

DRUGDEX-EV 1345

MICROMEDEX

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## OXCARBAZEPINE

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### 0.0] Overview

#### 1) Class

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

Anticonvulsant  
Dibenzazepine Carboxamide

#### 2) Dosing Information

##### a) Adult

##### 1) Partial seizure, monotherapy

a) initiation of monotherapy, 300 mg ORALLY twice a day, then increase the dosage by 300 mg/day every third day to 1200 mg/day OR 2400 mg/day in patients converted from other antiepileptic drug therapy to [oxcarbazepine](#) monotherapy [1]

b) conversion to monotherapy, initial, 300 mg ORALLY twice a day; may increase dosage by up to 600 mg/day at weekly intervals to 2400 mg/day reached in about 2-4 weeks while simultaneously reduce the dose of concomitant antiepileptic drugs over 3-6 weeks [1]

##### 2) Partial seizure; Adjunct

a) initial, 300 mg ORALLY twice a day; may increase dosage by up to 600 mg/day at weekly intervals to 1200 mg/day [1]

##### b) Pediatric

1) with adjunctive therapy, children 2 to less than 4 years of age may require up to twice the [oxcarbazepine](#) dose per body weight compared to adults; and children 4 to less than or equal to 12 years of age may require a 50% higher [oxcarbazepine](#) dose per body weight compared to adults [1]

**a) Partial seizure, monotherapy**

**1) 4 to 16 year old, initiation of monotherapy, 8-10 mg/kg/day ORALLY in 2 divided doses; may increase dose by 5 mg/kg/day every 3 days to the recommended maintenance dose [1]**

**2) 4 to 16 year old, conversion to monotherapy, initial, 8-10 mg/kg/day ORALLY in 2 divided doses; may increase doses by up to 10 mg/kg/day at weekly intervals to the recommended maintenance dose; simultaneously reduce the dose of concomitant antiepileptic drugs over 3-6 weeks [1]**

**3) 4 to 16 year old, maintenance, 600 to 900 mg/day for 20 kg children; 900 to 1200 mg/day for 25 to 30 kg; 900 to 1500 mg/day for 35 to 40 kg children; 1200 to 1500 mg/day for 45 kg children; 1200 to 1800 mg/day for 50 to 55 kg children; 1200 to 2100 mg/day for 60 to 70 kg children [1]**

**b) Partial seizure; Adjunct**

**1) 4 to 16 years old, initial, 8-10 mg/kg/day ORALLY in 2 divided doses; MAX: 600 mg/day[1]**

**2) 4 to 16 years old, maintenance, target maintenance dose of oxcarbazepine should be achieved over 2 weeks, and is dependent upon patient weight: (20 to 29 kg, 900 mg/day); (29.1 to 39 kg, 1200 mg/day); and (greater than 39 kg, 1800 mg/day) [1]**

**3) 2 to less than 4 years old, initial, 8-10 mg/kg/day ORALLY in 2 divided doses; MAX: 600 mg/day; patients under 20 kg, consider initial dose of 16-20 mg/kg/day in 2 divided doses [1]**

**4) 2 to less than 4 years old, maintenance, should be titrated over 2 to 4 weeks; MAX: 60 mg/kg/day in 2 divided doses [1]**

**3) Contraindications**

**a) hypersensitivity to [oxcarbazepine](#) or to any component of the product [14]**

**4) Serious Adverse Effects**

**a) [Agranulocytosis](#)**

**b) [Anaphylaxis](#)**

**c) [Angioedema](#)**

**d) [Aplastic anemia](#)**

**e) [Erythema multiforme](#)**

**f) [Hyponatremia](#)**

**g) [Immune hypersensitivity reaction](#), multiorgan**

h) [Pancreatitis](#)

i) [Pancytopenia](#)

j) [Pneumonia](#)

k) [Status epilepticus](#)

l) [Stevens-Johnson syndrome](#)

m) Suicidal thoughts

n) [Toxic epidermal necrolysis](#)

## 5) Clinical Applications

a) FDA Approved Indications

1) Partial seizure, monotherapy

2) Partial seizure; 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 Index)

B) Synonyms

[Oxcarbazepine](#)

C) Physicochemical Properties

1) Molecular Weight

a) 252.27 [153]

2) Solubility

a) Systemic: [Oxcarbazepine](#) is slightly soluble in acetone, chloroform, dichloromethane, and methanol. It is practically insoluble in ethanol, ether, and water.[153]

### 1.2] Storage and Stability

A) Oral route

1) Oral suspension of [oxcarbazepine](#) should be stored between 15 and 30 degrees Celsius (59 and 86 degrees Fahrenheit) [125].

## 1.3] Adult Dosage

### 1.3.1] Normal Dosage

#### 1.3.1.A] Oral route

##### 1.3.1.A.1] Partial seizure, monotherapy

###### a) Conversion

1) For conversion of therapy from other antiepileptic drugs (AEDs) to [oxcarbazepine](#) monotherapy, [oxcarbazepine](#) therapy should be initiated with a dose of 600 milligrams/day (mg/day) in two divided doses; simultaneously, reduction of the dosage of the concomitant AEDs should begin. The [oxcarbazepine](#) dose may be increased at weekly intervals, as clinically indicated, by a maximum of 600 mg/day to achieve a daily dose of 2400 mg/day. The maximum dose of [oxcarbazepine](#) should be reached in approximately 2 to 4 weeks while therapy with concomitant AEDs should be terminated gradually over approximately 3 to 6 weeks. Close monitoring of the patient is recommended during the [transition](#) phase [1].

###### b) Initiation

1) In patients not currently treated with any antiepileptic drugs, [oxcarbazepine](#) therapy should be initiated at a dose of 600 milligrams/day (mg/day) in two divided doses. This dose is then increased every third day by 300 mg/day to achieve a dose of 1200 mg/day [1].

###### c) Withdrawal

1) Withdrawal of [oxcarbazepine](#) therapy should be gradual [1].

##### 1.3.1.A.2] Partial seizure; Adjunct

a) [Oxcarbazepine](#) should be initiated with a dose of 600 milligrams per day (mg/day), in two divided doses. This dose may be increased at weekly intervals, as clinically indicated, by a maximum of 600 mg/day. The recommended maintenance dose of [oxcarbazepine](#) for adjunctive use is 1200 milligrams/day (mg/day) in 2 divided doses. Although daily doses greater than 1200 mg were more effective, most patients are not able to tolerate the 2400 mg/day dose due to adverse central nervous system effects. Close monitoring of the patient and plasma concentrations of concomitant antiepileptic drugs is recommended during the titration phase, especially at doses greater than 1200 mg/day [1].

##### 1.3.1.B) Equivalent Doses

1) [Oxcarbazepine](#) oral suspension and film-coated tablets may be interchanged at equal doses [1].

### 1.3.2] Dosage in Renal Failure

A) For patients with [impaired renal function](#) ([creatinine clearance](#) less than 30 milliliters/minute), [oxcarbazepine](#) therapy should be initiated at 300 milligrams/day, one-half the usual starting dose, and increased at a slower rate than usual based on clinical response [1].

### 1.3.3] Dosage in Hepatic Insufficiency

A) Dose adjustments are generally not required in patients with mild to moderate [hepatic impairment](#) [1].

### 1.3.4] Dosage in Geriatric Patients

**A)** No specific guidelines exist for [oxcarbazepine](#) dosing in the elderly. Maximum plasma concentrations and values for area under the concentration-time curve were 30% to 60% higher in elderly volunteers (60 to 82 years of age) than in younger volunteers (18 to 32 years of age). Differences are presumed to be due to age-related reductions in [creatinine clearance](#) [1]. Because [oxcarbazepine](#) is initiated at a low dosage and titrated until a maintenance dosage is reached, these pharmacokinetic differences are felt to have no significant clinical implications [12].

