial seizure, Adjunct or monotherapy
   1) (chewable dispersible or orally disintegrating tablets; added to antiepileptic drug regimen with valproic acid) 25 mg/day ORALLY for 2 weeks; may increase dosage by 25 mg/day every 1 to 2 weeks to the usual maintenance dose of patients adding lamotrigine to valproic acid ALONE ranges from 100 to 200 mg/day (Prod Info LAMICTAL chewable disintegrating tablets, 2009)
   2) (chewable dispersible or orally disintegrating tablets; added to antiepileptic drug regimen not containing enzyme-inducing antiepileptic drugs or valproic acid) 25 mg/day ORALLY every 2 weeks; may increase dosage by 50 mg/day every 1 to 2 weeks to the usual maintenance dose of 225 mg/day (Prod Info LAMICTAL chewable disintegrating tablets, 2009)
   3) (chewable dispersible or orally disintegrating tablets; added to antiepileptic drug regimen containing enzyme-inducing antiepileptic drugs) 50 mg/day ORALLY for 2 weeks; then 100 mg/day (in 2 divided doses) for 2 weeks; may increase dosage by 50 mg/day ORALLY every 1 to 2 weeks to the usual maintenance dose of lamotrigine in patients taking valproic acid is 100 mg/day (Prod Info LAMICTAL chewable disintegrating tablets, 2009)
   4) (chewable dispersible or orally disintegrating tablets; conversion to monotherapy in patients, 16 yr and older) (Prod Info LAMICTAL chewable dispersible oral tablets, 2009)
   5) (chewable dispersible or orally disintegrating tablets; conversion to monotherapy in patients, 16 yr and older) (Prod Info LAMICTAL chewable dispersible oral tablets, 2009)
   6) (extended-release tablets; added to antiepileptic drug regimen with valproic acid) weeks 1 and 2, 25 mg/day; weeks 3 and 4, 50 mg/day; week 5, 100 mg/day; week 6, 150 mg/day; weeks 7 onwards to maintain; 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 onwards at weekly intervals, 300 to 400 mg/day (Prod Info LAMICTAL XR oral extended-release tablets, 2009)
(extended-release tablets; conversion from immediate-release lamotrigine tablets) initial, should match need adjustments depending on therapeutic response after conversion (Prod Info LAMICTAL XR oral extended-release tablets) 2) safety and efficacy in pediatric patients with acute mood disorders has not been established (Prod Info LAMICTAL XR oral extended-release tablets, oral tablets) 3) efficacy in pediatric patients (age range, 1 to 24 months) for the treatment of partial seizures was not demonstrated in 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 0.1 mg/kg/day) ORALLY in 1 to 2 divided doses for 2 weeks, then 0.3 mg/kg/day (rounded down to the nearest whole tablet) (Prod Info LAMICTAL XR oral extended-release tablets, oral tablets, orally disintegrating tablets, 2009) 2) (2 to 12 yr; added to antiepileptic drug regimen not containing enzyme-inducing antiepileptic drugs or valproic acid) 0.6 mg/kg/day in 1 to 2 divided doses for 2 weeks, then 1.2 mg/kg/day (rounded down to the nearest whole tablet) (Prod Info LAMICTAL XR oral extended-release tablets, oral tablets, orally disintegrating tablets, 2009) 3) (2 to 12 yr; added to enzyme-inducing antiepileptic drug regimen without valproic acid) 0.6 mg/kg/day in 1 to 2 divided doses for 2 weeks, then 1.2 mg/kg/day (rounded down to the nearest whole tablet) (Prod Info LAMICTAL XR oral extended-release tablets, oral tablets, orally disintegrating tablets, 2009) 4) (over age 12; added to antiepileptic drug regimen with valproic acid) 25 mg/day ORALLY every 1 to 2 weeks to the usual maintenance dose of 100 to 400 mg/day for 2 weeks; may increase dosage by 50 mg/day every 1 to 2 weeks to the usual maintenance dose of 225 to 700 mg/day for 2 weeks, then 0.3 mg/kg/day (rounded down to the nearest whole tablet) ORALLY in 1 to 2 divided doses for 2 weeks, then 0.6 mg/kg/day (rounded down to the nearest whole tablet) ORALLY in 1 to 2 divided doses for 2 weeks, then 1.2 mg/kg/day (rounded down to the nearest whole tablet) (Prod Info LAMICTAL XR oral extended-release tablets, oral tablets, orally disintegrating tablets, 2009) 5) (over age 12; added to antiepileptic drug regimen not containing enzyme-inducing antiepileptic drugs or valproic acid) 50 mg/day orally every 1 to 2 weeks for 2 weeks; may increase dosage by 50 mg/day ORALLY every 1 to 2 weeks to the usual maintenance dose of 225 to 700 mg/day for 2 weeks, then 0.3 mg/kg/day (rounded down to the nearest whole tablet) ORALLY in 1 to 2 divided doses for 2 weeks, then 0.6 mg/kg/day (rounded down to the nearest whole tablet) ORALLY in 1 to 2 divided doses for 2 weeks, then 1.2 mg/kg/day (rounded down to the nearest whole tablet) (Prod Info LAMICTAL XR oral extended-release tablets, oral tablets, orally disintegrating tablets, 2009) 6) (over age 12; added to enzyme-inducing antiepileptic drug regimen without valproic acid) 50 mg/day ORALLY every 1 to 2 weeks for 2 weeks; may increase dosage by 50 mg/day ORALLY every 1 to 2 weeks to the usual maintenance dose of 225 to 700 mg/day; usual maintenance dose for children adding lamotrigine to valproic acid ALONE ranges from 1 to 3 mg/kg/day for 2 weeks; may increase dosage by 0.3 mg/kg/day every 1 to 2 weeks (rounded down to the nearest whole tablet) ORALLY in 1 to 2 divided doses for 2 weeks, then 0.6 mg/kg/day (rounded down to the nearest whole tablet) ORALLY in 1 to 2 divided doses for 2 weeks, then 1.2 mg/kg/day (rounded down to the nearest whole tablet) (Prod Info LAMICTAL XR oral extended-release tablets, oral tablets, orally disintegrating tablets, 2009) 7) use with caution in ADULTS 8) safety and efficacy in adult patients with acute mood disorders has not been established (Prod Info LAMICTAL XR oral extended-release tablets, oral tablets, orally disintegrating tablets, 2009)
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 antiepileptic drug regimen with valproic acid) ORALLY for 2 weeks, then 100 mg/day (in 2 divided doses) for 2 weeks; may increase dosage by 100 mg/day every 2 weeks to the usual maintenance dose of 300 to 500 mg/day (in 2 divided doses) (Prod Info LAMICTAL chewable dispersible oral tablets, or 7) (extended-release tablets; age 13 and older; added to antiepileptic drug regimen with valproic acid) ORALLY for 2 weeks, then 200 mg/day (in 2 divided doses) for 2 weeks; may increase dosage by 100 mg/day at weekly intervals, 200 to 250 mg/day (Prod Info LAMICTAL XR oral extended-release tablets, orally disintegrating tablets, over age 12; added to antiepileptic drug regimen containing enzyme-inducing antiepileptic drugs or nearest whole tablet) ORALLY for 2 weeks, then 50 mg/day (rounded down to the nearest whole tablet) to the usual maintenance dose of 5 mg/kg/day for children adding lamotrigine to valproic acid ALONE ranges from 1 to 5 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 the nearest whole 1 mg/kg/day in 2 divided doses (max 300 mg/day) (Prod Info LAMICTAL chewable dispersible oral tablets, over age 12; 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 doses for 2 weeks; may increase dosage by 0.6 mg/kg/day every 2 weeks to the usual maintenance dose of 1 to 3 mg/kg/day oral tablets, orally disintegrating tablets, 2009) 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 doses for 2 weeks; may increase dosage by 0.6 mg/kg/day every 2 weeks to the usual maintenance dose of 1 to 3 mg/kg/day oral tablets, orally disintegrating tablets, 2009) 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 mg/kg/day (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009) 5) (over age 12; 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 the nearest whole 1 mg/kg/day in 2 divided doses (max 300 mg/day) (Prod Info LAMICTAL chewable dispersible oral tablets, over age 12; 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 doses for 2 weeks; may increase dosage by 0.6 mg/kg/day every 2 weeks to the usual maintenance dose of 100 mg/kg/day (Prod 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 for 2 weeks; may increase dosage by 100 mg/day ORALLY every 1 to 2 weeks to the usual maintenance dose of 500 to 1000 mg/day oral tablets, orally disintegrating tablets, 2009). 3) Contraindications  a) hypersensitivity to lamotrigine or any component of the product (Prod Info LAMICTAL chewable dispersible oral tablets, over age 12; added to enzyme-inducing 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 the nearest whole 1 mg/kg/day in 2 divided doses (max 300 mg/day) (Prod Info LAMICTAL chewable dispersible oral tablets, over age 12; 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 doses for 2 weeks; may increase dosage by 0.6 mg/kg/day every 2 weeks to the usual maintenance dose of 100 mg/kg/day (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating 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 Info).
B) Synonyms
   Lamotrigine
C) Orphan Drug Status
   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 molar 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 juice or milk to nearest whole tablet. Disperse by adding tablets to a small amount of liquid (1 teaspoon, or enough to cover a tablet dispersed (approximately 1 min), swirl solution and consume entire volume immediately (Prod Info LAMICTAL chewable dispersible oral tablets, 2009).
      b) Orally Disintegrating Tablets
         1) Orally disintegrating tablets should be placed onto the tongue and moved around in the mouth. The tablet may be taken without water and may be taken with or without food (Prod Info LAMICTAL chewable dispersible oral tablets, 2009).
      c) Extended-Release Tablets
         1) Extended-release tablets must be swallowed whole with or without food. The tablet must not be chewed or crushed (Prod Info LAMICTAL extended-release tablets, 2009).
B) Lamotrigine 25 milligrams (mg) tablets and lamotrigine chewable dispersible 2 mg, 5 mg and 25 mg tablets should be stored at 25 degrees C (77 degrees F) with excursions permitted between 15 to 30 degrees C (59 to 86 degrees F) in a dry place. Lamotrigine stored at 25 degrees C (77 degrees F) with excursions permitted between 15 to 30 degrees C (59 to 86 degrees F) in the (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 monotherapy benefit was observed at 400 mg/day as compared to 200 mg/day (Prod Info LAMICTAL chewable dispersible oral 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 LAMICTAL chewable dispersible oral 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 drugs is 100 mg/day (Prod Info LAMICTAL chewable dispersible oral 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 enzyme-inducing drugs:
      e) Adjustment - Discontinuation of Valproic Acid
         1) For patients discontinuing valproic acid, the dose of lamotrigine should be doubled over a 2-week period. 

   f) Adjustment - Discontinuation of Carbamazepine
      1) For patients discontinuing carbamazepine or other enzyme-inducing agents, the dose of lamotrigine should be decreased by half over a 2-week period. The dose may then be reduced to the target dose.

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 acid:
         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

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**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 |

**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 |
Week 5 and onward: Doses may be increased by 25 to 50 mg/day every 1 to 2 weeks to achieve 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 ranges from 100 to 400 mg/day (1 or 2 divided doses).

b) Without Valproic Acid

1) For adult patients receiving enzyme-inducing antiepileptic drugs (EIAED) (carbamazepine, phenytoin, or primidone) without valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, 2009):

- Extended-release lamotrigine added to EIAED regimen without valproic acid:
  - Weeks 1 and 2: 25 milligrams (mg) once every other day
  - Weeks 3 and 4: 50 mg once daily
  - Week 5: 100 mg once daily
  - Week 6: 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 antiepileptic drug (AED) regimen not containing enzyme-inducing properties or valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, 2009):

- Chewable dispersible or orally disintegrating lamotrigine added to 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 achieve 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 ranges from 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 antiepileptic drug (AED) regimen not containing enzyme-inducing 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: 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

b) Without Valproic Acid

1) (extended-release tablets) For patients 13 years or older receiving enzyme-inducing antiepileptic drug (EIAED) (carbamazepine, phenytoin, phenobarbital, or primidone) without 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: 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-inducing antiepileptic drugs (EIAED) (carbamazepine, phenytoin, or primidone) without valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, 2009):

- Chewable dispersible or orally disintegrating lamotrigine added to EIAED regimen without valproic acid:
  - Weeks 1 and 2: 25 mg once daily
  - Weeks 3 and 4: 25 mg once daily
  - Week 5: 50 mg once daily
  - Week 6: 100 mg once daily
  - Week 7: 200 mg once daily
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 acid 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 mg/day every 1 to 2 weeks to achieve target dose. Weekly dose is gradually increased until the target dose is achieved. The usual maintenance dose in patients adding lamotrigine to valproic acid alone ranges from 200 to 500 mg/day.

b) Without Valproic Acid

1) For adult patients receiving enzyme-inducing antiepileptic drugs (EIAED) (carbamazepine, phenytoin) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):

   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 achieve maintenance. The 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 ranges from 200 to 500 mg/day.

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 enzyme-inducing antiepileptic drug (EIAED) (carbamazepine, phenytoin) (Prod Info 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
   
   Week 5 and onward: Doses may be increased by 50 mg/day every 1 to 2 weeks to achieve maintenance. The usual maintenance dose: 225 to 375 mg/day (in 2 divided doses).

   Conversion to Immediate-Release to Extended-Release Formulation

1) The initial dose of extended-release lamotrigine in patients age 13 years and older should match the daily dose of immediate-release lamotrigine. Lamotrigine should be titrated as follows (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):

   Weeks 1 and 2: 50 mg/day
   
   Weeks 3 and 4: 100 mg/day (in 2 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 be considered each week.

2) For adult patients adding chewable dispersible or orally disintegrating lamotrigine to an antiepileptic properties or valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating oral tablets, oral tablets, orally disintegrating tablets, 2009):

   Lamotrigine added to EIAED regimen containing valproic acid:
   
   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 maintenance. The usual maintenance dose: 225 to 375 mg/day (in 2 divided doses).

   Conversion to Monotherapy, With Enzyme-Inducing Antiepileptic Drug

1) The recommended dose for conversion from adjunctive therapy with a single-enzyme-inducing a patient 16 years-old and older, is 500 milligrams/day (mg/day) given in 2 divided doses. Lamotrigine should be titrated as follows (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):

   Weeks 1 and 2: 50 mg/day
   
   Weeks 3 and 4: 100 mg/day (in 2 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 be considered 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. First, while maintaining the valproic acid dose at a fixed level. Lamotrigine should be titrated as follows (Prod Info LAMICTAL chewable dispersible oral 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 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 week 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 than trough plasma levels in the range of 1 to 4 micrograms/milliliter (Graves & Leppik, 1991; Jawad 2009).
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)

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 shoul
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 w
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 remover
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 dosin

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 h,
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 concentr
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 convulsions in the newborn. In neonates who were taking enzyme-inducing agents, doses up to 10 milligrams per kilogram were used. In infants between 1 and 12 months of age, taking valproate and enzyme inducers, were dosed between 5 to 10 mg/kg/day. In infants between 12 months and 2 years of age, the final dose was the maximum achieved (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/kilogram (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 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 nearest whole number.

Week 5 and onward: Doses may be increased every 1 to 2 weeks by 0.3 mg/kg/day, rounded to 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 doses).