**1.3.6] Dosage in Other Disease States**

**A) Pregnancy**

**1)** Dose-normalized plasma concentrations of [oxcarbazepine](#) and mono-hydroxy-carbazepine (MHD), the active metabolite, decreased during pregnancy and appeared to return to prepregnancy levels during the postpartum period in a [pharmacokinetic study](#) in 5 pregnant women on [oxcarbazepine](#) monotherapy. Although prepregnancy concentrations were not available in any of the women, plasma concentrations of MHD and [oxcarbazepine](#) were measured during each trimester in 4 women, during the last trimester in 1 woman, and at least once during the 3 months after delivery in all women. The lowest dose-normalized concentrations were noted after the 20th gestation-week. Furthermore, postpartum dose-normalized plasma concentrations of MHD and [oxcarbazepine](#) increased between 1.7 to 2.9 fold compared with the third trimester in 4 of the 5 pregnant women. The postpartum increase was observed as soon as 7 to 8 days after delivery. In 1 out of the 5 women no increase in the postpartum concentrations were noted [13].

**1.4] Pediatric Dosage**

**1.4.1] Normal Dosage**

**1.4.1.A] Oral route**

**1.4.1.A.1] Partial seizure, monotherapy**

**a) Conversion**

**1)** For conversion of therapy from other antiepileptic drugs (AEDs) to [oxcarbazepine](#) monotherapy in children 4 to 16 years, [oxcarbazepine](#) therapy should be initiated with a dose of 8 to 10 milligrams/kilogram/day (mg/kg/day) in two divided doses; simultaneously, reduction of the dosage of the concomitant AEDs should begin. The [oxcarbazepine](#) dose may be increased at weekly intervals, as clinically indicated, by a maximum of 10 mg/kg/day to achieve the recommended daily dose. Concomitant AEDs should be terminated gradually over approximately 3 to 6 weeks. Close monitoring of the patient is recommended during the [transition](#) phase. The recommended total daily dose of [oxcarbazepine](#) is as follows [10]:

Patient Weight (in kg)	Target Maintenance Dose Range (m
20	600 to 900
25	900 to 1200
30	900 to 1200
35	900 to 1500
40	900 to 1500
45	1200 to 1500
50	1200 to 1800
55	1200 to 1800
60	1200 to 2100
65	1200 to 2100

70

1500 to 2100

**b) Initiation**

**1)** In children 4 to 16 years not currently treated with any antiepileptic drugs, [oxcarbazepine](#) therapy should be initiated at 8 to 10 milligrams/kilogram/day (mg/kg/day) in two divided doses. Doses should be increased by 5 mg/kg/day every 3 days until the recommended daily dose is reached. The recommended total daily dose of [oxcarbazepine](#) is as follows [10]:

Patient Weight (in kg)	Target Maintenance Dose Range (m
20	600 to 900
25	900 to 1200
30	900 to 1200
35	900 to 1500
40	900 to 1500
45	1200 to 1500
50	1200 to 1800
55	1200 to 1800
60	1200 to 2100
65	1200 to 2100
70	1500 to 2100

**1.4.1.A.2] Partial seizure; Adjunct**

**a) 4 to 16 Year Olds**

For adjunctive therapy in pediatric patients aged between 4 to 16 years, [oxcarbazepine](#) should be initiated at a daily dose of 8 to 10 milligrams/kilogram/day (mg/kg/day) in two divided doses, usually not to exceed 600 mg/day. The target maintenance dose, according to the chart below, should be attained within 2 weeks. The median dose reached during clinical trials was 31 mg/kg/day (6 to 51 mg/kg/day) [1]:

Patient Weight (in kg)	Target Maintenance Dose (mg/day)
20 to 29	900
29.1 to 39	1200
greater than 39	1800

Children 4 to less than or equal to 12 years of age may require a 50% higher [oxcarbazepine](#) dose per body weight compared to adults. Children require a higher dose per body weight relative to adults because the apparent clearance increases with decreasing age [1].

**b) 2 to 4 Year Olds**

**1)** For adjunctive therapy in pediatric patients 2 years old to less than 4 years old, [oxcarbazepine](#) should be initiated at a daily dose of 8 to 10 milligrams/kilogram/day (mg/kg/day) in two divided doses, usually not to exceed 600 mg/day. For patients under 20 kilogram, a starting dose of 16 to 20 mg/kg/day in 2 divided doses may be considered. The maximum maintenance dose of [oxcarbazepine](#) should be achieved over 2 to 4 weeks and should not exceed 60 mg/kg/day in two divided doses. The final dose reached during clinical trials in children 2 to 4 years of age was 55 mg/kg/day [1].

**2)** Children 2 to less than 4 years of age may require up to twice the [oxcarbazepine](#) dose per body weight compared to adults. Children require a higher dose per body weight relative to adults because the apparent clearance increases with decreasing age [1].

3)) Children 2 to 4 years of age may require up to twice the [oxcarbazepine](#) dose per body weight compared to adults. Children require a higher dose per body weight relative to adults because the apparent clearance increases with decreasing age [1].

c)) In children beginning [oxcarbazepine](#) therapy, doses have been titrated up to 30 milligrams/kilogram/day (mg/kg/day) over 1 to 3 weeks. In those switching from [carbamazepine](#), an overnight change of 1.5 times their [carbamazepine](#) dose has been utilized. The mean effective dose for children achieving at least a 50% decrease in seizures has been 47 mg/kg/day with a range of 21 to 75 mg/kg/day [6].

#### 1.4.1.B)) Equivalent Doses

1)) [Oxcarbazepine](#) oral suspension and film-coated tablets may be interchanged at equal doses [1].

#### 1.4.2] Dosage in [Renal Failure](#)

A)) For patients with [impaired renal function](#) ([creatinine clearance](#) less than 30 milliliters/minute), [oxcarbazepine](#) therapy should be initiated at one-half the usual starting dose, and increased slowly according to the clinical response [1].

#### 1.4.3] Dosage in [Hepatic Insufficiency](#)

A)) Dose adjustments are generally not required in patients with mild to moderate [hepatic impairment](#) [1].

## 2.0] Pharmacokinetics

### [Onset and Duration](#)

### [Drug Concentration Levels](#)

### [ADME](#)

#### 2.1] Onset and Duration

##### A)) Onset

##### 1)) Initial Response

a)) [Trigeminal neuralgia](#), oral: 24 hours [102].

#### 2.2] Drug Concentration Levels

##### A)) Therapeutic Drug Concentration

1)) [Epilepsy](#), not established [102].

##### B)) Time to Peak Concentration

1)) Oral: 4.5 hours (tablets), 6 hours (suspension) [1].

a)) After the administration of a single dose of [oxcarbazepine](#) tablets, under fasted conditions, in healthy, male volunteers, the median time to peak concentration (T<sub>max</sub>) was 4.5 hours (range 3 to 13 hours). The median T<sub>max</sub> was 6 hours in healthy male volunteers administered a single-dose of [oxcarbazepine](#) suspension, under fasted conditions [1]. The active metabolite, 10-hydroxycarbazepine, reaches peak levels at 4.5 to 8 hours [105][106][107].

b) After the administration of a single dose of [oxcarbazepine](#) oral suspension, under fasted conditions, in healthy, male volunteers, the median time to peak concentration (Tmax) was 6 hours [104].

2) Steady-state plasma concentrations of 10-hydroxy-carbazepine, the active metabolite, are achieved within 2 to 3 days with twice-a-day dosing [1].

3) Maximum serum concentrations of the S- and R- enantiomers of 10-hydroxy-carbazepine were 4.49 and 0.99 mg/L, respectively, but the median time to peak concentration was similar for both [103].

#### C) Area Under the Curve

1) 129.8 mg/L/hr (S-enantiomer); 26.3 mg/L/hr (R-enantiomer) [103].

a) Approximately 5-fold greater AUC for S-10-hydroxy-carbazepine than for R-10-hydroxy-carbazepine [103].

b) AUC values were 30% to 60% higher in elderly volunteers (60 to 82 years of age) than in younger volunteers (18 to 32 years of age). Differences are presumed to be due to age-related reductions in [creatinine clearance](#) [104].

c) Dose adjusted AUC values were 30% to 40% lower in children below the age of 8 years than in children above 8 years of age [104].

### 2.3] ADME

#### 2.3.1] Absorption

##### A) Bioavailability

1) Oral: rapidly absorbed [105][107].

##### B) Effects of Food

1) none [1].