The usual maintenance dose in patients adding lamotrigine to valproic acid alone is 1 to 5 mg/kg/day.

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

INITIAL WEIGHT BASED DOZING GUIDE:

Patient weight 6.7 to 14 kg, dose for weeks 1 and 2 is 2 mg every other day; dose for weeks 3 and 4 is 4 mg every other day; dose for weeks 5 and onward is 8 mg every day.

Patient weight 14.1 to 27 kg, dose for weeks 1 and 2 is 4 mg every day; dose for weeks 3 and 4 is 8 mg every day; dose for weeks 5 and onward is 12 mg every day.

Patient weight 27.1 to 34 kg, dose for weeks 1 and 2 is 6 mg every day; dose for weeks 3 and 4 is 12 mg every day; dose for weeks 5 and onward is 16 mg every day.

Patient weight 34.1 to 40 kg, dose for weeks 1 and 2 is 8 mg every day; dose for weeks 3 and 4 is 16 mg every day; dose for weeks 5 and onward is 20 mg every day.

2) Without Valproic Acid

a) For patients age 2 to 12 years old receiving enzyme-inducing antiepileptic drugs (EIAED) (or not) without valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):

Lamotrigine added to EIAED 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 nearest whole number.

Week 5 and onward: Doses may be increased every 1 to 2 weeks by 0.3 mg/kg/day, rounded to 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 doses).

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

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 containing valproic acid:

Lamotrigine added to an antiepileptic drug (AED) regimen not containing drug-inducing enzyme-inducing antiepileptic drugs (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):

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 nearest whole number.

Week 5 and onward: Doses may be increased every 1 to 2 weeks by 0.3 mg/kg/day, rounded to 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 doses).

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

b) Age 12 Years and Older

1) With Valproic Acid

For patients 12 years of age adding lamotrigine to an antiepileptic drug (AED) regimen containing valproic acid:

Lamotrigine added to an antiepileptic drug (AED) regimen containing valproic acid in patients 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 nearest whole number.

Week 5 and onward: Doses may be increased every 1 to 2 weeks by 0.3 mg/kg/day, rounded to 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 doses).

Maintenance doses in patients weighing less than 30 kg may need to be increased.
a) For patients 12 years and older adding lamotrigine to an antiepileptic drug (AED) regimen containing valproic acid:

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) (carbamazepine, phenobarbital, or primidone) without valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):

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 achieve

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 not containing drug-inducing AED or valproic acid (Prod Info 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
- 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)

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 antiepileptic drug regimen containing valproic acid (Prod 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 antiepileptic drugs (carbamazepine, phenobarbital, or primidone) without 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: 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) 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 drug regimen not containing drug-inducing AED or valproic acid (Prod Info LAMICTAL XR oral extended-release tablets, 2009):

Extended-release lamotrigine added to AED regimen not containing drug inducing AED or 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) Conversion from Immediate-Release to Extended-Release Formulation

a) The initial dose of extended-release lamotrigine in patients age 13 years and older should be lamotrigine. Depending on the therapeutic response after conversion, the total daily dose may be increased (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 lamotrigine to valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009):
Chewable dispersible or orally disintegrating lamotrigine added to AED regimen containing

<table>
<thead>
<tr>
<th>Initial Weight Based Dosing Guide</th>
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<td><strong>Without Valproic Acid</strong></td>
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</table>
| a) For patients age 2 to 12 years old receiving enzyme-inducing antiepileptic drugs (EIAED) (carbamazepine or phenytoin) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets) containing enzyme-inducing properties or valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets) | **Usual maintenance dose:** 1 to 5 mg/kg/day (maximum 200 mg/day in 2 divided doses)
- **Patient weight 6.7 to 14 kg, dose for weeks 1 and 2 is 2 mg every OTHER day:**
  - **Dose for weeks 1 and 2:** 2.5 mg every other day
  - **Usual maintenance dose:** 100 to 400 mg/day (1 or 2 divided doses)
- **Patient weight 14.1 to 27 kg, dose for weeks 1 and 2 is 2 mg every OTHER day:**
  - **Dose for weeks 1 and 2:** 25 mg every day
  - **Usual maintenance dose:** 100 to 400 mg/day (1 or 2 divided doses)
- **Patient weight 27.1 to 34 kg, dose for weeks 1 and 2 is 4 mg every day:**
  - **Dose for weeks 1 and 2:** 50 mg/day
  - **Usual maintenance dose:** 100 to 400 mg/day (1 or 2 divided doses)
- **Patient weight 34.1 to 40 kg, dose for weeks 1 and 2 is 5 mg every day:**
  - **Dose for weeks 1 and 2:** 62.5 mg/day
  - **Usual maintenance dose:** 100 to 400 mg/day (1 or 2 divided doses)
- **Patient weight 40.1 to 50 kg, dose for weeks 1 and 2 is 6 mg every day:**
  - **Dose for weeks 1 and 2:** 75 mg/day
  - **Usual maintenance dose:** 100 to 400 mg/day (1 or 2 divided doses)

| **With Valproic Acid**           |
| a) For patients 12 years and older adding chewable dispersible or orally disintegrating lamotrigine to valproic acid alone | **Usual maintenance dose:** 1 to 5 mg/kg/day (maximum 200 mg/day in 2 divided doses)
- **Weeks 1 and 2:** 0.15 mg/kg/day in one or two divided doses, r
- **Weeks 3 and 4:** 0.3 mg/kg/day in two divided doses, r
- **Weeks 5 and onward:** Doses may be increased every 1 to 2 weeks by 0.5 mg/kg/day, r
- **Maintenance dose:** 1 to 5 mg/kg/day (maximum 200 mg/day in 2 divided doses)

| **Without Valproic Acid**        |
| a) For patients 12 years and older receiving enzyme-inducing antiepileptic drugs (EIAED) (carbamazepine or phenytoin) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets) containing enzyme-inducing properties or valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets) | **Usual maintenance dose:** 1 to 5 mg/kg/day (maximum 400 mg/day in 2 divided doses)
- **Patient weight 6.7 to 14 kg, dose for weeks 1 and 2 is 2 mg every OTHER day:**
  - **Dose for weeks 1 and 2:** 2.5 mg every other day
  - **Usual maintenance dose:** 100 to 400 mg/day (1 or 2 divided doses)
- **Patient weight 14.1 to 27 kg, dose for weeks 1 and 2 is 2 mg every OTHER day:**
  - **Dose for weeks 1 and 2:** 25 mg every day
  - **Usual maintenance dose:** 100 to 400 mg/day (1 or 2 divided doses)
- **Patient weight 27.1 to 34 kg, dose for weeks 1 and 2 is 4 mg every day:**
  - **Dose for weeks 1 and 2:** 50 mg/day
  - **Usual maintenance dose:** 100 to 400 mg/day (1 or 2 divided doses)
- **Patient weight 34.1 to 40 kg, dose for weeks 1 and 2 is 5 mg every day:**
  - **Dose for weeks 1 and 2:** 62.5 mg/day
  - **Usual maintenance dose:** 100 to 400 mg/day (1 or 2 divided doses)
- **Patient weight 40.1 to 50 kg, dose for weeks 1 and 2 is 6 mg every day:**
  - **Dose for weeks 1 and 2:** 75 mg/day
  - **Usual maintenance dose:** 100 to 400 mg/day (1 or 2 divided doses)

| **With Valproic Acid**           |
| a) For patients 2 to 12 years of age receiving enzyme-inducing antiepileptic drugs (EIAED) (carbamazepine or phenytoin) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets) containing enzyme-inducing properties or valproic acid (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets) | **Usual maintenance dose:** 1 to 5 mg/kg/day (maximum 200 mg/day in 2 divided doses)
- **Patient weight 6.7 to 14 kg, dose for weeks 1 and 2 is 2 mg every OTHER day:**
  - **Dose for weeks 1 and 2:** 2.5 mg every other day
  - **Usual maintenance dose:** 100 to 400 mg/day (1 or 2 divided doses)
- **Patient weight 14.1 to 27 kg, dose for weeks 1 and 2 is 2 mg every OTHER day:**
  - **Dose for weeks 1 and 2:** 25 mg every day
  - **Usual maintenance dose:** 100 to 400 mg/day (1 or 2 divided doses)
- **Patient weight 27.1 to 34 kg, dose for weeks 1 and 2 is 4 mg every day:**
  - **Dose for weeks 1 and 2:** 50 mg/day
  - **Usual maintenance dose:** 100 to 400 mg/day (1 or 2 divided doses)
- **Patient weight 34.1 to 40 kg, dose for weeks 1 and 2 is 5 mg every day:**
  - **Dose for weeks 1 and 2:** 62.5 mg/day
  - **Usual maintenance dose:** 100 to 400 mg/day (1 or 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-year-old 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 containing valproic acid in patients 2 to 12 years of age:
         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, round down to the nearest whole mg/kg/day
         Week 5 and onward: Doses may be increased every 1 to 2 weeks by 0.3 mg/kg/day, rounded down to the nearest whole mg/kg/day
         The usual maintenance dose: 1 to 5 mg/kg/day (maximum 200 mg/day in 1 or 2 divided doses)
         Maintenance doses in patients adding lamotrigine to valproic acid alone:
         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 increased
   2) Without Valproic Acid
      a) For patients age 2 to 12 years old receiving enzyme-inducing antiepileptic drugs (EIAED) (carbamazepine, phenytoin, phenobarbital) in the absence of valproic acid:
         Lamotrigine added to EIAED regimen in the absence of valproic acid:
         Weeks 1 and 2: 0.6 milligram/kilogram/day (mg/kg/day) in two divided doses, tablets should be used for dosing
         Weeks 3 and 4: 1.2 mg/kg/day in two divided doses, round down to the nearest whole mg/kg/day
         Week 5 and onward: Doses may be increased every 1 to 2 weeks by 1.2 mg/kg/day, rounded down to the nearest whole mg/kg/day
         The 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 increased
   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 containing valproic acid in patients 2 to 12 years of age:
         Lamotrigine added to antiepileptic drug (AED) regimen containing valproic acid:
         Weeks 1 and 2: 0.3 milligram/kilogram/day (mg/kg/day) in one or two divided doses, tablets should be used for dosing
         Weeks 3 and 4: 0.6 mg/kg/day in two divided doses, round down to the nearest whole mg/kg/day
         Week 5 and onward: Doses may be increased every 1 to 2 weeks by 0.6 mg/kg/day, rounded down to the nearest whole mg/kg/day
         The 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 increased
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 containing valproic acid:
         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 achieve maintenance
         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) (carbamazepine, phenytoin, phenobarbital) in the absence of valproic acid:
         Lamotrigine added to EIAED regimen in the absence of 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 achieve maintenance
         Usual maintenance dose: 300 to 500 mg/day (in 2 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 containing valproic acid:
         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
         Week 5 and onward: Doses may be increased by 50 mg/day every 1 to 2 weeks to achieve maintenance
         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 of age (2009).
2) The risk of developing a potentially life-threatening rash is appreciably higher in children than in adults. Dose escalation regimens (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2007) (Prod 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 impaired renal function since lamotrigine disposition may be altered in the presence of impaired renal function. Use with caution in patients with impaired renal function since lamotrigine disposition may be altered in the presence of impaired renal function. Use with caution in patients with impaired renal function since lamotrigine disposition may be altered in the presence of impaired renal function.

B) Dosage of lamotrigine need not be altered in the presence of impaired renal function since lamotrigine disposition may be altered in the presence of impaired renal function. Use with caution in patients with impaired renal function since lamotrigine disposition may be altered in the presence of impaired renal function.

C) Twenty volunteers with chronic renal failure (mean creatinine clearance 13 milliliters/min) were given a single 6 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, 2006).

1.4.3 Dosage in Hepatic Insufficiency

A) The manufacturer recommends that in patients with moderate and severe liver impairment without ascites, the lamotrigine dose be reduced by approximately 25%. In patients with severe hepatic impairment with ascites, the initial, 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 h3

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, 1993b; IV

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

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

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

4) 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) 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 fl decreased by 17%, 34% and 37% for extended-release lamotrigine administered concomitantly with enz 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 Lamictal XR oral extended-release tablets, 2009).
   a) Peak plasma concentrations increased linearly from 0.58 to 4.63 mg/L in healthy subjects administered single oral doses of lamotrigine (Mikati et al, 2003).
   b) In two small studies of patients with epilepsy, plasma concentrations increased linearly with doses of 50 to 112/295.

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 increase in AUC.
   2) Analysis of the data based on concomitant AED use showed, the decrease in Cmax was 12% in patients receiving lamotrigine (Mikati et al, 2003).

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 disintegrating tablets, 2009).
   2) Oral (elderly) 91.8 mg x hr/L (Garnett, 1997).
   3) Oral, (adult) 56.6 mg x hr/L (Garnett, 1997).

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).

2.3 ADME

Absorption
2.3.1 Absorption
A) Bioavailability
1) Oral tablets: 98% (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating; oral tablets, orally disintegrating tablets, 2009).
   a) Lamotrigine is rapidly and completely absorbed after oral administration with an absolute bioavailability of 98%. (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
   b) Lamotrigine chewable/dispersible tablets are equivalent to the compressed tablets in terms of rate and extent of absorption after oral administration in healthy volunteers (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
   c) The relative bioavailability was 0.52 when a lamotrigine 100-mg chewable dispersible tablet was administered orally and swallowed whole in 12 healthy adults (Birnbaum et al, 2001). The rectal suspension was prepared by placing it into 6 mL of tap water (room temperature), followed by two 2-mL syringe-tubing rinses, with under the curve (AUC) for rectally administered lamotrigine was 29.68 mcg/mL x hr compared with 54.94 mcg/mL x hr for orally administered lamotrigine.

B) Effects of Food
1) No effect on systemic availability (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
   a) The bioavailability of lamotrigine is not affected by food (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating 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 disintegrating tablets, 2009).
      1) Lamotrigine is approximately 55% bound to human plasma proteins at concentration from 1 to 10 mcg/mL (Prod Info LAMICTAL chewable dispersible 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 disintegrating tablets, 1999)
      1) The mean apparent volume of distribution of lamotrigine after oral administration ranges from 0.9 to 1.3 L/kg in healthy volunteers (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 1999).
      2) The volume of distribution in patients receiving concurrent antiepileptic therapy is 1.2 to 1.5 L/kg in adult patients with epilepsy (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
      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 tablets, 2009).
   2) Lamotrigine is metabolized primarily by glucuronic acid conjugation into inactive metabolites. When given alone, approximately 60% to 80% of lamotrigine is metabolized (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
   3) When given concomitantly with valproic acid, lamotrigine clearance may be increased (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally 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 LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
      1) The mean apparent plasma clearance of lamotrigine was between 0.44 and 0.58 mL/min/kg in healthy volunteers, between 0.18 and 0.3 mL/min/kg in patients taking concomitant valproic acid (n=24) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
      2) The mean apparent plasma clearance of lamotrigine in adult patients with epilepsy taking concomitant valproic acid and an enzyme-inducing antiepileptic medication was 0.53 mL/min/kg (n=25) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
   b) Elderly, 0.26 to 0.48 mL/min/kg (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
      1) In 12 elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance, 61 mL/min), the mean apparent plasma clearance of lamotrigine was 0.30 mL/min/kg (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
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 disintegrating tablets, 2009).
   1) In general, the clearance of lamotrigine is not affected by gender. However, during dose escalat
   d) Hepatic Impairment, 0.15 to 0.3 mL/min/kg (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
   1) Following a single 100-mg dose of lamotrigine the mean apparent clearances of lamotrigine in patients with 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 dispersible oral 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 range
   antiepileptic medication regimen was 2.54 mL/min/kg (n=7). When lamotrigine was taken concomitantly with an enzyme-inducing antiepileptic medication regimen, the mean plasma clearance was 0.89 mL/min/kg (n=8), and was 0.2 mL/min/kg (n=3) (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
   3) The mean apparent plasma clearance of lamotrigine in pediatric patients with epilepsy (age range
   4) The mean apparent clearance in infants less than 2 months old was 0.119 liter per hour per kilogram (Prod Info LAMICTAL chewable dispersible oral 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, 2009).
       1) Following oral administration in healthy volunteers, 94% of the drug was recovered in the urine (oral tablets, orally disintegrating tablets, 2009; Peck, 1991e).
       2) Elimination Half-life
          a) Adult, (healthy volunteers) 25.4 to 70.3 hours; (epilepsy), 12.6 to 58.8 hours (Prod Info LAMICTAL chewable dispersible oral tablets, 2009).
             1) The elimination half-life of lamotrigine in healthy adult volunteers (n=215) taking no other medications was 46.9 hours (n=24) (Prod Info LAMICTAL chewable dispersible oral tablets, 2009).
             2) The elimination half-life of lamotrigine in adult patients with epilepsy taking lamotrigine concomitantly with valproic acid was 50.7 hours when taken concomitantly with valproic acid and an enzyme-inducing antiepileptic medication regimen was 41 (Prod Info LAMICTAL chewable dispersible oral tablets, 2009).
      b) Elderly, 31.2 hours (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
         1) In 12 elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance, 61 mL
         2) Hepatic Impairment, 46 +/- 20 hours to 100 +/- 48 hours (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
         3) Pediatric, 7 hours to 65.8 hours (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
            1) The elimination half-life of lamotrigine in pediatric patients with epilepsy (age range, 10 months to 12 years) was 46.7 hours when taken concomitantly with an enzyme-inducing antiepileptic medication regimen was 41 (Prod Info LAMICTAL chewable 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 12 years) was 46 +/- 48 hours.
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 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, oral tablets, orally 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 elir 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 treatment. Stevens-Johnson syndrome, is approximately 0.8% (8 per 1,000) in pediatric patients (2 to 16 years of age) taking Lamictal as 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 pediatric patients (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009).
   b) Other than age, there are as yet no factors identified that are known to predict the risk of occurrence or the severity of rash.
   c) Other than age, there are as yet no factors identified that are known to predict the risk of occurrence or the severity of rash.
   d) Nearly all cases of life-threatening rashes caused by the immediate-release formulation of lamotrigine have occurred in patients undergoing hemodialysis. 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 progress to life-threatening rash. Lamotrigine should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug-related. Duration of therapy potential risk heralded by the first appearance of a rash.

2) Oral (Tablet; Tablet, Chewable; Tablet, Disintegrating; Tablet, Extended Release)
   a) Skin rash, serious and potentially life-threatening, has been reported; discontinue drug if alternate etiology for rash is not identified (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009; Prod Info LAMICTAL XR oral extended-release tablets, 2009).
   b) Concomitant use with valproic acid; dose adjustment may be required (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 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 oral tablets, oral tablets, orally disintegrating tablets, 2009; 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 LAMICTAL chewable dispersible oral tablets, oral tablets, 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 LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009; 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 tablet, 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 rash is not identified (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009; Prod Info LAMICTAL XR oral extended-release tablets, 2009).

B) Concomitant use with valproic acid; dose adjustment may be required (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 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 oral tablets, oral tablets, orally disintegrating tablets, 2009; 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 LAMICTAL chewable dispersible oral tablets, oral tablets, 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 LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009; Prod Info LAMICTAL XR oral extended-release tablets, 2009).
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

3.3.1.1   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
3.3.1.B EKG finding
1) Premarketing studies have shown a minor incidence of increased PR interval, which were not clinically significant (Matsuo et al, 1993a). One case of a patient who had first-degree heart block was also reported (Betts et al, 1991).
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 inverted electrocardiogram (EKG) performed 2 weeks after discontinuing lamotrigine was still abnormal, so this was a literature report.

3.3.1.C Hypotension
1) Two children had hypotensive episodes, with blood pressure 77/45 millimeters of mercury in one child, after treatment with lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod Info LAMICTAL XR oral extended-release tablets, 2009).

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 evident in 1% who received placebo (n=121) (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3.3.2.B Erythema multiforme
1) Summary
   a) Multiforme erythema has been rarely reported during clinical trials of pediatric and adult patients receiving lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod Info LAMICTAL XR oral extended-release tablets, 2009).
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. Leptodactyly 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 history included spinocerebellar degeneration; his medications were haloperidol 1 to 5 milligrams (mg) as required, baclofen 10 mg at bedtime. For the previous month and one-half, the patient had been taking lamotrigine 50 mg twice daily was added to the valproate. Due to poor control of his seizures, lamotrigine 50 mg twice daily was added to the valproate. A rash developed, described as red to violaceous, round patches and plaques with central erosions or vesicles in the periorbital area and subsequently spread to the trunk and extremities. Skin biopsy revealed extensive vascular infiltration of lymphocytes, histiocytes, eosinophils, and melanophages. Fixed drug eruption due to lamotrigine was withdrawn, and Solu-Medrol 40 mg/day initiated. Rapid improvement occurred. Nine weeks later, patch test revealed lamotrigine was the causal agent. When patch-test lamotrigine was applied to previously uninvolved areas, the rash 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 occur determined the following significant (p less than 0.05) risk factors: higher starting dose, concomitant soid 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 one 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, respect 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 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 ve 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 rash 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 success 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

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

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, 2C
3) A Stevens-Johnson-like syndrome appeared in one of 16 patients during the first year of lamotrigine treat
5) 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 diagno
to the drug. The patient developed a skin eruption and had complaints of influenza-like symptoms (Sach

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 la

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 repc
adult and 0.8% of pediatric epilepsy patients. Serious rashes were also reported in clinical trials of adult patie
ceiving 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 lamotri
globlastoma multiforme brain tumor. The patient was also receiving allopurinol, captopril, and valproic ac
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 t
rash, which progressed in 4 days to TEN. After 5 days the lamotrigine was discontinued and the patient &

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 milli
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

http://www.thomsonhc.com/hcs/librarian/PFDefaultActionId/pf.PrintReady
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 e 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 dyspe palpitate (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 app 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 or LAMICTAL XR oral extended-release tablets, 2009)
2) Immediate Release
Nausea has been reported in 7% of adult partial seizure patients treated with lamotrigine compared with epilepsy patients receiving lamotrigine compared with 10% of placebo patients, and in 10% of pediatric epilepsy patients receiving lamotrigine compared with 11% with placebo (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

3.3.4.G vomiting

1) Incidence: 9% (immediate-release) (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).
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 valproic acid. Incidence of vomiting was dose-related, increasing from 11% with 300 mg to 18% with 500 mg, compared with 2% 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, vomiting was reported in 500 mg, compared with 11% with placebo (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

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 reported in 500 mg, compared with 2% who received placebo (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

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, hereditary spherocytosis, idiopathic anemia) were reversible after discontinuation of lamotrigine. Patients with anemias were also taking other anticonvulsants, and lamotrigine was discontinued (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006; Pulik et al, 2000; Esfahani & Dasheiff, 1999).
2) Literature Reports
a) Complete erythroblastopenia occurred several weeks after initiation of lamotrigine (50 milligrams for uncontrolled epilepsy in a 29-year-old woman who had been diagnosed at age 4 months with Diamox therapy). Treatment with folic acid 25 mg/day returned hemoglobin levels to normal within 2 months, and treatment was continued for 23 months due to macrocytic anemia (Cocito et al, 2000).

3.3.5.B Disseminated intravascular coagulation

1) Two children (3.5- and 11-years-old) suffered multiorgan dysfunction and disseminated intravascular coagulation after starting lamotrigine therapy and included a syndrome of urticarial/maculopapular rash, hepatic, and renal dysfunction, hypoalbuminemia, and changes in alertness. Disseminated intravascular coagulation was also reported, along with evidence of rhabdomyolysis in one patient. No seizures were noted during this period. This probably represents lamotrigine-associated anticonvulsant hypersensitivity syndrome (Chat et al, 2000).
previously been maintained on carbamazepine and clonazepam for seizures with poor control prior to lamotrigine
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, pan 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, 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 disord 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 decl decreased by 50 mg/day. Briefly her counts returned to baseline only to continue downward. Consequently, li on therapy for approximately 10 months. Her WBC count and neutrophil count at discontinuation was 2.8 x 1t returned to baseline without any recurrence of neutropenia. A year and a half later, the patient was rechalleng decreased once again after 2 months of lamotrigine therapy. Following discontinuation, her counts returned to 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 reacti 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 syn amoxicillin therapy, and the patient was admitted. An atypical headache, hyperthermia, drowsiness, and maj 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
3.3.6.B Hyperbilirubinemia
1) Slight elevations in plasma bilirubin have been reported with lamotrigine (Cohen et al, 1987b); however, if
2) Hyperbilirubinemia is present, such as fever, or lymphadenopathy, the patient should be evaluated immediatel
3) Hepatitis is a common manifestation of drug-induced liver disease. In a case report, a 6-year-old boy developed
4) Elevated serum transaminases (ALT) and alkaline phosphatase (ALP) were reported in a 11-year-old fea
5) Liver function tests 2 months prior to admission were normal, and the patient was afibrile with no signs of infe
6) Based on aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum levels of 960 units/L
7) Instead, the patient was restarted on aripiprazole, titrating up to 25 mg/day. Five days after stopping lamotrig
8) Increased liver enzymes
1) A case report described acute liver failure with significant elevations in liver enzymes in a 21-year-old mal
2) Liver function tests 2 months prior to admission were normal, and the patient was afibrile with no signs of infect
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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
2) A 35-year-old woman, with a history of bipolar disorder and poly substance abuse, developed a fatal prog
3) An 8-year-old boy developed acute hepatic failure 2 weeks after beginning lamotrigine therapy. The pati
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
2) Literature Reports
   a) Anticonvulsant hypersensitivity syndrome (AHS) - consisting of fever, skin eruption or lymphadenopathy
   b) Acute granulomatous interstitial nephritis, along with colitis and ileitis, occurred in a 17-year-old wom
   c) A 6-year-old boy being treated with lamotrigine and valproic acid for generalized tonic-clonic seizures
by clonazepam (1 milligram/day continuous intravenous infusion). Two days after admission, the patient bec
peaked on day 3, then declined and became normal within 2 weeks, when she was discharged. A liver biops
lunchocytes 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, if
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3) A case report described acute liver failure with significant elevations in liver enzymes in a 21-year-old mal
Lamotrigine was discontinued but the symptoms persisted until valproic acid was discontinued 2 days later. Laboratory abnormalities (Brown et al., 1999).

d) A 27-year-old female developed multisystem hypersensitivity reaction, with disseminated intravascular dysfunction, 11 days after starting lamotrigine therapy. Adjunctive therapy included phenobarbital. After spontaneous resolution 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 amyotrophy and had lamotrigine titrated to 50 milligrams/day over 1 month. He developed a rash, fever, and 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., 2006).

f) A 35-year-old man developed pseudolymphoma (which may develop as a hypersensitivity reaction to valproate and had lamotrigine titrated to 50 milligrams/day over 1 month. He developed a rash, fever, and 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., 2006).

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 discontinued.

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) oral tablets, chewable dispersible oral tablets, 2006).

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 was treatment with lamotrigine extended-release (n=118) compared with 0% who received placebo (n=121) (Prod Info LAMICTAL XR oral extended-release tablets, 2009).

3.3.8.C Rhabdomyolysis

1) Rhabdomyolysis has been reported in hypersensitive patients during postmarketing surveillance (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral 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 units/liter). This probably represents lamotrigine-associated anticonvulsant hypocalcemia (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

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

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, on
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 dispersi

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 intelli
was accompanied by marked electroencephalographic (EEG) activation, especially during sleep, when a patt
weaning from lamotrigine, EEG patterns and language function returned to pre-lamotri
gine levels (Batta

3.3.9.C Aseptic meningitis
1) A 25-year-old woman developed aseptic meningitis 8 days after starting lamotrigine 25 mg/day for epilep
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 cerebro
 erythrocytes, and leukocytes were elevated; however, CSF cultures for bacteria, fungi, and viruses were neg
empic ceftriaxone 2 g twice daily was initiated The patient had mild leukopenia and thrombocytopenia were
meral 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 pati
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 it
was started on lamotrigine 25 mg daily 7 months prior to the current incident. Lamotrigine was also discontin
subsequently discharged with a presumptive diagnosis of aseptic meningitis. The time between the administ
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 c
2) In premarketing clinical trials of adjunctive epilepsy therapy, ataxia was reported in 22% of adult patients r
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 j
4) In a controlled, monotherapy trial, ataxia was reported in greater than 2% and less than 5% of adult pati
5) In placebo-controlled, adjunctive trials, ataxia was reported in 11% of pediatric patients with epilepsy rece

3.3.9.E Aura, Loss
1) Three patients experienced loss of aura after switching from conventional antiepileptic therapy to lamotrigine
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 mechanism
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 coon

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
2) In a randomized, placebo-controlled, parallel study, dizziness was one of the more common dose-relk
and 27% of adult patients with epilepsy treated with lamotrigine 300 mg/day (n=71), lamotrigine 500 mg/i
3) In a controlled, monotherapy trial, dizziness was reported in 7% of adult patients with epilepsy who re
4) In placebo-controlled, adjunctive trials, dizziness was reported in 14% of pediatric patients with epilep

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

3.3.9.J Encephalopathy
1) Reversible encephalopathy associated with high lamotrigine blood levels (19 mg/L), with a concurrent urin
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

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 tics resolved within 2 weeks and the OCD symptoms resolved over si
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 lamotrigine patients, and resulted in drug discontinuation in 3.1% of lamotrigine patients (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 2009).

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, 2009).
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 monotherapy oral tablets, oral tablets, 2009).
4) In two placebo-controlled trials, insomnia was reported in 10% of adults with bipolar I disorder receiving lamotrigine after being converted from add-on therapy with other psychotropic medications compared to 6% of those receiving placebo 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 16-year-old, 17.7 mg/L, and another 20 m/L). Mysynto) effects began within the first 2 to 3 years of lamotrigine-valproic acid therapy resulting in a seizure-free period. In both cases, the lamotrigine serum level was higher than usual, which 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 reported in lamotrigine extended-release (n=118) compared with 1% who received placebo (n=121) (Prod Info LAMICTAL XR oral extended-release tablets, 2009).