#### 2.3.2] Distribution

##### A) Distribution Sites

##### 1) Protein Binding

a) 40% to 60% [1][108].

1) Approximately 33% to 40% of 10-hydroxy-carbazepine is bound to serum proteins, predominantly albumin [1][108].

2) Serum concentration within the therapeutically relevant range does not influence protein binding [1].

3) No difference in binding between males and females was observed [108].

#### 2) OTHER DISTRIBUTION SITES



a) SALIVA, correlates to serum concentrations [106].

1) A good correlation between saliva and serum concentrations of 10-hydroxy-carbazepine has been reported from 8 to 72 hours following oral administration of oxcarbazepine [106].

## B) Distribution Kinetics

### 1) Volume of Distribution

a) 49 L (10-hydroxy-carbazepine) [104]

## 2.3.3] Metabolism

### A) Metabolism Sites and Kinetics

1) LIVER, rapid and extensive metabolism [109][105][110][107].

a) Metabolized via stereoselective reduction by cystolic enzymes of the carbonyl group in position 10 of [oxcarbazepine](#) [109][105][110][107].

b) Lacks auto-inducing properties [105][111][112].

c) Dose-dependent enzyme induction has been reported with higher doses producing effects similar to [carbamazepine](#) [113].

### B) Metabolites

1) 10-monohydroxy-carbazepine, active [1][109][105][110][107].

a) Primarily responsible for the therapeutic effects of [oxcarbazepine](#) [1][109][113][105][112][107].

b) The metabolite 10-hydroxy-carbazepine is primarily excreted in the urine as the glucuronide conjugate [114][112][110][107].

2) Two isomeric 10,11-diols, inactive [114][112][110][107].

a) The trans-diol (10,11-dihydro-10,11-trans-dihydroxy-carbamazepine) predominates [114][112][110][107].

3) Other minor metabolic pathways include direct O-glucuronidation and O-sulfation with the enol form [105].

## 2.3.4] Excretion

### A) Kidney

#### 1) Renal Excretion (%)

a) 95% to 96% [1][110].

2j) Only small amounts of unchanged [oxcarbazepine](#) are recovered (less than 1%) and the majority of renal excretion is accounted for by 10-hydroxy-carbazepine (up to 80%), primarily as the glucuronide conjugate. Only negligible amounts of the trans- and cis-10,11-diol are found in the urine (approximately 3%) [1][105][110].

**Bj) Total Body Clearance**

1j) The younger and lower in weight the faster the weight-adjusted clearance is for 10-monohydroxy-carbazepine (MHD). In children 2 years to less than 4 years of age, weight-adjusted clearance is approximately 80% higher on average than that of adults. When treated with a similar weight-adjusted dose, the corresponding MHD exposure in these children is expected to be about 50% of adult exposure. In children 4 to 12 years of age, weight-adjusted clearance is approximately 40% higher on average than that of adults. When treated with a similar weight-adjusted dose, the corresponding MHD exposure in these children is expected to be about 75% of adult exposure. The weight-adjusted MHD clearance in children 13 years and older is expected to reach that of adults [1].

**Cj) Other**

**1j) OTHER EXCRETION**

a) FECES, less than 4% [1].

**2.3.5] Elimination Half-life**

**Aj) Parent Compound**

**1j) ELIMINATION HALF-LIFE**

a) 1 to 2.5 hours [1][114].

1j) The half-life is prolonged to 19 hours in patients with renal impairment (creatinine clearance less than 30 mL/min) [1].

**Bj) Metabolites**

1j) 10-hydroxy-carbazepine, 8 to 11 hours [1][105][114][107].

a) The half-life of 10-monohydroxy-carbazepine was 9 hours [1].

b) Half-lives of the R- and S- enantiomers were 11.9 and 13 hours, respectively [103].

**3.0] Cautions**

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

[Teratogenicity/Effects in Pregnancy/Breastfeeding](#)

[Drug Interactions](#)

**3.1] Contraindications**

A) hypersensitivity to [oxcarbazepine](#) or to any component of the product [14]

### 3.2] Precautions

- A)] **anaphylaxis** and **angioedema** of larynx, glottis, lips, and eyelids have been reported; immediate and permanent discontinuation recommended [14]
- B)] cognitive and neuropsychiatric adverse events have been reported, including psychomotor slowing, difficulty with concentration, speech or language problems, somnolence or fatigue, coordination abnormalities (eg, ataxia and gait disturbances) [14]
- C)] concomitant medications known to decrease serum sodium levels; **hyponatremia** risk; monitoring recommended [14]
- D)] concomitant use with hormonal contraceptives; therapy renders hormonal contraceptive less effective [14]
- E)] decreases in T4 may occur; without decreases in T3 or **TSH** [14]
- F)] hematological events (eg, **pancytopenia**, **agranulocytosis**, and **leukopenia**) have occurred; consider discontinuation of drug if any evidence of hematological events develop [14]
- G)] hypersensitivity to **carbamazepine**; 25% to 30% of those hypersensitive to **carbamazepine** will be hypersensitive to **oxcarbazepine**; use only if benefit justifies the risk and discontinue immediately if signs or symptoms of hypersensitivity develop [14]
- H)] **hyponatremia** (sodium less than 125 mmol/L), especially during the first 3 months of therapy, but also more than 1 year after therapy initiation, may occur; levels may normalize on dose reduction or discontinuation; monitoring recommended [14]
- I)] multiorgan **hypersensitivity reactions**, some requiring hospitalization and life-threatening, have occurred; if suspected, permanent discontinuation and alternative treatment recommended [14]
- J)] rapid withdrawal of **oxcarbazepine** therapy; may result in increased seizure frequency; gradual discontinuation recommended [14]
- K)] **renal impairment** (CrCl less than 30 mL/min); elimination of active metabolite is slowed resulting in a 2-fold increase in exposure; dosage adjustment recommended [14]
- L)] skin reactions, some life-threatening and fatal (eg, **Stevens-Johnson syndrome**, **toxic epidermal necrolysis**), have occurred and recurred on rechallenge; permanent discontinuation and switching to another antiepileptic agent should be considered if a skin reaction develops [14]
- M)] suicidality, increased risk; antiepileptic drugs, including **oxcarbazepine**, increase the risk of suicidality as early as 1 week after initiation and during treatment; monitoring recommended [14]

### 3.3] Adverse Reactions

#### 3.3.2] Dermatologic Effects

##### 3.3.2.A] **Cutaneous hypersensitivity**

- 1)] Desensitization to **oxcarbazepine**, following the development of a generalized **pruritic rash**, was accomplished using a dose of 0.1 mg daily and doubling the dose every 2 days until a therapeutic dosage was reached [49].
- 2)] Allergic skin reactions have been reported less frequently with **oxcarbazepine** as compared to **carbamazepine** in some clinical studies [50][19][22].
- 3)] There is evidence that **oxcarbazepine** can be used safely as an alternative in some patients with carbamazepine-induced hypersensitivity (Zakrzewska & Ivanni, 1988)[22][27].
- 4)] In 1 Danish study, a cross-reaction to **oxcarbazepine** was seen in only 12 of 47 patients (25%) with allergic skin reactions to **carbamazepine** [29].

##### 3.3.2.B] **Erythema multiforme**

- 1)] **Erythema multiforme** has been reported with postmarketing use of **oxcarbazepine** [16]

### 3.3.2.C] Maculopapular eruption

#### 1) Pediatrics

a) Drug discontinuation due to maculopapular rash was reported in 1.3% of pediatric patients ages 4 years and older with no previous antiepileptic drug experience (n=152) treated with [oxcarbazepine](#) in monotherapy trials [16].

### 3.3.2.D] Purpura

#### 1) Incidence: 2%[16]

2) [Purpura](#) was reported in 2% and 0% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

### 3.3.2.E] Rash

#### 1) Incidence: 4%[16]

#### 2) Adults

a) Rash was reported in 4% of patients treated with [oxcarbazepine](#) (n=55) compared with 2% treated with placebo (n=49) in a controlled clinical trial of [oxcarbazepine](#) monotherapy among adults with no previous antiepileptic drug experience [16].

b) Drug discontinuation due to rash was reported in 1.7% of adults (n=295) during a clinical trial of [oxcarbazepine](#) monotherapy among adults with no previous antiepileptic drug experience [16].

c) Drug discontinuation due to rash was reported in 1.4% of adult patients previously treated with other antiepileptic drugs (n=1537) in [oxcarbazepine](#) adjunctive or monotherapy trials [16].

d) Skin rash has been a frequently described adverse effect of [oxcarbazepine](#) therapy, also occurring with the discontinuation of [oxcarbazepine](#) therapy. Rash may be associated with a mild [eosinophilia](#), and was reported in 7% of patients on [oxcarbazepine](#) monotherapy in one study [43] [49].

#### 3) Pediatrics

a) Drug discontinuation due to rash was reported in 5.3% of pediatric patients ages 4 years and older with no previous antiepileptic drug experience (n=152) treated with [oxcarbazepine](#) in monotherapy trials [16].

### 3.3.2.F] Stevens-Johnson syndrome

1) A 9-year-old Taiwanese boy developed [Stevens-Johnson syndrome](#) (SJS) within 14 days of initiating [oxcarbazepine](#) for treatment of seizures. The patient had a history of seizures first occurring at the age of 6 months and was treated with [phenytoin](#) for several months and then the [phenytoin](#) was discontinued without recurrence of seizures until he was 9 years old. Upon presentation, the patient's seizure was characterized by clonic movement of his hands and legs, with loss of consciousness. The results of the [electroencephalogram](#) and physical examination were unremarkable. The patient was started on [oxcarbazepine](#) 300 mg daily and the dose was increased to 600 mg daily after 1 week. Fourteen days after beginning therapy with [oxcarbazepine](#), the patient developed maculopapule rashes on his face and thigh along with high fever. Two days later, he developed [blisters on his thigh](#), multiple [oral ulcers](#) and hyperemic conjunctivae. The patient was admitted to the emergency department with the diagnosis of

presumed SJS. Laboratory analyses revealed [leukocytosis](#) (WBC 13,930/mcL; normal range, 4000 to 10,000/mcL), elevated C-reactive protein (50.59 mcg/mL; range, 0 to 5 mcg/mL). Human [leukocyte](#) antigen (HLA) [genotyping](#) showed HLA-B\*1518/B\*4001 and skin pathology finding revealed lymphohistiocytic infiltration around the blood vessels and scanty eosinophils, which was consistent with SJS. The patient improved with steroid and antihistamine treatment for 7 days and was discharged 12 days later. Authors concluded that similar to carbamazepine-induced SJS, the role of the HLA-B15 variant may be associated with the development of oxcarbazepine-induced SJS [51].

2) Serious, sometimes life-threatening cases of [Stevens-Johnson syndrome](#) have been reported with the use of [oxcarbazepine](#) in children and adults. Some patients have required hospitalization, and rare cases of death have been reported. Additionally, rechallenge with the drug has resulted in recurrence of the dermatologic reactions. The rate at which these dermatologic events have been reported in association with [oxcarbazepine](#) use exceeds the rate at which these events are reported in the general population by 3- to 10-fold. The median time of onset in reported cases was 19 days. Discontinuation of [oxcarbazepine](#) should be considered in any patient who develops a skin reaction while using the drug [16].

3) [Stevens-Johnson syndrome](#) has occurred during postmarketing use of [oxcarbazepine](#) [16].

### 3.3.2.G] Toxic epidermal necrolysis

1) Serious, sometimes life-threatening cases of [toxic epidermal necrolysis](#) have been reported with the use of [oxcarbazepine](#) in children and adults. Some patients have required hospitalization, and rare cases of death have been reported. Additionally, rechallenge with the drug has resulted in recurrence of the dermatologic reactions. The rate at which these dermatologic events have been reported in association with [oxcarbazepine](#) use exceeds the rate at which these events are reported in the general population by 3- to 10-fold. The median time of onset in reported cases was 19 days. Discontinuation of [oxcarbazepine](#) should be considered in any patient who develops a skin reaction while using the drug. [Toxic epidermal necrolysis](#) has occurred during postmarketing use of [oxcarbazepine](#) [16].

## 3.3.3] Endocrine/Metabolic Effects

### 3.3.3.A] Abnormal androgen

1) Antiepileptic agents have been associated with changes in serum concentrations of male reproductive hormones. When compared to healthy controls (n=41), carbamazepine-treated men with [partial epilepsy](#) (n=15) had lower serum dehydroepiandrosterone sulfate concentrations (3068 ng/mL for controls versus 1952 ng/mL for [carbamazepine](#); p less than 0.001). No statistically significant differences in dehydroepiandrosterone levels were detected between controls and [oxcarbazepine](#) treated (n=18) or [valproic acid](#) treated (n=27) men with [generalized epilepsy](#). It was also found that men in the [valproic acid](#) group had higher androstendione levels (5.9 ng/mL) when compared to the control group (2.2 ng/mL; p less than 0.001) whereas the other arms did not. There were no statistically significant differences in serum [testosterone](#), sex hormone binding globulin, free androgen index, [luteinizing hormone](#), [follicle stimulating hormone](#), prolactin and inhibin B measurements among the 4 groups. Whether the differences in reproductive hormones are epilepsy-induced changes or antiepileptic agent-induced changes remains to be determined [46].

2) Reproductive hormone levels in men with [epilepsy](#) may be affected by use of [valproic acid](#) or [carbamazepine](#), with some effect shown by [oxcarbazepine](#) at high doses. In valproate-treated men (n=21), androstenedione levels were significantly increased compared with controls (n=25) (p less than 0.001), and more than half of the cohort taking [valproate](#) (57%) had serum concentrations of [testosterone](#), androstenedione, or dehydroepiandrosterone (DHEA) above the reference range (p less than 0.001). [Follicle stimulating hormone](#) levels were abnormally low in [valproate](#)-treated men (p less than 0.05). Among carbamazepine-treated men (n=40), serum concentrations of DHEA were low (p less than 0.001) and sex hormone-binding globulin (SHBG) levels were high (p less than 0.05). In men taking high doses

of [oxcarbazepine](#) (900 mg/day or more), serum concentrations of [testosterone](#), [luteinizing hormone](#), and SHBG were high ( $p=0.008$ ,  $p=0.02$ ,  $p=0.005$ , respectively). The authors noted that serum [insulin](#) levels were high across all groups [47].

### 3.3.3.B] Abnormal thyroid hormone

1) Data from clinical trials revealed use of [oxcarbazepine](#) was associated with decreases in T4, but not in T3 or thyroid stimulating hormone (TSH) [16].

2) One study found that [carbamazepine](#) and [oxcarbazepine](#) both decrease [serum thyroxine](#) (T4) and free thyroxine (FT4) in girls with [epilepsy](#). These effects were reversible upon discontinuation of therapy. Patients between the ages of 8 and 18 years were compared with 54 age-matched controls. Mean T4 and FT4 levels in patients receiving [carbamazepine](#) ( $n=19$ ) was 11.5 nM and 70.2 nM compared to 14.4 nM and 96.6 nM in the control group ( $p$  less than 0.01 and 0.001, respectively). Mean T4 and FT4 in patients receiving [oxcarbazepine](#) ( $n=18$ ) were 11.3 nM and 74.9 nM ( $p$  less than 0.001 for both measures when compared control). [Thyrotropin](#) and free triiodothyronine levels were not significantly different. A second evaluation, taken a mean of 5.8 years later, was performed. Thyroid hormone levels in patients who had discontinued therapy (10 [carbamazepine](#) patients and 10 [oxcarbazepine](#) patients) did not significantly differ from the controls. Patients had been off therapy for a mean of 5 and 4.8 years, respectively [33].

### 3.3.3.C] Acute intermittent porphyria

See Drug Consult reference: DRUGS CONSIDERED UNSAFE- [ACUTE PORPHYRIAS](#)

### 3.3.3.D] Hyperlipidemia

1) Increased serum lipids, specifically low-density lipoproteins and [serum cholesterol](#), were reported in 16-year-old girl. High-density lipoproteins, [triglycerides](#), and liver function tests remained within normal limits. [Oxcarbazepine](#) is metabolized primarily by ketone reductase and glucuronosyltransferase causing minimal hepatic enzyme-induction in humans. An increase in lipid levels had occurred previously in the patient when she was treated with [carbamazepine](#), but was thought to be less probable with [oxcarbazepine](#). The authors suggested monitoring lipid levels in patients treated with [oxcarbazepine](#) as well as in those treated with [carbamazepine](#) [34].