3.3.9.P Somnolence
1) Incidence: adults, 9% to 14%; children, 17% (Prod Info LAMICTAL(R) chewable dispersible oral tablets, 2009)
2) Immediate Release
   a) In premarketing clinical trials of adjunctive epilepsy therapy, somnolence was reported in 14% of adult patients receiving placebo (n=419) (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 2009).
   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 LAMICTAL XR oral extended-release tablets, 2009)
   c) In two placebo-controlled trials, somnolence was reported in 9% of adults with bipolar I disorder receiving lamotrigine 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 titration of 300 mg/day. Her neurological status improved over the next 2 weeks following discontinuation of lamotrigine (Prod Info LAMICTAL XR oral extended-release tablets, 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 Info LAMICTAL XR oral extended-release tablets, 2009).
2) An 8-year-old female diagnosed 4 years previously with Lennox-Gastaut syndrome developed myoclonic clonazepam/vigabatrin regimen. Lamotrigine had been initiated at 2 mg/kg, then gradually increased to 20 mg/kg. The parents reported increasing frequent episodes of irregular multifocal jerks. Long-term electroencephalogram (EEG) myoclonus, which resolved shortly upon lamotrigine discontinuation (Guerrini et al, 1999).

3.3.9.R Tremor
1) Incidence: adults, 4%; children, 10% (Prod Info LAMICTAL(R) chewable dispersible oral tablets, 2009)
2) Immediate Release
   a) In premarketing clinical trials of adjunctive epilepsy therapy, tremor was reported in 4% of adult patients receiving placebo (n=419) (Prod Info LAMICTAL(R) chewable dispersible oral tablets, oral tablets, 2009).
   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 XR oral extended-release tablets, 2009).
   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 (Reuten et al, 2009).
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) (Prod 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

3.3.10.A Blurred vision
1) Incidence: 11% to 25% (immediate-release) (Prod Info LAMICTAL(R) oral tablets, chewable dispersible or 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 lamotrigine therapy. The mean lamotrigine dose and duration were 5.5 milligrams/kilogram/day (mg/kg) and 22 weeks, respectively. In placebo-controlled studies, the mean dose and duration were 2.9 mg/kg/day and 22 weeks, respectively. In placebo-controlled studies, the frequency among lamotrigine recipients included diplopia at 5.4% (Messenheimer et al, 2000).
3) Extended Release
   a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, blurred visi
treatment with lamotrigine extended-release (n=118) compared with 2% who received placebo (n=121) (Prod 2009).

3.3.10.B Diplopia
1) Incidence: 24% to 49% (immediate-release) (Prod Info LAMICTAL(R) oral tablets, chewable dispersible or 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 therapy. The mean lamotrigine dose and duration were 5.5 milligrams/kilogram/day (mg/kg) and 22 weeks, respectively. In placebo-controlled studies, the frequency among lamotrigine recipients included diplopia at 5.4% (Messenheimer et al, 2000).
3) A comprehensive review of manufacturer data encompassing 13 clinical trials (n=1096) characterize lamotrigine recipients. As add-on therapy, the mean lamotrigine dose and duration were 5.5 milligrams/kilogram/day (mg/kg) and 22 weeks, respectively. In placebo-controlled studies, a frequency among lamotrigine recipients included diplopia at 5.4% (Messenheimer et al, 2000).

3.3.12 Psychiatric Effects

3.3.12.A Anxiety

Depression

Dyssomnia

Suicidal thoughts

Visual hallucinations
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 with low-dose valproate (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2009).

3) Extended Release
a) In a 19-week, double-blind, placebo-controlled study of patients with partial onset seizure, anxiety was 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 type subsequent dose increase to 50 mg/day, then 100 mg/day in 2 week intervals. Initial symptoms after dose increasing 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 lamotrigine disturbances and nightmares returned within 1 week of a dose increase to 75 mg/day. Three months later, the disturbed sleep and nightmares. She continued on 100 mg/day, which resulted in visual hallucinations described that she perceived as real. The events occurred at times of clear consciousness during both daytime and nighttime in hallucinations resolving over 3 days. Hallucinations and nightmares have not recurred despite continued treatment 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 psychiatric disorders, or other conditions were all at an increased risk for suicidality compared to placebo. Ck 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 type subsequent dose increase to 50 mg/day, then 100 mg/day in 2 week intervals. Initial symptoms after dose increasing 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 lamotrigine disturbances and nightmares returned within 1 week of a dose increase to 75 mg/day. Three months later, the disturbed sleep and nightmares. She continued on 100 mg/day, which resulted in visual hallucinations described that she perceived as real. The events occurred at times of clear consciousness during both daytime and nighttime in hallucinations resolving over 3 days. Hallucinations and nightmares have not recurred despite continued treatment 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); in overall clinical experience with the drug, hematuria infrequently occurred (1% or less) (Prod Info LAMICTAL 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. Serum 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 reported 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 Info 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 congestion adjunctive treatment with lamotrigine extended-release (n=118) compared with 0% respectively who received 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 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) (Prod 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 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)
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, che

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 adjective treatment with lamotrigine extended-release (n=118) compared with 5% who received placebo (n=
tables, 2009).

3.3.16.C Drug withdrawal

1) A 26-year-old man developed anhedonia, visual hallucinations, tremor, slight tachycardia, and hyperhidro: 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 followin: 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, i

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 synd 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 (Chal

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 p: 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 potential risk.
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 age 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 mother manufacturer maintains a Lamotrigine Pregnancy Registry to monitor outcomes of exposure to lamotrigine dl, encouraged to report such prenatal exposure, before fetal outcome (eg, ultrasound, amniocentesis results, bi

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 to 1.01, 95% CI, 1.03 to 5.57), and isolated and multiply malformed CP (adjOR equal to 0.79, 9 exposure. There were 72 lamotrigine mono- or polytherapy-exposed registraions, 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) preq 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 simi 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 dr 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 oc 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 conger 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 phenobarbital and valproic acid). One infant was delivered abdominal intestinal obstruction. The mother had been exposed to labetalol and had experienced pre-eclamps
   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 with 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 ex mother's breast milk are not known, breast-feeding is not recommended in infants with lamotrigine, 2007).
3) Literature Reports
   a) Lamotrigine milk to plasma (M/P) ratio was 41.3% (95% confidence interval (CI), 33% to 49.6%) and infant M/P ratio, calculated using each participant’s mean breast milk concentration, ranged from 5.7% to 147.1%. M/P concentrations for each participant, M/P ratios were 26.5% (95% CI, 20.2% to 32.9%) and 63.1% (95% CI, 4 free lamotrigine concentration was 30.9% (95% CI, 13.4% to 48.3%), 1.7 times higher than the total. Infants t 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 l
were significant predictors of lamotrigine breast milk concentration (p values less than 0.0001) in a regression 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 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. The 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
Ethyl 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. Rem
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 concen
7) Probable Mechanism: increased renal clearance
8) Literature Reports
   a) Acetaminophen enhances the urinary elimination of lamotrigine after single doses of the anticonvulsant
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 l
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 (Gos
1991a; Mikati et al, 1989a; Jawad et al, 1987a). In addition, increased serum concentrations of carbamazepi
carbamazepine) and neurotoxicity have been reported during concomitant administration of carbamazepine.
   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, carbamazepi
   (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, verti
increase lamotrigine doses and/or reduce carbamazepine doses. It may be advantageous to monitor the seri
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 o
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 clearanc
   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 within

http://www.thomsonhc.com/hcs/librarian/PFDefaultActionId/pf.PrintReady

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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 lamotri
lamotrigine concentrations was increased by 1 mg/kg/day every other week until clinical response or side effects c
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 b
and a beta-agonist were used for an obstructive lung disease. A current pneumonia was being treated w
was 1.7 mcg/mL and a trough carbamazepine was 11 mcg/mL. The patient continued to suffer from
levitiracetam (1500 mg twice daily) within 4 weeks. After 4 weeks of levitiracetam therapy the patient’s cr
lamotrigine plasma levels were 12.1 mcg/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 signi
Info ORTHO EVRA(R) transdermal system patch, 2008). A sudden change in a patient’s clinical condition can t
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 u
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 l
lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contrace
crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgest
ea 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose) a
and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%) c
contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glut
(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 absent c
concentrations after oral contraceptives were initiated. Two other patients, one with simple partial seizures d
 discontinued their oral contraceptives. Plasma levels of lamotrigine in these two patients had increased by
plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when oral
when oral contraceptives were discontinued. These effects were independent of whether the oral contrace
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. e
oral contraceptives, and 30 who did not. The mean lamotrigine dose was 349 mg/day among women who did not. Mean plasma level of lamotrigine was 13 mcg/mL in patients on oral contraceptives f
(p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sab e
 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, 2

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 inhibition (Rosenhagen et al, 2006). Exercise caution when using both drugs concurrently and monitor for signs and symptoms of myoclonus.

3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use caution if escitalopram and lamotrigine are used concurrently as this resulted in resolved after escitalopram was withdrawn (Rosenhagen et al, 2006). Monitor for signs and symptoms of myoclonus.

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 treatment in a patient with 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 therapy. 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 depression. Lamotrigine plasma levels were similar to baseline level drawn prior to the next dose and after escitalopram was withdrawn. Monitor for signs and symptoms of myoclonus.

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 significant decreases in lamotrigine plasma concentrations (Christensen et al, 2007; Sabers et al, 2003; Sabers et al, 2000). The mechanism of this effect is likely the induction of CYP2C19 and CYP2D6 enzymes, which metabolizes lamotrigine. 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 anxiety disorder. Lamotrigine plasma levels were similar to baseline level drawn prior to the next dose and after escitalopram was withdrawn. Monitor for signs and symptoms of myoclonus.

3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease lamotrigine plasma levels (Sabers et al, 2001; Sabers et al, 2003). Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal contraceptives. Dosage adjustments may be necessary when starting or discontinuing use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal contraceptives. Dosage adjustments may be necessary when starting or discontinuing use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal contraceptives. Dosage adjustments may be necessary when starting or discontinuing use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal contraceptives. Dosage adjustments may be necessary when starting or discontinuing use.

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 is well tolerated and effective in women receiving oral contraceptives. All patients were treated with lamotrigine monotherapy and taking combination oral contraceptives. Lamotrigine plasma concentrations increased by 84% (95% CI, -20% to 134%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 patients during placebo therapy. The mechanism of the interaction is likely the induction of CYP2C19 and CYP2D6 enzymes, which metabolizes lamotrigine. 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 depression. Lamotrigine plasma levels were similar to baseline level drawn prior to the next dose and after escitalopram was withdrawn. Monitor for signs and symptoms of myoclonus.

b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the plasma levels of lamotrigine in patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absence seizures) have been reported. In one case, two patients, one with simple partial seizures and the other with absent seizures, were started on oral contraceptives while receiving lamotrigine. Plasma levels of lamotrigine in these two patients who had increased plasma levels of lamotrigine 47% to 64% (mean 55%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 patients during placebo therapy. The mechanism of the interaction is likely the induction of glucuronidation by combination contraceptive.

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 409 mg/day among women who did not. Mean plasma level of lamotrigine was 13 mcg/mL in patients on oral contraceptives and 27 mcg/mL in patients not on oral contraceptives (p < 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabers et al, 2001). 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 409 mg/day among women who did not. Mean plasma level of lamotrigine was 13 mcg/mL in patients on oral contraceptives and 27 mcg/mL in patients not on oral contraceptives (p < 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabers et al, 2001).

d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1 mg norethindrone) changed the plasma levels of lamotrigine as well as the plasma levels of lamotrigine in patients who were seizure-free (one with epilepsy, two with complex partial seizures, and two with absence seizures) have been reported. In one case, two patients, one with simple partial seizures and the other with absent seizures, were started on oral contraceptives while receiving lamotrigine. Plasma levels of lamotrigine in these two patients who had increased plasma levels of lamotrigine 47% to 64% (mean 55%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 patients during placebo therapy. The mechanism of the interaction is likely the induction of glucuronidation by combination contraceptive.
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 signifi-
can decreased plasma concentrations of lamotrigine. Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the p-glycoprotein substrate ethinyl estradiol have been reported. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%) 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-glucuronide, was increased by 54% (95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 patients during placebo therapy. The mechanism of the interaction is likely the induction of glutathione S-transferase and dihydropyridine receptor (Sabers et al, 2007).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease
the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et al)

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 signifi-
can decreased plasma concentrations of lamotrigine. Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the p-glycoprotein substrate ethinyl estradiol have been reported. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%) 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-glucuronide, was increased by 54% (95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 patients during placebo therapy. The mechanism of the interaction is likely the induction of glutathione S-transferase and dihydropyridine receptor (Sabers et al, 2007).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease
the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et al)

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 contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glucuronide, was increased by 54% (95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 patients during placebo therapy. The mechanism of the interaction is likely the induction of glutathione S-transferase and dihydropyridine receptor (Sabers et al, 2007).
   b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the p-gly-
   c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive co-medication.
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 pi
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 at
plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when oral
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 wom
those who did not. Mean plasma level of lamotrigine was 13 mcml/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 incap
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, 2C

### 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 sign
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 al, 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**

• **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 contraceptives in a crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgestrel 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-gluc
(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).

• **Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the pi
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 at
plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when oral
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).

• **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 wom
those who did not. Mean plasma level of lamotrigine was 13 mcml/L in patients on oral contraceptives a
(p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabe

• **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 incap
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, 2C

### 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 seen with fosphenytoin. Potent hepatic enzyme-inducing drugs including phenytoin enhance the metabolic clearance of fosphenytoin, with steady-state elimination half-life of approximately 24 to 30 hours, coadministration of fosphenytoin reduces the half-life.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Higher doses of lamotrigine are needed when given concurrently with enzyme-inducer.
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 increased risk of other anticonvulsants. The teratogenicity of these drugs is largely or wholly related to the levels of the metabolites.
   b) The epoxide/parent drug ratio is generally increased when phenytoin is given in combination with an enzyme-inducing antiepileptic agent.
   c) When given in combination with an enzyme-inducing antiepileptic agent, the manufacturer recommends increasing the lamotrigine dose.
   d) The manufacturer recommends adjusting the dose of lamotrigine in patients with epilepsy.

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 developed seizures after ingesting ginkgo (Granger, 2001a). An infant developed seizures from ingestion of ginkgo seeds (Yagi, 1993a). The compound 4′-O-methylpyridoxine, a neurotoxin, is found 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 used in monotherapy and about 10-fold over background rates.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use of ginkgo and anticonvulsants in patients with epilepsy. If seizures cannot be controlled by anticonvulsant medication, inquire about the use of ginkgo seed or leaf extract. If the patient must continue the ginkgo product, use with caution and monitor the patient closely.
7) Probable Mechanism: neurotoxin 4′-O-methylpyridoxine (found in leaves and seeds of ginkgo biloba) may be present in sufficient amounts to be problematic in vulnerable populations.
8) Literature Reports
   a) The serum of a 21-month-old patient with ginko food poisoning was assayed for 4′-O-methylpyridoxine micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds. Decreasing to 0.05 mcg/mL at 1 day.
   b) The serum of a 3-month-old patient with ginko food poisoning was assayed for 4′-O-methylpyridoxine micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds. Decreasing to 0.05 mcg/mL at 1 day.
   c) The serum of a 21-month-old patient with ginko food poisoning was assayed for 4′-O-methylpyridoxine micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds. Decreasing to 0.05 mcg/mL at 1 day.
   d) The serum of a 3-month-old patient with ginko food poisoning was assayed for 4′-O-methylpyridoxine micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds. Decreasing to 0.05 mcg/mL at 1 day.
   e) The serum of a 21-month-old patient with ginko food poisoning was assayed for 4′-O-methylpyridoxine micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds. Decreasing to 0.05 mcg/mL at 1 day.
   f) The serum of a 3-month-old patient with ginko food poisoning was assayed for 4′-O-methylpyridoxine micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds. Decreasing to 0.05 mcg/mL at 1 day.
   g) The serum of a 21-month-old patient with ginko food poisoning was assayed for 4′-O-methylpyridoxine micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds. Decreasing to 0.05 mcg/mL at 1 day.
   h) The serum of a 3-month-old patient with ginko food poisoning was assayed for 4′-O-methylpyridoxine micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds. Decreasing to 0.05 mcg/mL at 1 day.
   i) The serum of a 21-month-old patient with ginko food poisoning was assayed for 4′-O-methylpyridoxine micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds. Decreasing to 0.05 mcg/mL at 1 day.
   j) The serum of a 3-month-old patient with ginko food poisoning was assayed for 4′-O-methylpyridoxine micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds. Decreasing to 0.05 mcg/mL at 1 day.