### 3.3.3.E] Hyponatremia

#### 1) Summary

a) Significant [hyponatremia](#) (sodium less than 125 mmol/L) generally occurs during the first 3 months of therapy, but may occur more than one year after therapy initiation. Dose reduction, therapy discontinuation, or restriction of fluid intake may be required. In patients who discontinued therapy in clinical trials, sodium levels normalized within a few days without further treatment. Monitoring of serum sodium should be considered, especially in patients at risk or in patients who develop symptoms of [hyponatremia](#). Patients are at risk if they receive concomitant medications known to decrease serum sodium levels [16].

b) [Hyponatremia](#) has occurred with the administration of [oxcarbazepine](#) and is associated with a greater incidence of [hyponatremia](#) as compared with the use of [carbamazepine](#) [36]. The mechanism is thought to be an antidiuretic hormone-like action on the kidney. Hyponatremic coma has been described with [oxcarbazepine](#) use. Some investigators feel that [hyponatremia](#) from [oxcarbazepine](#) may severely limit its use as an anticonvulsant. Most patients with [hyponatremia](#) remain asymptomatic, but some may experience drowsiness, increase in seizure frequency, and



impaired consciousness. **Hyponatremia** with **oxcarbazepine** occurs most commonly in elderly patients and during administration of high doses of the drug [37][38][39][29][40][22][26][27][41][42].

2) Incidence: 1% to 23%[16]

3) Adults

a) **Hyponatremia** was reported in 5% and 0% of patients treated with **oxcarbazepine** 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose **oxcarbazepine** from other antiepileptic drugs [16].

b) **Hyponatremia** was reported in 3%, 1%, 2%, and 1% of patients treated with adjunctive **oxcarbazepine** 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with **epilepsy** [16].

c) Drug discontinuation due to **hyponatremia** was reported in 1% of patients (n=1537) during **oxcarbazepine** treatment in adjunctive or monotherapy trials in adults previously treated with other antiepileptic drugs [16].

d) In 14 controlled **epilepsy** studies, 2.5% of patients treated with **oxcarbazepine** (n=1524) had a sodium level of less than 125 mmol/L at some point during treatment compared with 0% of patients treated with placebo or active control (**carbamazepine** and **phenobarbital** for adjunctive and monotherapy substitution studies, and **phenytoin** and **valproate** for the monotherapy initiation studies). **Hyponatremia** has occurred during postmarketing use of **oxcarbazepine** [16].

e) The results of one study indicate that **oxcarbazepine** use is associated with a greater incidence of **hyponatremia** as compared with the use of **carbamazepine**. In a cross-sectional study, the sodium levels of patients receiving treatment with either **oxcarbazepine** (n=97; mean age 36.3 years) or **carbamazepine** (n=451; mean age 38.2 years) were evaluated for the presence of **hyponatremia**. **Hyponatremia** was defined as a sodium level less than or equal to 134 milliequivalents/liter (mEq/L); severe **hyponatremia** was defined as a sodium level less than or equal to 128 mEq/L. **Hyponatremia** was observed in a significantly greater number of **oxcarbazepine**-treated patients, as compared with those receiving **carbamazepine** therapy (29.9% (29/97) vs 13.5% (61/451), respectively; p less than 0.0001). The incidence of severe **hyponatremia** was also higher in the **oxcarbazepine** group as compared with the **carbamazepine** group (12.4% (12/97) vs 2.8% (13/451), respectively). Severe **hyponatremia** accounted for 41.3% (12/29) of all **hyponatremia** cases in **oxcarbazepine**-treated patients, while only accounting for 21.3% (13/61) of all **hyponatremia** cases reported in patients receiving **carbamazepine** therapy (p less than 0.0001). The investigators also found that, for both groups, **hyponatremia** was more likely to occur in older patients. **Hyponatremia** was observed in 62.2% and 20.6% of **oxcarbazepine**- and **carbamazepine**-treated patients 40 years of age or older, as compared with 10% and 7.9% of **oxcarbazepine**- and **carbamazepine**-treated patients less than 40 years of age, respectively (p less than 0.0001, both values) [36].

f) **Hyponatremia** was reported in 80 of 350 (23%) patients whose serum-sodium concentrations were monitored during **oxcarbazepine** therapy. Ten percent of patients had low serum sodium prior to receiving **oxcarbazepine** treatment [43].

g) Hyponatremic coma, with a serum sodium level of 115 mmol/L, was reported in a 50-year-old female following almost 1 year of therapy with **oxcarbazepine** 2100 mg/day. On discontinuation of the drug, serum sodium levels improved after 2 days, with resolution of somnolence and coma [39].

h)) Significant reductions in mean serum sodium levels (less than 135 mmol/L) have been reported in 50% to 80% of patients in some studies. Available data suggested that the incidence of hyponatremia with oxcarbazepine may be greater than that observed with carbamazepine [40][42].

#### 4)) Pediatrics

a)) Hyponatremia, defined as at least 1 serum sodium measurement below 132 mcmol/L, was observed in 8 of 34 children (24%) with intellectual disability treated with oxcarbazepine [44].

b)) In a study involving children, hyponatremia occurred in 7 out of 53 patients treated with oxcarbazepine [45].

#### 3.3.3.F) Hypothermia

1)) Transient hypothermia has been reported rarely during administration of oxcarbazepine [20].

#### 3.3.3.G) Increased body temperature

1)) Despite several changes in drug therapy, a fever was reported in a 20-year-old female which persisted for a follow-up period of approximately 3 years following the initial occurrence during oxcarbazepine therapy. The authors concluded that the patient had actually experienced a change in "set point" for body temperature regulation rather than having a febrile reaction. The oxcarbazepine dose was 300 mg twice daily for 2 weeks, then increased to 300 mg 3 times a day. The patient's body temperature had steadily ranged between 36.5 and 36.8 degrees C for several years. After oxcarbazepine treatment, she achieved good seizure control, but her temperature rose to over 37 degrees C. The oxcarbazepine was gradually reduced and valproate 1500 mg was substituted, resulting in a gradual return to pretreatment temperature, but an increase in simple seizures. After a return to temperatures over 37 degrees C (37 to 37.6 degrees C) 4 months later, the valproate was reduced to 800 mg/day and vigabatrin 1500 mg was added. Eventually, good seizure control was achieved with doses of lamotrigine up to 150 mg/day and vigabatrin 2000 mg/day; however, the patient's temperature never returned to the pretreatment range. The mechanism for this effect was hypothesized to be the influence of antiepileptic drugs on ion concentration, as the inherent ratio of sodium to calcium ions in the posterior hypothalamus has been suggested as the physiological basis for the "set point" of temperature control [35].

#### 3.3.3.H) Weight increased

1)) Incidence: 1% to 2%[16]

2)) Weight increase was reported 1%, 2%, 2%, and 1% of patients treated with adjunctive oxcarbazepine 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with epilepsy [16].

3)) Weight gain has been reported as a relatively frequent adverse effect during oxcarbazepine therapy [29].

### 3.3.4) Gastrointestinal Effects

#### 3.3.4.A) Abdominal pain

1)) Incidence: 3% to 13%[16]

2)) Abdominal pain was reported in 10%, 13%, 11%, and 5% of patients treated with adjunctive oxcarbazepine 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively in a controlled clinical trial of adults with epilepsy [16].

3)) Abdominal pain occurred in 5% and 3% of patients treated with oxcarbazepine 2400 mg/day (n=86) and 300 mg/day (n=86), respectively in a controlled clinical trial of adult patients converted to either high- or low-dose oxcarbazepine from other antiepileptic drugs [16].