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

http://www.thomsonhc.com/hcs/librarian/PFDefaultActionId/pf.PrintReady
7/1/2009
2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in signif

Exhibit E.15, page 42

Note: The text is not fully visible due to the image quality.
3.5.1.N Mestranol
1) Interaction Effect: decreased plasma lamotrigine concentrations
2) Summary: The coadministration of combined hormonal contraceptives and mestranol has resulted in significant changes in the levels of mestranol (Christensen et al, 2007; Sabers et al, 2003; Sabers et al, 2006). Mestranol concentrations following introduction of oral contraceptives and reports of increased lamotrigine concentrations in women taking mestranol. Dosage adjustments may be necessary when starting or discontinuing mestranol for clinical reasons (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 mestranol concentrations. Carefully monitor and adjust mestranol doses in women who choose estrogen-containing hormonal contraceptives. Seizures occurred in 3 patients during placebo therapy. The mechanism of the interaction is likely the induction of glucose-6-phosphate dehydrogenase (G6PD). Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive therapy.
7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive therapy.
8) Literature Reports
a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that lamotrigine was not affected by mestranol monotherapy and taking combination oral contraceptives. A crossover fashion to receive either placebo or contraceptive (35 mcg ethinyl estradiol/250 mcg norgestrel) 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-glucuronide (95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 patients during placebo therapy. The mechanism of the interaction is likely the induction of glutathione S-transferase (GST) and G6PD. Probable Mechanism: hepatic induction by mestranol of lamotrigine metabolism (May et al, 1999a).
b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the plasma levels of methsuximide, two with complex partial seizures, and two with absent seizures after oral contraceptives were initiated. Two other patients, one with simple partial seizures and one with complex partial seizures, showed no change in plasma levels of lamotrigine in these two patients had increased plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when oral contraceptives were discontinued. These effects were independent of whether the oral contraceptive contained mestranol or norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lamotrigine dose when methylprednisolone is co-administered. Methsuximide levels were 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 women who did not. Mean plasma level of lamotrigine was 13 mcg/mL in patients on oral contraceptives (∼p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine (Sabers et al, 2006). In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mcg ethinyl estradiol/1 mg norethindrone) clearance of 300 mcg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and in clearance gradually increased and were approximately 2-fold higher at the end of the week of inactive lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in women taking mestranol (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lamotrigine is necessary when mestranol is co-administered. Methsuximide levels were reduced by greater than 50% during oral contraceptive co-medication.

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 lamotrigine concentrations. Lamotrigine concentrations were 69.7% lower than compared to lamotrigine monotherapy (May et al, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Monitor seizure control and anticipate a possible need to increase lamotrigine dose when methsuximide is withdrawn from therapy. Dosages of lamotrigine may need to be increased. Probable Mechanism: hepatic induction of lamotrigine metabolism (May et al, 1999a).
8) Literature Reports
a) Lamotrigine serum concentrations from 222 patients receiving lamotrigine monotherapy (n = 64) or cc evaluated. Thirteen patients were being treated with lamotrigine and methsuximide. In the lamotrigine group 7.14 mcg/mL while the mean dose was 7.27 mg/dose/kg. The lamotrigine level-to-dose ratio (LDR) was 3.06 mg/dose/kg. Lamotrigine LDR in this group was 0.31 mcg/mL/mg/kg, demonstrating the inducing properties of methsuximide.

3.5.1.P Norethindrone
1) Interaction Effect: decreased plasma lamotrigine concentrations
2) Summary: The concomitant use of combined hormonal contraceptives and norethindrone has resulted in significant change in a patient's clinical condition and the use or changes in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et al, 2006). A sudden change in a patient's clinical condition and the use of norethindrone in the use of oral contraceptives (Christensen et al, 2007; Sabers et al, 2003; Sabers et al, 2006).
lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine concentrations in women taking lamotrigine. Dosage adjustments may be necessary when starting or discontinuing hormonal co-medication. 

3.5.1.Q \textbf{Norgestimate} 

\begin{enumerate}
\item \textbf{Severity:} moderate 
\item \textbf{Onset:} delayed 
\item \textbf{Substantiation:} established 
\item \textbf{Clinical Management:} Estrogen-containing oral contraceptives have been shown to significantly decrease lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine concentrations in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont

\begin{enumerate}
\item \textbf{Severity:} moderate 
\item \textbf{Onset:} delayed 
\item \textbf{Substantiation:} established 
\item \textbf{Clinical Management:} Estrogen-containing oral contraceptives have been shown to significantly decrease lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine concentrations in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont

\begin{enumerate}
\item \textbf{Severity:} moderate 
\item \textbf{Onset:} delayed 
\item \textbf{Substantiation:} established 
\item \textbf{Clinical Management:} Estrogen-containing oral contraceptives have been shown to significantly decrease lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine concentrations in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont

\begin{enumerate}
\item \textbf{Severity:} moderate 
\item \textbf{Onset:} delayed 
\item \textbf{Substantiation:} established 
\item \textbf{Clinical Management:} Estrogen-containing oral contraceptives have been shown to significantly decrease lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine concentrations in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont

\begin{enumerate}
\item \textbf{Severity:} moderate 
\item \textbf{Onset:} delayed 
\item \textbf{Substantiation:} established 
\item \textbf{Clinical Management:} Estrogen-containing oral contraceptives have been shown to significantly decrease lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine concentrations in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont

\begin{enumerate}
\item \textbf{Severity:} moderate 
\item \textbf{Onset:} delayed 
\item \textbf{Substantiation:} established 
\item \textbf{Clinical Management:} Estrogen-containing oral contraceptives have been shown to significantly decrease lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine concentrations in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont

\begin{enumerate}
\item \textbf{Severity:} moderate 
\item \textbf{Onset:} delayed 
\item \textbf{Substantiation:} established 
\item \textbf{Clinical Management:} Estrogen-containing oral contraceptives have been shown to significantly decrease lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine concentrations in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont

\begin{enumerate}
\item \textbf{Severity:} moderate 
\item \textbf{Onset:} delayed 
\item \textbf{Substantiation:} established 
\item \textbf{Clinical Management:} Estrogen-containing oral contraceptives have been shown to significantly decrease lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine concentrations in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont

\begin{enumerate}
\item \textbf{Severity:} moderate 
\item \textbf{Onset:} delayed 
\item \textbf{Substantiation:} established 
\item \textbf{Clinical Management:} Estrogen-containing oral contraceptives have been shown to significantly decrease lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine concentrations in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont

\begin{enumerate}
\item \textbf{Severity:} moderate 
\item \textbf{Onset:} delayed 
\item \textbf{Substantiation:} established 
\item \textbf{Clinical Management:} Estrogen-containing oral contraceptives have been shown to significantly decrease lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine concentrations in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont

\begin{enumerate}
\item \textbf{Severity:} moderate 
\item \textbf{Onset:} delayed 
\item \textbf{Substantiation:} established 
\item \textbf{Clinical Management:} Estrogen-containing oral contraceptives have been shown to significantly decrease lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine concentrations in women taking lamotrigine. Dosage adjustments may be necessary when starting or discont
plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when oral contraceptives were discontinued. These effects were independent of whether the oral contraceptive used contained ethinyl estradiol or 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. In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mg ethinyl estradiol/1 mg norethindrone) caused a decrease of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and in plasma concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti

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 significant changes in the use or changes in the use of oral contraceptives. (Christensen et al, 2007; Sabers et al, 2003) Lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine concentrations in women taking lamotrigine. Dosage adjustments may be necessary when starting or discontinuing hormonal contraception (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 lamotrigine plasma concentrations. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal contraception (Prod Info ORTHO EVRA(R) transdermal 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 levels are reduced by greater than 50% during oral contraceptive co-medication. Patients were treated with lamotrigine monotherapy and taking combination oral contraceptives. (Sabers et al, 2001). Lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%) following contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glucuronide, was approximately 2-fold higher at the end of the active hormone cycle. This increase occurred in women taking lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of oral contraceptives (Prod Info LAMICTAL(R) oral tablets, chewable dispersible oral tablets, 2006).

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 metabolite. When lamotrigine and oxcarbazepine were co-administered concurrently, seizure control decreased 28.7% compared to lamotrigine monotherapy (May et al, 1999c). In two patients who had received lamotrigine and oxcarbazepine co-therapy, plasma levels of lamotrigine 41% to 64% (mean 49%). As a result, seizure control deteriorated when oral contraceptives were discontinued. These effects were independent of whether the oral contraceptive used contained ethinyl estradiol or 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. In a study of 16 female volunteers, estrogen-containing oral contraceptive (30 mg ethinyl estradiol/1 mg norethindrone) caused a decrease of 300 mg/day lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and in plasma concentrations gradually increased and were approximately 2-fold higher at the end of the week of inacti

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doses may need to be reduced. Additionally, the patient may need to be monitored over several 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 weeks after initiation of therapy. In the first case, a 35-year-old woman being treated for bipolar II disorder (BD II), hypothyroidism, and depression, developed one week of worsening depression and two days of suicidal thoughts and treated with oxcarbazepine, lithium, naproxen, pantoprazole, amoxicillin, and levethoxyroxine. On day 2, lamotrigine was decreased and stopped by day 5, and she was discharged on oxcarbazepine, escitalopram, naproxen, pantoprazole, levethoxyroxine, and hydroxyzine. On day 42 (41 days after oxcarbazepine initiation), she developed a small tongue ulcer. Subsequently, lamotrigine was stopped the following day and the patient was symptom free.

b) Lamotrigine serum concentrations from 222 patients receiving lamotrigine monotherapy (n = 64) or co-prescribed oxcarbazepine were evaluated. Fourteen patients were being treated with lamotrigine and oxcarbazepine. In the lamotrigine group, the lamotrigine level-to-dose ratio (LDR) in this group was 0.71 mcg/mL/mg/kg, demonstrating the inducing properties of oxcarbazepine.

3.5.1.5 Phenobarbital

1) Interaction Effect: reduced lamotrigine efficacy, loss of seizure control

2) Summary: Potent hepatic enzyme-inducing drugs including phenobarbital enhance the metabolic clearance of lamotrigine. In the first case, lamotrigine was decreased and stopped by day 5, and she was symptom free.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Higher doses of lamotrigine are needed when given concurrently with enzyme-inducing drugs including phenobarbital.

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 lamotrigine in children over the age of 2 years and young adults with epilepsy that was not controlled with a single agent was 25.4 hours with repeated dosing (Prod Info Lamictal(R), 2003).

b) In 13 patients treated with either carbamazepine or phenobarbital with lamotrigine, the half-life of lamotrigine in children over the age of 2 years and young adults with epilepsy that was not controlled with a single agent was 25.4 hours with repeated dosing (Prod Info Lamictal(R), 2003).

3.5.1.6 Phenytoin

1) Interaction Effect: reduced lamotrigine efficacy

2) Summary: Potent hepatic enzyme-inducing drugs including phenytoin enhance the metabolic clearance of lamotrigine. Lamotrigine has no significant effect on steady-state phenytoin concentrations (Prod Info Lamictal(R), 2003). When given in combination with an enzyme-inducing antiepileptic agent, the manufacturer recommends an initial lamotrigine dose of 50 mg/day by day 2. Oxcarbazepine dose was decreased and stopped by day 5, and she was discharged on oxcarbazepine, escitalopram, naproxen, pantoprazole, levethoxyroxine, and hydroxyzine. On day 42 (41 days after oxcarbazepine initiation), she developed a small tongue ulcer. Subsequently, lamotrigine was stopped and the patient was symptom free.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Higher doses of lamotrigine are needed when given concurrently with enzyme-inducing drugs including phenytoin. When given in combination with an enzyme-inducing antiepileptic agent, the manufacturer recommends an initial lamotrigine dose of 50 mg/day by day 2. Oxcarbazepine dose was decreased and stopped by day 5, and she was discharged on oxcarbazepine, escitalopram, naproxen, pantoprazole, levethoxyroxine, and hydroxyzine. On day 42 (41 days after oxcarbazepine initiation), she developed a small tongue ulcer. Subsequently, lamotrigine was stopped and the patient was symptom free.

7) Probable Mechanism: increased metabolism of lamotrigine

8) Literature Reports

a) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially higher incidence of adverse effects compared to other anticonvulsants. The teratogenicity of these drugs is largely or wholly related to the levels of the enzymes that metabolize these drugs in humans. In pregnant women, there is a substantially higher incidence of adverse effects compared to other anticonvulsants. The teratogenicity of these drugs is largely or wholly related to the levels of the enzymes that metabolize these drugs in humans. The Epoxide/Parent Drug Ratio is generally increased when enzyme-inducing antiepileptic agents are used. The Epoxide/Parent Drug Ratio is generally increased when enzyme-inducing antiepileptic agents are used. The Epoxide/Parent Drug Ratio is generally increased when enzyme-inducing antiepileptic agents are used. The Epoxide/Parent Drug Ratio is generally increased when enzyme-inducing antiepileptic agents are used. The Epoxide/Parent Drug Ratio is generally increased when enzyme-inducing antiepileptic agents are used. The Epoxide/Parent Drug Ratio is generally increased when enzyme-inducing antiepileptic agents are used. The Epoxide/Parent Drug Ratio is generally increased when enzyme-inducing antiepileptic agents are used. The Epoxide/Parent Drug Ratio is generally increased when enzyme-inducing antiepileptic agents are used. The Epoxide/Parent Drug Ratio is generally increased when enzyme-inducing antiepileptic agents are used. The Epoxide/Parent Drug Ratio is generally increased when enzyme-inducing antiepileptic agents are used. The Epoxide/Parent Drug Ratio is generally increased when enzyme-inducing antiepileptic agents are used. The Epoxide/Parent Drug Ratio is generally increased when enzyme-inducing antiepileptic agents are used.

b) Phenobarbital enhances the metabolic clearance of lamotrigine. Such combinations increase the risk of lamotrigine toxicity.

3.5.1.6.1 Literature Reports

a) In 13 patients treated with either carbamazepine or phenobarbital with lamotrigine, the half-life of lamotrigine in children over the age of 2 years and young adults with epilepsy that was not controlled with a single agent was 25.4 hours with repeated dosing (Prod Info Lamictal(R), 2003). When given in combination with an enzyme-inducing antiepileptic agent, the manufacturer recommends an initial lamotrigine dose of 50 mg/day by day 2. Oxcarbazepine dose was decreased and stopped by day 5, and she was discharged on oxcarbazepine, escitalopram, naproxen, pantoprazole, levethoxyroxine, and hydroxyzine. On day 42 (41 days after oxcarbazepine initiation), she developed a small tongue ulcer. Subsequently, lamotrigine was stopped and the patient was symptom free.

b) In 13 patients treated with either carbamazepine or phenobarbital with lamotrigine, the half-life of lamotrigine in children over the age of 2 years and young adults with epilepsy that was not controlled with a single agent was 25.4 hours with repeated dosing (Prod Info Lamictal(R), 2003). When given in combination with an enzyme-inducing antiepileptic agent, the manufacturer recommends an initial lamotrigine dose of 50 mg/day by day 2. Oxcarbazepine dose was decreased and stopped by day 5, and she was discharged on oxcarbazepine, escitalopram, naproxen, pantoprazole, levethoxyroxine, and hydroxyzine. On day 42 (41 days after oxcarbazepine initiation), she developed a small tongue ulcer. Subsequently, lamotrigine was stopped and the patient was symptom free.
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 is decreased (vanderLee et al., 2006).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Higher doses of lamotrigine are needed when given concurrently with enzyme-inducing antiepileptic agents.
7) Probable Mechanism: increased lamotrigine clearance

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 approximately 40% (Prod Info NORVIR(R), 2006). Use caution if these agents are coadministered. Monitor patients for decreased lamotrigine exposure.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Coadministration of lamotrigine and rifampin has led to significantly increased lamotrigine clearance.
7) Probable Mechanism: decreased lamotrigine serum concentrations

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 after starting lamotrigine treatment (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 when coadministered.
7) Probable Mechanism: unknown
8) Literature Reports
   a) Increased risperidone plasma concentrations and subsequent toxicity were reported in a patient receiving lamotrigine and clozapine (Bienentreu & Kronmuller, 2005). The patient, a 26-year-old woman diagnosed with schizophrenia, had sustained lamotrigine concentrations of 225 mg daily, after which risperidone plasma concentrations increased to 412 ng/mL, accompanied by symptoms of toxicity.

3.5.1.Y Ritonavir
1) Interaction Effect: decreased lamotrigine serum concentrations
2) Summary: Coadministration of ritonavir and lamotrigine may result in decreased lamotrigine serum concentrations, with no increase in toxicity (Prod Info NORVIR(R) oral capsules, solution, 2006). Coadministration of lamotrigine and ritonavir in healthy subjects significantly decreased lamotrigine clearance in an open-label, sequential, 3-period trial. The postulated mechanism of action is enhanced glucuronidation of lamotrigine (vanderLee et al., 2006). If lamotrigine and ritonavir are coadministered, the dose of lamotrigine needs to be increased (Prod Info NORVIR(R) oral capsules, solution, 2006). Coadministration of lamotrigine and lopinavir/ritonavir in healthy subjects significantly decreased lamotrigine clearance (Prod Info NORVIR(R) oral capsules, solution, 2006). In one study, a doubling of the lamotrigine dose was required to maintain therapeutic levels.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Coadministration of lamotrigine and ritonavir may result in decreased lamotrigine serum concentrations, with no increase in toxicity (Prod Info NORVIR(R) oral capsules, solution, 2006). Coadministration of lamotrigine and lopinavir/ritonavir in healthy subjects significantly decreased lamotrigine clearance (Prod Info NORVIR(R) oral capsules, solution, 2006). In one study, a doubling of the lamotrigine dose was required to maintain therapeutic levels.
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 healthy volunteers increased lamotrigine clearance, and a doubling of the lamotrigine dose was required to increase lamotrigine serum concentrations (Prod Info NORVIR(R) oral capsules, solution, 2006). In one study, lamotrigine trough levels were measured between day 2 and day 10 (lamotrigine plus lopinavir/ritonavir) compared to day 10 (lamotrigine alone). The median AUC, Cmax, Cmin, and half-life of lamotrigine were not bioequivalent to those on day 10, with a geometric mean ratio (GMR) for lamotrigine AUC of 1.72 (Prod Info NORVIR(R) oral capsules, solution, 2006).
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 concentrative dependent on the concentration of rufinamide, so maximum changes will most likely occur in children and other 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 result in increased children in children and in other patients who achieve significantly higher levels of rufinamide (Prod Info).
7) Probable Mechanism: unknown

8) Literature Reports
a) A 23-year-old woman presented to the emergency room with generalized rash, redness and swelling of the face, tightness of the chest, and tachycardia. The patient had been taking lamotrigine 200 mg daily for 3 weeks due to her anti-epilepsy regimen. Her initial reactivity was 20 mg, and sertraline 25 mg daily was initiated. Six weeks later, the lamotrigine level was increased to 50 mg daily while lamotrigine was decreased to approximately 50% with a decrease in the lamotrigine level of 9.8 mg/mL at this time. The sertraline daily dose, resulting in a new steady-state lamotrigine level of 9.8 mg/mL decreased to approximately 50% with a 33% decrease in the sertraline daily dose, even though the lamotrigine level was increased to 400 mg daily.

b) Lamotrigine 450 mg daily was not controlling seizures in a 17-year-old female with mixed epileptic disorders and was titrated to 75 mg daily without any side effects. Lamotrigine was also increased to 600 mg daily, and fatigue, and decreased cognition. The lamotrigine level was increased to 800 mg daily, resulting in a new steady-state lamotrigine level of 9.8 mg/mL decreased to approximately 50% with a 33% decrease in the sertraline daily dose, even though the lamotrigine level was increased to 400 mg daily.

3.5.1.AA Sertriline
1) Interaction Effect: an increased risk of lamotrigine toxicity (fatigue, sedation, confusion, decreased cognition, and the blood level of lamotrigine stabilized at 70% of the baseline level).
2) Summary: Two case reports describe epileptic patients who experienced lamotrigine toxicity when sertraline was started. The lamotrigine level was increased to 800 mg daily, resulting in a new steady-state lamotrigine level of 9.8 mg/mL decreased to approximately 50% with a 33% decrease in the sertraline daily dose, even though the lamotrigine level was increased to 400 mg daily.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution should be exercised when combining sertraline and lamotrigine therapy. 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 lamotrigine level of 20 mg/mL. Intermittent explosive disorder, sertraline 25 mg daily was initiated. Six weeks later, the lamotrigine level was increased to 50 mg daily while lamotrigine was decreased to approximately 50% with a 33% decrease in the sertraline daily dose, even though the lamotrigine level was increased to 400 mg daily.

b) Lamotrigine 450 mg daily was not controlling seizures in a 17-year-old female with mixed epileptic disorders and was titrated to 75 mg daily without any side effects. Lamotrigine was also increased to 600 mg daily, and fatigue, and decreased cognition. The lamotrigine level was increased to 800 mg daily, resulting in a new steady-state lamotrigine level of 9.8 mg/mL decreased to approximately 50% with a 33% decrease in the sertraline daily dose, even though the lamotrigine level was increased to 400 mg daily.

3.5.1.AB Valproic Acid
1) Interaction Effect: increased elimination half-life of lamotrigine leading to lamotrigine toxicity (fatigue, drowsiness, and cognitive impairment).
2) Summary: Valproic acid interferes with the metabolic clearance of lamotrigine. The normal elimination half-life receiving concomitant valproic acid therapy, the half-life increases to approximately 40 to 60 hours. The median lamotrigine level was increased to 800 mg daily, resulting in a new steady-state lamotrigine level of 9.8 mg/mL decreased to approximately 50% with a 33% decrease in the sertraline daily dose, even though the lamotrigine level was increased to 400 mg daily.
3) Severity: major
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Dosage reductions of lamotrigine are necessary with concurrent valproic acid therapy. The manufacturer recommends a lamotrigine dose of 25 mg every other day for the first two weeks, advancing to a maintenance dose of 100 mg to 400 mg daily in increments of 25 mg to 50 mg only other antiepileptic medication, the usual maintenance dose of lamotrigine is 100 to 200 mg daily. Discontinue the drug 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 of the face, tightness of the chest, and tachycardia. The patient had been taking lamotrigine 200 mg daily for 3 weeks due to her anti-epilepsy regimen. Her initial reactivity was 20 mg, and sertraline 25 mg daily was initiated. Six weeks later, the lamotrigine level was increased to 50 mg daily while lamotrigine was decreased to approximately 50% with a 33% decrease in the sertraline daily dose, even though the lamotrigine level was increased to 400 mg daily.

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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 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 fever, extremities, neck, and back. He had been taking allopurinol 100 mg daily and captopril 50 mg daily for multifocal brain tumor, valproic acid and lamotrigine therapy was begun and the doses were titrated to 50 mg twice daily approximately four weeks prior to his hospital admission. By hospital day 7, the patient’s back, face, and trunk, accounting for more than 60% of his total body surface area. He continued to c hospital day 12. His death was attributed to toxic epidermal necrolysis probably due to lamotrigine therapy 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 patient 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 acid to maintain stable lamotrigine Cs. 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 ual, 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

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, prepregnna provide a reference concentration for comparison to concentrations during pregnancy, when concentrations c characteristics of lamotrigine (Tomson & Battino, 2007).

2) Physical Findings

a) Patients receiving lamotrigine for the treatment of epilepsy should be monitored for a therapeutic response 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 levels 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 identifi 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 cc epilepsy, psychiatric disorders, or other conditions were all at an increased risk for suicidality compared to pl

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:
   Table, 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 chang 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 c 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 tc This medicine comes with patient instructions. Read and follow these instructions carefully. Ask your doctor c

   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 c 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 carbamazepini 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 horm 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®, Trexal®) or pemetrexed (Alr

   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). Check
symptoms: fever, dark urine, headache, hives, muscle pain or stiffness, stomach pain, unusual tiredness, or
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 up
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 suicide
This medicine lowers the number of some types of blood cells in your body. Because of this, you may blee
problems, avoid being near people who are sick or have infections. Wash your hands often. Stay away from
bruised, cut, or injured. Brush and floss your teeth gently. Be careful when using sharp objects, including razc
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, c
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.
Nosebleed.
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 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.
Unusual bleeding, bruising, or weakness.
Wheezing or troubled breathing.
Yellowing of your skin or the whites of your eyes.

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 tat
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 binding
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 n
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
release in brain tissue, with no effect on potassium-induced amino acid release. This suggests that the drug acts on
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

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 ε
      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 resumpti
      treated with lamotrigine monotherapy after initial diagnosis also attained complete seizure control at a media
      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
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 bipolar disorder but did not otherwise specified. The primary measure for response was a "1" or "2" on the secondary measure for response was at least a 50% decrease in the Children's Depression Rating Scale-Re.

b) In a 41-year-old female with longstanding bipolar disorder, add-on lamotrigine effectively substituted for lithium. Despite escalating prednisone doses to 120 mg/day, her rash, but on further investigation, it was concluded that they experienced skin irritations, not true rash. Adverse effects included dizziness (29%), tremor (23%), somnolence (21%), headache (19%), nausea (15%), vomiting (13%), and diarrhea (6%).

c) Data from a 48-week open-label trial lend support to lamotrigine's effectiveness as add-on (n=60) or monotherapy for bipolar I or II disorder. Of 40 evaluable subjects with depressive symptoms, 48% and 20% responded to a combination of lamotrigine, paroxetine and levothyroxine. Some patients with rapid-cycling bipolar disorder succeeded on lamotrigine maintenance monotherapy (Plan et al, 2002).

d) 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 study. 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 placebo or lamotrigine, at baseline. lamotrigine was effective in delaying the time to occurrence of mood episodes in patients with bipolar disorder. Nonresponsive patients 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-D) score of 1 or 2) was attained by 11 of 19 (58%) responders. The percentage of patients able to complete 6 months of the randomized phase without added treatment was 18 weeks and the difference was not significant (p=0.177).

e) In an open trial of lamotrigine therapy in 7 patients with treatment-refractory mood disorder, mixed results were reported. Five patients showed marked and moderate improvement, respectively, with a mean 74% decrease in Mania Rating Scale scores. Of 31 evaluable subjects with treatment-refractory bipolar disorder, lamotrigine was effective in delaying the time to occurrence of mood episodes in patients with bipolar disorder. Nonresponsive patients were 19 evaluable patients with 16 (84%) considered responders by primary criteria and 12 (63%) considered responders. The percentage of patients able to complete 6 months of the randomized phase without added treatment was 18 weeks and the difference was not significant (p=0.177). Median survival time without added treatment was 18 weeks and the difference was not significant (p=0.177).

f) In a 41-year-old female with longstanding bipolar disorder, add-on lamotrigine effectively substituted for lithium. Prednisone was necessary to treat lithium-induced interstitial nephritis. Lamotrigine increased to 200 mg every 12 hours within 9 days. Despite escalating prednisone doses to 120 mg/day, her rash, but on further investigation, it was concluded that they experienced skin irritations, not true rash. Adverse effects included dizziness (29%), tremor (23%), somnolence (21%), headache (19%), nausea (15%), vomiting (13%), and diarrhea (6%).

g) In a 41-year-old female with longstanding bipolar disorder, add-on lamotrigine effectively substituted for lithium. Prednisone was necessary to treat lithium-induced interstitial nephritis. Lamotrigine increased to 200 mg every 12 hours within 9 days. Despite escalating prednisone doses to 120 mg/day, her rash, but on further investigation, it was concluded that they experienced skin irritations, not true rash. Adverse effects included dizziness (29%), tremor (23%), somnolence (21%), headache (19%), nausea (15%), vomiting (13%), and diarrhea (6%).

h) Some patients with rapid-cycling bipolar disorder succeeded on lamotrigine maintenance monotherapy (Plan et al, 2002). 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 study. 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 placebo or lamotrigine, at baseline. lamotrigine was effective in delaying the time to occurrence of mood episodes in patients with bipolar disorder. Nonresponsive patients were 19 evaluable patients with 16 (84%) considered responders by primary criteria and 12 (63%) considered responders. The percentage of patients able to complete 6 months of the randomized phase without added treatment was 18 weeks and the difference was not significant (p=0.177). Median survival time without added treatment was 18 weeks and the difference was not significant (p=0.177).
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, 2000).
3) Adult:
   a) Lamotrigine therapy in a case series of 13 patients with severe brain injury brought better than expected results as a 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); was oriented and animated, his short-term memory improved, his conversation became coherent, and his ability to discharge from his home. On the Rancho Los Amigos Cognitive Scale, he improved from level III to level VIII. In 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 dose was 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 days, 1 to a son's home, and 1 to a community residential program; after rehabilitation of mean 117 days, 3 were discharged.

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 infantile spasms per day (p=0.028) in patients diagnosed with intractable seizures. Enrolled infants had to have been diagnosed with infantile spasms, 1 was diagnosed with both infantile spasms and partial seizures. In this study, one patient had no response and no infants became seizure free. Doses were begun in 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 valproate and enzyme inducers, were dosed between 5 to 10 mg/kg/day. In infants between 1 and 12 months of age, 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
3) Adult:
   a) A 65-year-old female psychiatric inpatient with frontal lobe dementia (presenile condition) and resultant aggressive behavior greatly benefited from add-on lamotrigine. Wasting 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 benefit in the treatment of depersonalization disorder. Each month patients were assessed using the Present State Examination and the Cambridge Depersonalization study due to nonadherence to the study protocol. One other patient dropped out due to developing neutropenia. These individuals were not included in the statistical analyses. Analysis of the administered scale scores revealed that endpoint scores in both arms. Mild nausea, dizziness, and muscle aches were reported with lamotrigine use.