### 3.3.4.B] Constipation

1) Incidence: adults, 2% to 6%; pediatrics, 4%[16]

2) Adults

a) Constipation was reported in 5% of patients treated with [oxcarbazepine](#) (n=55) compared with 0% treated with placebo (n=49) in a controlled clinical trial of [oxcarbazepine](#) monotherapy among adults with no previous antiepileptic drug experience [16].

b) Constipation was reported in 2%, 2%, 6%, and 4% of patients treated with adjunctive [oxcarbazepine](#) 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with [epilepsy](#) [16].

3) Pediatrics

a) Constipation was reported in 4% of patients treated with [oxcarbazepine](#) (n=171) compared with 1% of patients treated with placebo (n=139) in an adjunctive therapy trial of pediatric patients previously treated with other antiepileptic drugs [16].

### 3.3.4.C] Diarrhea

1) Incidence: 5% to 7%[16]

2) Diarrhea was reported in 7% of patients treated with [oxcarbazepine](#) (n=55) compared with 2% treated with placebo (n=49) in a controlled clinical trial of [oxcarbazepine](#) monotherapy among adults with no previous antiepileptic drug experience [16].

3) Diarrhea was reported in 7% and 5% of patients with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

4) Diarrhea was reported in 5%, 6%, 7%, and 6% of patients treated with adjunctive [oxcarbazepine](#) 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with [epilepsy](#) [16].

5) Diarrhea was described with the administration of [oxcarbazepine](#) in 7% of patients, which stopped as therapy continued [29][21][20][24][39][40].

### 3.3.4.D] Indigestion

1) Incidence: adults, 1% to 6%; pediatrics, 2%[16]

2) Adults

a) Indigestion/[dyspepsia](#) was reported in 5%, 5%, 6% and 2% of patients treated with adjunctive [oxcarbazepine](#) 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with [epilepsy](#) [16].

b) Indigestion/[dyspepsia](#) was reported in 6% and 1% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

3) Pediatrics

a) Indigestion/[dyspepsia](#) was reported in 2% of patients treated with [oxcarbazepine](#) (n=171) and 0% of patients treated with placebo (n=139) in an adjunctive therapy trial of pediatric patients previously treated with other antiepileptic drugs [16].

### 3.3.4.E] Nausea

1) Incidence: adults, 7% to 29%; pediatrics, 19%[16]

2) Adults

a) Nausea was reported in 16% of patients treated with [oxcarbazepine](#) (n=55) compared with 12% treated with placebo (n=49) in a controlled clinical trial of [oxcarbazepine](#) monotherapy among adults with no previous antiepileptic drug experience [16].

b) Nausea was reported in 22% and 7% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

c) Nausea was reported in 15%, 25%, 29%, and 10% of patients treated with adjunctive [oxcarbazepine](#) 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with [epilepsy](#) [16].

d) Drug discontinuation due to nausea was reported in 1.7% of adults (n=295) during a clinical trial of [oxcarbazepine](#) monotherapy among adults with no previous antiepileptic drug experience [16].

e) Drug discontinuation due to nausea was reported in 4.9% of adult patients previously treated with other antiepileptic drugs in [oxcarbazepine](#) adjunctive or monotherapy trials (n=1537) [16].

3) Pediatrics

a) Nausea was reported in 19% of patients treated with [oxcarbazepine](#) (n=171) compared with 5% of patients treated with placebo (n=139) in an adjunctive therapy trial of pediatric patients previously treated with other antiepileptic drugs [16].

### 3.3.4.F] Pancreatitis

1) [Pancreatitis](#) has occurred during postmarketing use of [oxcarbazepine](#) [16].

### 3.3.4.G] Vomiting

1) Incidence: adults, 5% to 36%; pediatrics, 33%[16]

2) Adults

a) Vomiting was reported in 7% of patients treated with [oxcarbazepine](#) (n=55) compared with 6% treated with placebo (n=49) in a controlled clinical trial of [oxcarbazepine](#) monotherapy among adults with no previous antiepileptic drug experience [16].

b) Vomiting was reported in 15% and 5% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

c) Vomiting was reported in 13%, 25%, 36%, and 5% of patients treated with adjunctive [oxcarbazepine](#) doses of 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with [epilepsy](#) [16].

d) Drug discontinuation due to vomiting was reported in 5.1% of adult patients previously treated with other antiepileptic drugs in [oxcarbazepine](#) adjunctive or monotherapy trials (n=1537) [16].

3) Pediatrics

a)) Vomiting was reported in 33% of patients treated with [oxcarbazepine](#) (n=171) compared with 14% of patients treated with placebo (n=139) in an adjunctive therapy trial of pediatric patients previously treated with other antiepileptic drugs [16].

b)) Drug discontinuation due to vomiting was reported in 2% of pediatric patients ages 4 years and above previously treated with other antiepileptic drugs (n=456) who received [oxcarbazepine](#) during adjunctive or monotherapy trials [16].

### 3.3.5] Hematologic Effects

#### 3.3.5.A] Agranulocytosis

1)) Incidence: very rare[16]

2)) Very rarely, [agranulocytosis](#) has occurred during postmarketing use of [oxcarbazepine](#). Consider discontinuing [oxcarbazepine](#) if symptoms develop [16].

#### 3.3.5.B] Aplastic anemia

1)) Incidence: very rare[16]

2)) Very rarely, [aplastic anemia](#) has occurred during postmarketing use of [oxcarbazepine](#). Consider discontinuing [oxcarbazepine](#) if symptoms develop [16].

#### 3.3.5.C] Leukopenia

1)) [Thrombocytopenia](#), [thrombocytopenic purpura](#), and [leukopenia](#) were reported in a 10-year-old boy 2 weeks after beginning oral [oxcarbazepine](#) therapy for [epilepsy](#). The patient presented with a 3-day history of continuous fever, pinpoint [petechiae](#) on lower limbs, red pharynx, swollen tonsils and lymph nodes. He was not taking any other medication, had no history of [hematologic disease](#), and there were no abnormalities found in the CBC, electrolyte panel, or renal and hepatic function tests. On admission, 17 days after the initiation of [oxcarbazepine](#) (1000 mg/day), laboratory results revealed a low WBC of  $2 \times 10^9/L$ , [platelet](#) count of  $10 \times 10^9/L$ , and a potassium level of 3.15 mmol/L. There were high levels of C-reactive protein (11.7 mg/L; reference value, less than 8 mg/L) and [immune globulin E](#) (325 International Units/L), but there was no significant elevation of serum complement proteins C3 or C4. The BUN was slightly increased at 6.62 mmol/L and RBCs were observed in the urine (4/microL), indicating possible kidney damage. The prothrombin time, INR, [fibrinogen](#), and [thrombin](#) time were all within normal limits, and there was no evidence of acute infection by cytomegalovirus or Epstein Barr virus. [Oxcarbazepine](#) was continued and IV [immune globulin](#) (1 g/kg/day) was initiated resulting in an increase in the [platelet](#) count to  $103 \times 10^9/L$  and resolution of [skin petechiae](#). However, as [leukopenia](#) and moderate fever persisted, 5 days after admission, [oxcarbazepine](#) was discontinued and replaced by [levetiracetam](#). Two days following the discontinuation of [oxcarbazepine](#), the fever resolved and, by the 5th day, the potassium level and the WBC normalized. The patient's DNA was genotyped and he was found not to have the HLA-B\*1502, HLA-B\*5801, or HLA-A\*3101 genes [18].

#### 3.3.5.D] Pancytopenia

1)) Incidence: very rare[16]

2)) Very rarely, [pancytopenia](#) has occurred during postmarketing use of [oxcarbazepine](#). Consider discontinuing [oxcarbazepine](#) if symptoms develop [16].