4.5.1 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 with a diagnosis of depression, treatment-resistant, unipolar depression. Results of a retrospective chart review (n=37) showed that adjunctive lamotrigine was efficacious and well tolerated across a variety of antidepressant and/or combination augmentation strategies. The mean number of prior antidepressant and/or combination augmentation studies and there were no instances of skin rash or other dermatological toxicity.

3) Adult:

   a) General Information

      1) Treatment with oral lamotrigine used as an add-on to antidepressant therapy was safe and demonstrated treatment-refractory, unipolar depression. Patients who had experienced a negative response to at least two adequate trials (minimum of 6 weeks) of antidepressant therapy at a maximum daily dosage of 25 mg/day were included. Patients were randomized to receive either lamotrigine or lithium augmentation. Lamotrigine was initiated at 25 mg/day and titrated up to 250 mg/day over a 6-week period. Lithium was titrated to a blood level of 0.6 to 0.8 millimoles/liter. Prior antidepressant therapy (n=20), atypical antipsychotics (n=27), and right unilateral electroconvulsive therapy (n=5), and 4 mg/day were discontinued. Based on clinical need, concomitant use of benzodiazepines (n=27) were taken by patients during this study. Weekly assessments were conducted using the HRS rating scale. Prior to study initiation, most patients had received treatment with a variety of augmentation or combination strategies. A retrospective chart review (n=37) revealed that add-on treatment with lamotrigine led to similar efficacy results as lithium augmentation in patients with depression, treatment-resistant, unipolar depression. A review of the literature revealed that lamotrigine augmentation (Schindler & Anghelescu, 2007). Two other retrospective chart reviews found similar improvement in depression scores, which were culled retrospectively from chart notes. Patients included in the open-label study as adult patients with a diagnosis of depression, treatment-refractory, unipolar depression in adults (Barbee & Jamhour, 2002).

   b) Clinical Trials

      1) In an open-label, randomized, prospective study (n=34), treatment with add-on oral lamotrigine was safe and demonstrated efficacy in patients with treatment-resistant, unipolar depression. Patients who had experienced a negative response to at least two adequate trials (minimum of 6 weeks) of antidepressant therapy at a maximum daily dosage of 25 mg/day were included. Patients were randomized to receive either lamotrigine or lithium augmentation. Lamotrigine was initiated at 25 mg/day and titrated up to 250 mg/day over a 6-week period. Lithium was titrated to a blood level of 0.6 to 0.8 millimoles/liter. Prior antidepressant therapy (n=20), atypical antipsychotics (n=27), and right unilateral electroconvulsive therapy (n=5), and 4 mg/day were discontinued. Based on clinical need, concomitant use of benzodiazepines (n=27) were taken by patients during this study. Weekly assessments were conducted using the HRS rating scale. Prior to study initiation, most patients had received treatment with a variety of augmentation or combination strategies. A retrospective chart review (n=37) revealed that add-on treatment with lamotrigine led to similar efficacy results as lithium augmentation in patients with depression, treatment-resistant, unipolar depression. A review of the literature revealed that lamotrigine augmentation (Schindler & Anghelescu, 2007). Two other retrospective chart reviews found similar improvement in depression scores, which were culled retrospectively from chart notes. Patients included in the open-label study as adult patients with a diagnosis of depression, treatment-refractory, unipolar depression in adults (Barbee & Jamhour, 2002).

   2) A retrospective chart review (n=37) revealed that add-on treatment with lamotrigine was efficacious in the treatment of depression. Charts of patients (mean age 50.22 years; range, 18-75 years) with a diagnosis of major depression who had received lamotrigine augmentation following failure of at least two adequate trials (minimum of 6 weeks) were reviewed. Patients with current psychotic symptoms, or hypomania/mania were excluded. Lamotrigine was initiated at 25 mg/day for 2 weeks and then increased to 50 mg/day for 2 weeks; further dosage increases were made if the patient was no longer able to tolerate further dosage increases. Patients included in the study had a diagnosis of depression that had not responded to at least two adequate trials (minimum of 6 weeks) of antidepressant therapy. A review of the literature revealed that lamotrigine augmentation (Schindler & Anghelescu, 2007). Two other retrospective chart reviews found similar improvement in depression scores, which were culled retrospectively from chart notes. Patients included in the open-label study as adult patients with a diagnosis of depression, treatment-refractory, unipolar depression in adults (Barbee & Jamhour, 2002).
medications during lamotrigine therapy. The mean duration of lamotrigine treatment was 35.41 weeks (r
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)) were evaluated retrospectively based on extensive, detailed progress notes r
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-handed,
epilepsy. Although most effects were only partial, 28.8% of patients had a reduction of 50% or more in seizu
reduction of 50% or more in seizures, myoclonic seizures, typical absence seizures, and atypical absence seizures. A complete respons
b) Lamotrigine was reported to be useful in treating 10 adult patients (23 to 44 years old) with intractable abs
start ed in childhood and persisted into adulthood. Lamotrigine was initially started at 0.2 milligrams/kilogram
maxim um of 5 mg/kg. All patients were receiving valproic acid. Except for valproic acid, all other antiepileptic
optim al 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

4) Pediatric:

a) 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 0.0006), with 6 of these subjects remaining seizure-free. Three of m
marked improvement in behavior, although seizure frequency was unchanged. Higher response rates were o
ymptoms of cerebral malformation. Seizure worsening occurred in 9 patients; transient rash developed in s
starting daily dose was 0.2 to 2.5 milligrams/kilogram (mg/kg) titrated over 2 to 4 weeks to an initial maintena
sequently adjusted based on clinical response up to a maximum of 1.8 to 15 mg/kg/day; mean dose was valp
rate, median dose was 4.8 mg/kg/day; for those on enzyme-inducing drugs except valproate, median dc
b) In an open trial, 16 out of 63 children had a complete response to lamotrigine add-on treatment for their r
es with a mean of 1.72 seizure types per child. Seizure types included infantile spasms, simple partial seiz
s, myoclonic seizures, typical absence seizures, and atypical absence seizures. A complete response achieved a 50% to 90% decrease in seizures (Buoni et al, 1998).

b) 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 i
11 of 24 children with other symptomatic generalized epilepsy (p less than 0.09). Rash occurred in 4 patien
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) l
more of more than 50% and 8 of these patients became seizure-free. Lamotrigine was most effe
absences, and atonic seizures (Coppola & Pascoetto, 1997).

e) Fourteen children suffering from refractory epilepsy received lamotrigine as add-on therapy. A decrease i
lamotrigine was observed in 6 of the 7 patients who completed the study. The median total seizure frequency s
seizure frequency had decreased by more than 50% in 2 patients, by more than 75% in 2 patients, ar
seizure frequency was unchanged (Battino et al, 1996)(Battino et al, 1996b).

f) In one series, 8 of 10 children with various seizure disorders had decreased total seizure count when lamc
used in increasing doses up to 2 milligrams/kilogram/day (mg/kg/day) in patients taking valproic acid, and in t
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 dec
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 common valp

http://www.thomsonhc.com/hcs/librarian/PFDefaultActionId/pf.PrintReady
12 children with severe or life-threatening epilepsy received lamotrigine (250 to 900 milligrams/day) for 12 to 61 months with 4 on monotherapy. No patient was hospitalized for status epilepticus. No adverse effects of lamotrigine were noted.

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 RATING

2) Summary:
Effective in 2 case reports (DeLeon & Furmaga, 1999)

3) Adult:
- Two cases were presented describing patients with epilepsy-related psychosis that was resistant to antipsychotic therapies. The first was a 39-year-old woman with seizures and psychosis that included thought broadcasting, clonazepam, phenytoin and gabapentin without improvement in seizure control or decrease in psychotic symptoms. Her treatment consisted of clonazepam twice daily and the man was titrated to 450 mg daily. Also in both cases risperidone was tapered and discontinued 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 RATING

2) Summary:
In 1 study, lamotrigine was useful as adjunctive therapy for seizures associated with infantile neuronal ceroid lipofuscinosis (DeLeon & Furmaga, 1999)

3) Pediatric:
- Lamotrigine was useful in treating seizures associated with infantile neuronal ceroid lipofuscinosis. Lamotrigine was started in 16 children (2.5 to 12 years old) at a dose of 0.5 milligrams/kilogram and increased every 2 weeks as needed. Ten patients seizure frequency decreased by more than 50%. In 4 children seizures decreased by 100%. Monotherapy was 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 RATING

2) Summary:
Exacerbation of myoclonus reported in juvenile myoclonic epileptic patients treated with lamotrigine (Biraben et al, 2000)

3) Adult:
- A group of 7 patients 16 to 32 years of age with juvenile myoclonic epilepsy (JME) experienced immediate side effects of lamotrigine. Three patients began lamotrigine as add-on therapy to valproic acid. In either instance, JME deteriorated, with worsening of myoclonus in all 7 patients and appearance of side effects. The patients were switched back to valproic acid or to topiramate without further adverse sequelae. Dosing of lamotrigine was given as monotherapy and 150 to 200 mg/day when combined with valproate (Biraben et al, 2000).

4) Pediatric:
- A group of 7 patients 16 to 32 years of age with juvenile myoclonic epilepsy (JME) experienced immediate side effects of lamotrigine. Three patients began lamotrigine as add-on therapy to valproic acid. In either instance, JME deteriorated, with worsening of myoclonus in all 7 patients and appearance of side effects. The patients were switched back to valproic acid or to topiramate without further adverse sequelae. Dosing of lamotrigine was 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 RATING

2) Summary:
Indicated as adjunctive therapy for the generalized seizures of Lennox-Gastaut syndrome (Prod Info LABA)
orally disintegrating tablets, 2009)

3) Adult:
   a) In a double-blind, placebo-controlled study, lamotrigine as add-on therapy was effective for seizures associated with Lennox-Gastaut syndrome (age 5.5 to 27 years) received lamotrigine 100 to 400 mg/day, seizure-free after 2 months to 2 years of treatment. Eight of 13 achieved control of at least 1 seizure type. Six patients receiving lamotrigine and valproic acid developed rash.

   b) In a double-blind, placebo-controlled study, lamotrigine as add-on therapy was effective for seizures associated with Lennox-Gastaut syndrome (age 5.5 to 27 years) received lamotrigine and valproic acid developed rash.

   c) As part of a larger open, prospective trial, 11 of 15 children with Lennox-Gastaut syndrome were improved.

4) Pediatric:
   a) In a double-blind, placebo-controlled study, lamotrigine as add-on therapy was effective for seizures associated with Lennox-Gastaut syndrome (age 5.5 to 27 years) received lamotrigine and valproic acid developed rash.

   b) Thirteen patients with Lennox-Gastaut syndrome (age 5.5 to 27 years) received lamotrigine 100 to 200 milligrams for other patients. For all seizure types, the median frequency changed from 16.4 and 13.5 per week to 9.9 and 14.2 per week after 16 weeks of treatment, respectively (p less than 0.002). Reduction of seizure frequency was seen in the lamotrigine group and in 16% of the placebo group (p less than 0.01). The results were similar for drop attacks and absence seizures did not significantly change. Two patients on lamotrigine and valproic acid developed rash.

   c) Thirteen patients with Lennox-Gastaut syndrome (age 5.5 to 27 years) received lamotrigine and valproic acid developed rash.

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.

   a) Lamotrigine appears to act specifically on the aura mechanism in relieving migraine headaches and appears to be effective in patients with an aura before their migraine (Lampl et al, 1999).

   b) Lamotrigine appears to act specifically on the aura mechanism in relieving migraine headaches and appears to be effective in patients with an aura before their migraine (D'Andrea et al, 1999).

3) Adult:
   - Lamotrigine appears to act specifically on the aura mechanism in relieving migraine headaches and appears to be effective in patients with an aura before their migraine (D'Andrea et al, 1999).

   a) In one study, 21 patients receiving lamotrigine 100 milligrams/day had attacks from 6.1/month at baseline to 0.7/month after 3 months (p less than 0.0001). In 13 patients the attacks were reduced. In 5 patients with migraine without aura, there was no change (D'Andrea et al, 1999).

   b) In one study, 21 patients receiving lamotrigine 100 milligrams/day had attacks from 6.1/month at baseline to 0.7/month after 3 months (p less than 0.0001). In 13 patients the attacks were reduced. In 5 patients with migraine without aura, there was no change (D'Andrea et al, 1999).

   c) In one study, 21 patients receiving lamotrigine 100 milligrams/day had attacks from 6.1/month at baseline to 0.7/month after 3 months (p less than 0.0001). In 13 patients the attacks were reduced. In 5 patients with migraine without aura, there was no change (D'Andrea et al, 1999).

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, 2003).

   a) In a single case report, lamotrigine improved symptoms of pathological laughing and crying in a 60-year-old patient with left frontal and temporal lobes affected. The patient had developed symptoms of pathological laughing and crying in a 60-year-old patient with left frontal and temporal lobes affected. 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 decreased from 23 minutes at baseline to 3 minutes (p less than 0.001) (Lampl et al, 1999).

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-controlled trial. Mixed results observed in neuropathic pain due to diabetes (Eisenberg et al, 2001) and HIV (Simont et al, 2002) in randomized, double-blind, placebo-controlled trials.

No appreciable effect seen with lamotrigine for intractable neuropathic pain (McCleane, 1999) or neuropathic pain in patients with spinal cord injury (SCI) but did reduce pain in a subset of the sample, which was characterized by incomplete lesions.

3) Adult:

a) Lamotrigine was not effective for relieving neuropathic pain symptoms in 125 patients with chemotherapy-induced peripheral neuropathy in a phase 3 randomized, placebo-controlled study. Patients with symptomatic CIPN with pain scores of either greater than or equal to 3 on a 0 to 10 Numerical Rating Scale (NRS) were e-nrolled. The treatment group (n=63) or placebo (n=62). The primary efficacy measure, patient-reported "average" daily pain score, was assessed weekly. Secondary efficacy measures, such as the World Health Organization (WHO) clinical pain score, evoked pain threshold, and sensory testing, were also evaluated. The results showed that lamotrigine was not effective for relieving neuropathic pain symptoms in 125 patients with chemotherapy-induced peripheral neuropathy in a phase 3 randomized, placebo-controlled study.

b) Lamotrigine effectively improved numerical pain scores in patients with diabetic neuropathy but failed to meet its primary endpoint of a 30% improvement in pain intensity score (pain intensity score at week 12 with lamotrigine vs. placebo). The median difference in pain intensity scores (pain intensity score at week 12 with lamotrigine vs. placebo) for lamotrigine was 3.6 (p=0.22), and symptoms using ENS were 2 and 1.9 (p=0.31) for lamotrigine and placebo, respectively. The most common toxicities were rash, pruritus, fatigue, and headache, which were more common in the lamotrigine group compared to the placebo group. Adverse effects were similar for both groups, although patients receiving lamotrigine were more likely to experience rash (5% vs. 1%), pruritus (2% vs. 0%), fatigue (2% vs. 0%), and headache (0% vs. 4%) (Rao et al, 2008).

In a randomized, double-blind, placebo-controlled clinical trial conducted in Israel, patients (n=53) with neuropathic pain of at least 6 months duration, and pain scores of at least 4 on a scale of 0 to 10 at the time of enrollment, the proportion of patients reporting at least 50% pain relief after 12 weeks of treatment was similar between the lamotrigine and placebo groups (60% vs. 59%, respectively). Lamotrigine was not effective for relieving neuropathic pain symptoms in a subset of the sample, which was characterized by incomplete lesions.

Rash occurred in 2 patients (1 with lamotrigine and 1 with placebo) during the maintenance phase of the study. The median difference in pain intensity scores (pain intensity score at week 12 with lamotrigine vs. placebo) for lamotrigine was 3.6 (p=0.22), and symptoms using ENS were 2 and 1.9 (p=0.31) for lamotrigine and placebo, respectively. The most common toxicities were rash, pruritus, fatigue, and headache, which were more common in the lamotrigine group compared to the placebo group. Adverse effects were similar for both groups, although patients receiving lamotrigine were more likely to experience rash (5% vs. 1%), pruritus (2% vs. 0%), fatigue (2% vs. 0%), and headache (0% vs. 4%) (Rao et al, 2008).

b) Lamotrigine was not effective for relieving neuropathic pain symptoms in a subset of the sample, which was characterized by incomplete lesions.
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 sensitivities 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 weight subjects who took placebo, lamotrigine showed a statistically significant difference in mean change in BMI (Merideth, 2006).

3) Adult:
   a) In a single center, double-blind, placebo-controlled, randomized study (n=40) of healthy adult volunteers with BMI greater or equal to 30 but less than 40), while there was no statistically significant mean change in BMI weight 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 endpoint difference in baseline body weight between the 2 groups (lamotrigine mean +/- standard deviation (SD) 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 change and -0.1 +/- 1.05 for lamotrigine and placebo, respectively (p=0.0421). A greater change in quality of life sati lamotrigine group (p=0.0065). Other secondary outcomes showed no significant differences. No serious adverse in the placebo group discontinued treatment due to edema. No lamotrigine subjects discontinued treatment d the most frequently reported adverse event with an 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 spasms (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 mg/day. Multiple sclerosis-related pain syndromes refractory to multiple other medications. Improvement in paroxysm in 82 (38%) patients, with five of 21 (24%) experiencing improvement in painful tonic spasms. The y in some cases. These results require confirmation in a placebo-controlled trial (Cianchetti et al, 1999)
   b) Postoperative Pain
      1) Lamotrigine may be effective in reducing postoperative pain In a double-blind, placebo-controlled stx 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 2 pain score over the last week of treatment from 7 to 5 (p=0.01 compared with placebo). Twelve of 27 su 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 cc lamotrigine (p=0.02 and p=0.01, respectively); the trend favored lamotrigine on other secondary end poi events occurred at similar rates in the 2 periods. Mild rash was associated with lamotrigine use in 2 pat during the lamotrigine period due to mild rash, severe headache, and severe pain (Vestergaard et al, 201
1) An open-label, non-comparative study involving 14 patients suggests that lamotrigine may be effective for radiculopathy for 12 to 36 months. They underwent a 1 week washout period from previous analgesics and lamotrigine was initiated at 25 milligrams (mg) once daily and was doubled weekly up to the maintenance dose of 400 mg for 4 weeks. Of the 14 patients, only 7 completed the full 11 weeks. Diarrhea, dizziness and person discontinued. In patients who received at least 1 week of lamotrigine and in whom drug plasma concentrations were found to be within therapeutic range, numerical pain scale scores for spontaneous pain decreased from 7.6 to 4.5 at the end of 11 weeks (p<0.001). 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-old admitted to psychiatric services because of an acute psychotic episode associated with excessive alcohol consumption. After alcohol detoxification and antipsychotic treatment (thioridazine 100 milligrams (mg) 3 times daily), he was patient reported gradual improvement, with disappearance of ear-clicking and slowing of the frequency of palatal motor 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 C
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 dose of 125 (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 choreoathetosis year-old girl, and a 10-year-old boy. The first boy was started on lamotrigine 5 milligrams (mg)/day, with titration up to 50 mg/day. On that dosage, his attacks were significantly decreased was attack-free. The girl received increasing doses, starting from 5 mg/day ranging up to 100 mg/day (4.7 mg/kg/day, she was attack-free also. The second boy began taking lamotrigine 10 mg/day, with titration biweekly to point his dystonic attacks ceased. In all cases, lamotrigine was well tolerated. Previous medications which had carbamazepine, phenobarbital, and flunarizine. The patients had used lamotrigine for 16, 19, and 27 months,
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 epilepsy tablets, oral tablets, orally disintegrating tablets, 2009). Indicated for conversion to monotherapy in patients receiving treatment with a single enzyme-inducing agent in 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 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 for partial seizures, the clinical status of 58% of patients were judged to have improved from baseline and the long-term incidence of adverse effects. Patients were recruited from 5 primary clinical studies of adjunctive lamotrigine.

c) As an add-on treatment, lamotrigine (LTG) was effective in the treatment of epileptic drop attacks (EDA) in 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 increased monthly while taking the maintenance dose. Prior medications were continued throughout the study. In patients under treatment with LTG, 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 was increased to 600 mg/day. In the last year, the maintenance dose was 37% of patients, miscellaneous reasons (7%), adverse events (5%) and administrative reasons (5%).

Overall clinical status was judged on a 7-point scale by the investigators. Mild, moderate, and marked improvement was recorded if the time of discontinuation, when comparing to pre-lamotrigine clinical status. No change was seen in 30% of patients 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 were w a serious adverse event by 0.4% of patients. No patients developed Stevens-Johnson syndrome (Faught et al, 2001).

d) Monotherapy with lamotrigine was successful in most patients with partial seizures converted from adjunctive therapy in a 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 lamotrigine for 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 lamotrigine was 69%. A low dose of valproate was used to demonstrate the efficacy of lamotrigine and provide some proof to demonstrate lamotrigine's superiority or equivalence (Gilliam et al, 1998).

e) Double-blind, placebo-controlled add-on trials demonstrated that lamotrigine is efficacious in treating refractory partial seizures with or greater reduction in seizure frequency in 48% of patients and 50% or greater reduction in seizures (n=216), observed median reductions in seizures relative to baseline were 8%, 20%, and 36% in patients receiving lamotrigine 500 mg/d, respectively (Matsuo et al, 1993). In addition, preliminary data indicate that lamotrigine does not achieve a significant improvement in EDA frequency. The average maximum LTG dosages were 200 mg/day with valproic acid and lamotrigine was 69%.

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 dropped to 26%.

g) Ten of the 27 patients with refractory complex partial, secondarily generalized tonic-clonic, atypical absences 12 months due to lack of efficacy. Patients were studied over a 2-year period with 11 of the remaining patients having 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 refractory reduction in seizure frequency (Sander et al, 1990). Nineteen patients withdrew from the study due to adverse effects: drowsiness, 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 refractory seizures showed improvement with lamotrigine treatment; the mean reduction in seizure frequency was 59% (considered improvement in simple and complex partial seizures; 8 of 15 showed improvement in secondarily generalized common adverse reactions included fatigue, diplopia, drowsiness, ataxia, and headache. These were not cor...
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/day) 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, a One case of skin rash, which subsided after a day, and one case of elevated liver enzymes, which subsided a Eleven of the 15 infants had no observed adverse effects (Mikati et al, 2003).

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 (Fa

3) Adult:
   a) Four adults with debilitating, refractory startle-induced seizure disorders gained relief from add-on lamotrigine 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 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 r the girl became seizure-free. Her abnormal hand movements, though continuing, were appreciably decrease 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 total symptom scores in patients resistant to clozapine therapy. Patients (n=34) were diagnosed with schizophrenia without epilepsy or current anticonvulsant or lithium therapy and who had an unsatisfactory response with clozapine for 12 weeks. Lamotrigine was initiated at 25 milligrams/day followed by 100 mg/day for 2 weeks and then 200 mg/day for 4 weeks. Doses were then titrated to a daily dose of 400 mg/day. PANSS negative symptoms scores changed from 31.34 to 29.38 in the lamotrigine arm and from 31.9 to 30.18 in the placebo arm. PANSS positive symptom scores improved from 17.24 to 16.24 the lamotrigine arm compared to a 1.26 point reduction in the placebo arm. General psychopathological symptoms scores changed from 31.34 to 29.38 in the lamotrigine arm and from 31.9 to 29.38 in the placebo arm. (Tiihonen et al, 2003)

b) In 3 patients who had responded poorly to 6 months of treatment with clozapine, addition of lamotrigine to 50% dose increase of lamotrigine 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 improvement in PANSS scores was obtained by 44% in the lamotrigine arm compared to a 19% improvement in the placebo arm. PANSS positive symptom scores improved from 17.24 to 16.24 the lamotrigine arm compared to a 0.2 point reduction in the placebo arm. General psychopathological symptoms scores changed from 31.34 to 29.38 in the lamotrigine arm and from 31.9 to 29.38 in the placebo arm. (Saba et al, 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 epilepsy responded to lamotrigine. In each case, lamotrigine was initiated and escalated while gabapentin was tapered with no further episodes through 15 months of follow-up (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 neuralgiform pain with conjunctival injection and tearing syndrome) (Malik et al, 2002)

3) Adult:
a) Symptoms of SUNCT syndrome resolved following lamotrigine treatment in one female patient. An 80-year-old woman with episodes occurring every 15 to 20 minutes failed to respond to treatment with carbamazepine, gabapentin, and hydrocodone/acetaminophen. Lamotrigine therapy was initiated at 25 milligrams (mg)/day for 1 week and titrated to 75 mg/day. The intensity of her attacks shrunk by half within 1 week of beginning lamotrigine. Her episodes were completely controlled after 1 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 attacks per day) improved with lamotrigine. 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 (up to 200 mg/day). (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 diazepam and gabapentin. More data are needed to ascertain the role of lamotrigine in the therapy of status epilepticus (Pisani et al, 2002).
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 increase in the 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 seizures. Discharged on lamotrigine, phenobarbital 100 mg twice a day, and carbamazepine 400 mg 3 times a day (Ps)

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 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 patients (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)
   The efficacy of lamotrigine as adjunctive therapy for primary generalized tonic-clonic seizures was demonstrated involving 117 adult and pediatric patients (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009)

3) Adult:
   a) Lamotrigine did not clearly demonstrate efficacy in ameliorating chronic tinnitus in a randomized, double-blind, placebo-controlled trial involving 117 adult and pediatric patients (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 2009). Patients assessed the loudness, annoyance, and awareness of tinnitus on visual analog scales (VAS) at baseline and observed between lamotrigine and placebo in terms of VAS scores or audiometry. According to patient questionnaires (35%) and 6 (19%) patients while on lamotrigine and placebo, respectively. The majority reported "no change relative to response to lamotrigine (Simpson et al, 1999).

4) Pediatric:
   a) The efficacy of lamotrigine as adjunctive therapy for primary generalized tonic-clonic seizures was demonstrated involving 117 adult and pediatric patients (Prod Info LAMICTAL chewable dispersible oral tablets, oral tablets, orally disintegrating tablets, 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-blinded compared to placebo in patients receiving steady doses of carbamazepine or phenytoin. Each drug was given 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 after improvement observed during lamotrigine therapy. The authors speculated that lamotrigine may have produced 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 trigeminal neuralgia while the second group consisted of 5 patients associated with multiple sclerosis. In the first group, 11 patients had a complete remission with 1 patient attaining 150 to 250 mg/day and 2 patients requiring 400 mg/day. Four patients continued to have pain at the 400 mg/day had full relief of pain with lamotrigine 150 to 200 mg/day. Patients with relief continued to be pain-free.

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. Spasms following the initiation of lamotrigine therapy (1.25 milligrams (mg) one to three times daily) after unsuccessful ACTH). The infants remained seizure-free at maintenance doses of lamotrigine 1.25 mg/day to 2.5 mg twice daily.

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 epilepsy randomly assigned to a fixed dosage titration of either carbamazepine or lamotrigine. After four weeks, all patients lamotrigine or 600 mg/day of carbamazepine; for the next 24 weeks, doses were adjusted according to efficacy guidelines. Patients who were seizure-free for the last 6 months of the study were 39% and 38% for lamotrigine and carbamazepine respectively, better tolerated, and more patients were able to complete the study period than patients treated with carbamazepine common with carbamazepine than lamotrigine (22% versus 12%, respectively) (Broderick et al, 1995).  
   b) As initial monotherapy in elderly patients newly diagnosed with epilepsy, lamotrigine demonstrated a superior comparative advantage to 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, respective duration. The median doses of lamotrigine and carbamazepine in study completers were 100 mg/day and 400 mg/day, respectively. Somnolence (29% versus 12%) was significantly more common with carbamazepine than lamotrigine, 42% and 18% of discontinuations, respectively. The hazard ratio for withdrawal with carbamazepine compared to 4). Efficacy measures were considered secondary endpoints in this trial. While no between-group differences were significant, more lamotrigine recipients remained seizure-free over the last 16 weeks of the study (39% versus 23%).

4.6.B Gabapentin  
   
4.6.B.1 Mood disorder  
   a) Preliminary results from a cross-over study (randomized, double-blinded) suggest that LAMOTRIGINE may be effective for the improvement of refractory mood disorders (n=31) (Frye et al, 2000). Study subjects included bipolar I (11), bipolar II (7), and 23 were rapid-cycling); all had tried other mood stabilizing agents previously. Percentages of those who had improvement with gabapentin, and 23% for placebo based on the Clinical Global Impression (CGI) scale modified for bipolar disorder.
responders were defined as those who were much or very much improved on the CGI scale. Both agents developed a rash caused by lamotrigine; the rash progressed to toxic epidermal necrolysis, requiring treatme
t trend showed that subjects tended to lose weight on lamotrigine relative to the weight gained on gabapentin.

4.6.B.2 Adverse Effects
a) In healthy volunteers, cognitive difficulties were associated with topiramate while gabapentin and lamotrigine
Healthy young adults (n=17) were randomized to receive topiramate 5.7 milligrams/kilogram (mg/kg), lamotrigine

titated up over 4 weeks. Neurobehavioral performances were then compared at baseline, 2 weeks, and 4 weeks. The group made significantly more errors during week 2 (p less than 0.02) and during week 4 (p less than 0.004).

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 the 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 intervention was between placebo as well as between lithium and placebo (p=0.003). Of the mood episodes, 20 lamotrigine patients, 8 lithium patients. This difference was statistically significant between the lithium and placebo arms (p=0.006). Of the mood episodes, 20 placebo patients developed depression. This was statistically different between the lamotrigine and placebo arms (p=0.09 and 0.36, respectively).

4.6.D Topiramate
1) Adverse Effects
a) In healthy volunteers, cognitive difficulties were associated with topiramate while gabapentin and lamotrigine
Healthy young adults (n=17) were randomized to receive topiramate 5.7 milligrams/kilogram (mg/kg), lamotrigine

titated up over 4 weeks. Neurobehavioral performances were then compared at baseline, 2 weeks, and 4 weeks. The group made significantly more errors during week 2 (p less than 0.02) and during week 4 (p less than 0.004).

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