#### 3.3.5.E] Thrombocytopenia

1)) Adult

a)) A case report described [thrombocytopenia](#) in a 63-year-old woman after being treated with [oxcarbazepine](#). The patient, who had a history of depression with psychotic features and multiple psychiatric hospitalizations, presented to the hospital with increasingly disorganized behavior and [paranoid ideation](#). [Platelet](#) count at time of admission was 300,000/microL. Initial treatment with [nortriptyline](#) and [risperidone](#) was unsuccessful, and the patient was switched to [aripiprazole](#) and [venlafaxine](#). After an inadequate response, [oxcarbazepine](#) 300 mg twice daily was added to her ongoing treatment of [aripiprazole](#) and [venlafaxine](#). The patient responded well to this, displaying an improvement in mood and energy levels. Following [oxcarbazepine](#) therapy for a few days, the patient developed a low-grade fever and [platelet](#) count dropped to 208,000/microL. [Idiopathic thrombocytopenic purpura](#) was ruled out and partial thromboplastin time, prothrombin time, and [international normalized ratio](#) were within normal limits. [Platelet](#) count continued to drop and was 18,000/microL by day 10 of treatment. [Oxcarbazepine](#) was discontinued and 4 days later, [platelet](#) count increased to 250,000/microL and was within normal limits 7 days after discontinuing [oxcarbazepine](#) [17].

## 2)) Pediatric

a)) [Thrombocytopenia](#), [thrombocytopenic purpura](#), and [leukopenia](#) were reported in a 10-year-old boy 2 weeks after beginning oral [oxcarbazepine](#) therapy for [epilepsy](#). The patient presented with a 3-day history of continuous fever, pinpoint [petechiae](#) on lower limbs, red pharynx, swollen tonsils and lymph nodes. He was not taking any other medication, had no history of [hematologic disease](#), and there were no abnormalities found in the CBC, electrolyte panel, or renal and hepatic function tests. On admission, 17 days after the initiation of [oxcarbazepine](#) (1000 mg/day), laboratory results revealed a low WBC of  $2 \times 10^9/L$ , [platelet](#) count of  $10 \times 10^9/L$ , and a potassium level of 3.15 mmol/L. There were high levels of C-reactive protein (11.7 mg/L; reference value, less than 8 mg/L) and [immune globulin E](#) (325 International Units/L), but there was no significant elevation of serum complement proteins C3 or C4. The BUN was slightly increased at 6.62 mmol/L and RBCs were observed in the urine (4/microL), indicating possible kidney damage. The prothrombin time, INR, [fibrinogen](#), and [thrombin](#) time were all within normal limits, and there was no evidence of acute infection by cytomegalovirus or Epstein Barr virus. [Oxcarbazepine](#) was continued and IV [immune globulin](#) (1 g/kg/day) was initiated resulting in an increase in the [platelet](#) count to  $103 \times 10^9/L$  and resolution of [skin petechiae](#). However, as [leukopenia](#) and moderate fever persisted, 5 days after admission, [oxcarbazepine](#) was discontinued and replaced by [levetiracetam](#). Two days following the discontinuation of [oxcarbazepine](#), the fever resolved and, by the 5th day, the potassium level and the WBC normalized. The patient's DNA was genotyped and he was found not to have the HLA-B\*1502, HLA-B\*5801, or HLA-A\*3101 genes [18].

### 3.3.6] Hepatic Effects

#### 3.3.6.A] [Acute hepatitis](#)

##### 1)) Pediatrics

a)) An 8-year-old girl treated for 14 days with [oxcarbazepine](#) 10 mg/kg/day for partial seizures experienced [acute hepatitis](#). On day 12 of therapy, she had a poor appetite and malaise. On day 13, she had a fever. Upon admission (day 14), elevated levels were observed for AST 1245 unit/L, [ALT](#) 1258 units/L, and [alkaline phosphatase](#) 128 international units/L, but [total bilirubin](#) was normal. Serology tests showed reactive IgG antibodies for [hepatitis A](#), but IgM antibodies were nonreactive. Other viral infections ([hepatitis B](#), [C](#), [Epstein-Barr virus](#), [cytomegalovirus](#)) and [autoimmune reaction](#) were ruled-out. [Oxcarbazepine](#) was switched to [levetiracetam](#) 20 mg/kg/day. Four days after discontinuing [oxcarbazepine](#), AST and [ALT](#) levels dropped to 159 units/L and

492 units/L, respectively. The patient's signs and symptoms resolved and she was discharged in stable condition. With her serological profile and no other hepatotoxic drug history, researchers concluded that the patient's [acute hepatitis](#) stemmed from [oxcarbazepine](#) use [48].

### 3.3.6.B] Increased liver function test

1) Elevations in serum gamma-glutamyl transpeptidase ([GGT](#)) have been observed in some patients treated with [oxcarbazepine](#) or 10-hydroxy-carbamazepine [21]. Although no severe hepatotoxic reactions have been reported, monitoring of liver function tests is advised during therapy.

### 3.3.7] Immunologic Effects

#### 3.3.7.A] Anaphylaxis

1) Rare cases of [anaphylaxis](#) have been reported in patients following initial or subsequent [oxcarbazepine](#) use. In the event of this reaction, therapy should be discontinued and the patient should not be rechallenged with [oxcarbazepine](#) [16].

#### 3.3.7.B] Cross sensitivity reaction

- 1) Incidence: 25% to 30%[16]
- 2) [Hypersensitivity reactions](#) to [oxcarbazepine](#) have occurred in 25% to 30% of patients who have had [hypersensitivity reactions](#) to [carbamazepine](#). Discontinue [oxcarbazepine](#) immediately if signs of hypersensitivity develop [16].
- 3) In 1 Danish study, a cross-reaction to [oxcarbazepine](#) was seen in 12 of 47 patients (25%) with allergic skin reactions to [carbamazepine](#) [29].
- 4) Although only a 25% cross-sensitivity has been reported between [oxcarbazepine](#) and [carbamazepine](#), dermatological reactions occurred in 3 patients treated with [oxcarbazepine](#) who had previously discontinued [carbamazepine](#) because of the development of skin reactions. Two patients developed a pruritic skin rash and 1 patient developed [exfoliative dermatitis](#) following 2 or 3 doses of [oxcarbazepine](#) [52].

#### 3.3.7.C] Immune hypersensitivity reaction, multiorgan

1) Although the number of cases has been limited, multiorgan [hypersensitivity disorders](#), often considered life-threatening and resulting in hospitalization, have been reported in association with the initiation of [oxcarbazepine](#) therapy (median time to detection 13 days, range 4 to 60 days). Multiorgan [hypersensitivity reactions](#) have generally presented as rash and fever, with involvement of other organs. Involvement of other organ systems has included hemic and lymphatic , hepatobiliary, renal, musculoskeletal, nervous, and respiratory systems, as well as [pruritus](#), [hepatorenal syndrome](#), and [angioedema](#). [Oxcarbazepine](#) treatment should be discontinued and replaced with an alternative therapy if a [hypersensitivity reaction](#) is suspected. Although there are no reports that cross-sensitivity with other agents (ie, [carbamazepine](#)) has caused this reaction, the possibility cannot be ruled out [16].

### 3.3.9] Neurologic Effects

#### 3.3.9.A] Abnormal gait

- 1) Incidence: adults, 5% to 28.7%; pediatrics, 8% to 23.2%[16]
- 2) Adults

a) Abnormal gait was reported in 5%, 10%, 17%, and 1% of patients treated with adjunctive [oxcarbazepine](#) 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with [epilepsy](#) [16].

b) Drug discontinuation due to abnormal gait was reported in 1.7% of adult patients previously treated with other antiepileptic drugs in [oxcarbazepine](#) adjunctive or monotherapy trials (n=1537) [16].

c) In a large, fixed-dose study with [oxcarbazepine](#) 2400 mg/day (target dose without dose reduction) and up to 3 concomitant antiepileptic therapies, 28.7% of patients treated with [oxcarbazepine](#) developed ataxia or gait disturbances compared with 6.4% treated with placebo [16].

### 3) Pediatrics

a) Abnormal gait was reported in 8% of patients treated with [oxcarbazepine](#) (n=171) compared with 3% of patients treated with placebo (n=139) in an adjunctive therapy trial of pediatric patients previously treated with other antiepileptic drugs [16].

b) In a large, fixed-dose study of pediatric patients (age, 3 to 17 years) treated with [oxcarbazepine](#) 30 to 46 mg/kg (based on body weight or fixed doses for predefined weight ranges), 23.2% of patients treated with [oxcarbazepine](#) developed ataxia or gait disturbances compared with 7% treated with placebo. Drug discontinuation due to ataxia or gait disturbances was reported in 1.4% of patients treated with [oxcarbazepine](#) compared with 0.8% treated with placebo [16].

### 3.3.9.B] Amnesia

1) Incidence: 1% to 5%[16]

2) Amnesia was reported in 5% and 1% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

3) Amnesia was reported in 4% of patients treated with [oxcarbazepine](#) (n=55) compared with 2% treated with placebo (n=49) in a controlled clinical trial of [oxcarbazepine](#) monotherapy among adults with no previous antiepileptic drug experience [16].

### 3.3.9.C] Asthenia

1) Incidence: adults, 3% to 6%; pediatrics, 2%[16]

2) Adults

a) Asthenia was reported in 6%, 3%, 6%, and 5% of patients treated with adjunctive [oxcarbazepine](#) 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with [epilepsy](#) [16].

3) Pediatrics

a) Asthenia was reported in 2% of patients treated with [oxcarbazepine](#) (n=171) compared with 1% of patients treated with placebo (n=139) in an adjunctive therapy trial of pediatric patients previously treated with other antiepileptic drugs [16].

### 3.3.9.D] Ataxia

1) Incidence: adults, 1% to 31%; pediatrics, 13% to 23.2%[16]

2) Adults



- a) Ataxia was reported in 5% of patients treated with [oxcarbazepine](#) (n=55) compared with 0% treated with placebo (n=49) in a controlled clinical trial of [oxcarbazepine](#) monotherapy among adults with no previous antiepileptic drug experience [16].
- b) Ataxia was reported in 7% and 1% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].
- c) Ataxia was reported in 9%, 17%, 31%, and 5% of patients treated with adjunctive [oxcarbazepine](#) 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with [epilepsy](#) [16].
- d) Drug discontinuation due to ataxia was reported in 5.2% of adult patients previously treated with other antiepileptic drugs in [oxcarbazepine](#) adjunctive or monotherapy trials (n=1537) [16].
- e) In a large, fixed-dose study with [oxcarbazepine](#) 2400 mg/day (target dose without dose reduction) and up to 3 concomitant antiepileptic therapies, 28.7% of patients treated with [oxcarbazepine](#) developed ataxia or gait disturbances compared with 6.4% treated with placebo [16].
- f) The incidence of dizziness, drowsiness, headache, and ataxia has been similar with [oxcarbazepine](#) as compared to [carbamazepine](#) in other studies [19][22].

### 3) Pediatrics

- a) Ataxia was reported in 13% of patients treated with [oxcarbazepine](#) (n=171) compared with 4% of patients treated with placebo (n=139) in an adjunctive therapy trial of pediatric patients previously treated with other antiepileptic drugs [16].
- b) Drug discontinuation due to ataxia was reported in 1.2% of pediatric patients ages 1 month to less than age 4 years (n=241) treated with [oxcarbazepine](#) during adjunctive or monotherapy trials, who had or had not been previously treated with other antiepileptic drugs [16].
- c) Drug discontinuation due to ataxia was reported in 1.8% of pediatric patients ages 4 years and above previously treated with other antiepileptic drugs (n=456) who received [oxcarbazepine](#) during adjunctive or monotherapy trials [16].
- d) In a large, fixed-dose study of pediatric patients (age, 3 to 17 years) treated with [oxcarbazepine](#) 30 to 46 mg/kg (based on body weight or fixed doses for predefined weight ranges), 23.2% of patients treated with [oxcarbazepine](#) developed ataxia or gait disturbances compared with 7% treated with placebo. Drug discontinuation due to ataxia or gait disturbances was reported in 1.4% of patients treated with [oxcarbazepine](#) compared with 0.8% treated with placebo [16].

#### 3.3.9.E] Confusion

- 1) Incidence: 7%[16]
- 2) Confusion was reported in 7% and 0% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

#### 3.3.9.F] Dizziness

- 1) Incidence: adults, 8% to 49%; pediatrics, 28%[16]

## 2) Adults

- a) Dizziness was reported in 22% of patients treated with [oxcarbazepine](#) (n=55) compared with 6% treated with placebo (n=49) in a controlled clinical trial of [oxcarbazepine](#) monotherapy among adults with no previous antiepileptic drug experience [16].
- b) Dizziness was reported in 28% and 8% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86) respectively, in a controlled clinical trial of patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].
- c) Dizziness was reported in 26%, 32%, 49%, and 13% of patients treated with adjunctive [oxcarbazepine](#) 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with [epilepsy](#) [16].
- d) Drug discontinuation due to dizziness was reported in 1.7% of adults (n=295) during a clinical trial of [oxcarbazepine](#) monotherapy among adults with no previous antiepileptic drug experience [16].
- e) Drug discontinuation due to dizziness was reported in 6.4% of adult patients previously treated with other antiepileptic drugs in [oxcarbazepine](#) adjunctive or monotherapy trials (n=1537) [16].
- f) The incidence of dizziness, drowsiness, headache, and ataxia has been similar with [oxcarbazepine](#) as compared to [carbamazepine](#) in other studies [19][22].

## 3) Pediatrics

- a) Dizziness was reported in 28% of patients treated with [oxcarbazepine](#) (n=171) compared with 8% of patients treated with placebo (n=139) in an adjunctive therapy trial of pediatric patients previously treated with other antiepileptic drugs [16].
- b) Drug discontinuation due to dizziness was reported in 1.3% of pediatric patients ages 4 years and above previously treated with other antiepileptic drugs (n=456) who received [oxcarbazepine](#) during adjunctive or monotherapy trials [16].

### 3.3.9.G] Feeling nervous

- 1) Incidence: 2% to 7%[16]
- 2) Nervousness was reported in 5% of patients treated with [oxcarbazepine](#) (n=55) compared with 2% treated with placebo (n=49) in a controlled clinical trial of [oxcarbazepine](#) monotherapy among adults with no previous antiepileptic drug experience [16].
- 3) Nervousness was reported in 7% and 0% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86) , respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].
- 4) Nervousness was reported in 2%, 4%, 2%, and 1% of patients treated with adjunctive [oxcarbazepine](#) 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with [epilepsy](#) [16].

### 3.3.9.H] Headache

- 1) Incidence: adults, 13% to 32%; pediatrics, 31%[16]
- 2) Adults



a) Headache was reported in 13% of patients treated with [oxcarbazepine](#) (n=55) compared with 10% treated with placebo (n=49) in a controlled clinical trial of [oxcarbazepine](#) monotherapy among adults with no previous antiepileptic drug experience [16].

b) Headache was reported in 31% and 15% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

c) Headache was reported in 32%, 28%, 26%, and 23% of patients treated with adjunctive [oxcarbazepine](#) 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with [epilepsy](#) [16].

d) Drug discontinuation due to headache was reported in 1.4% of adults (n=295) during a clinical trial of [oxcarbazepine](#) monotherapy among adults with no previous antiepileptic drug experience [16].

e) Drug discontinuation due to headache was reported in 2.9% of patients (n=1537) during [oxcarbazepine](#) treatment in adjunctive or monotherapy trials with adults previously treated with other antiepileptic drugs.[16].

f) The incidence of dizziness, drowsiness, headache, and ataxia has been similar with [oxcarbazepine](#) as compared to [carbamazepine](#) in other studies [19][22].

### 3) Pediatrics

a) Headache was reported in 31% of patients treated with [oxcarbazepine](#) (n=171) compared with 19% of patients treated with placebo (n=139) in an adjunctive therapy trial of pediatric patients previously treated with other antiepileptic drugs [16].

#### 3.3.9.I] Insomnia

1) Incidence: 2% to 6%[16]

2) Insomnia was reported in 6% and 3% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

3) Insomnia was reported in 4%, 2%, 3%, and 1% of patients treated with adjunctive [oxcarbazepine](#) 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with [epilepsy](#) [16].

#### 3.3.9.J] [Metabolic encephalopathy](#)

1) [Metabolic encephalopathy](#) has been reported in a patient due to [oxcarbazepine](#)-induced [hyponatremia](#) [32].

#### 3.3.9.K] Neurological symptom

##### 1) Summary

a) Severe headache, drowsiness, dizziness with ataxia, tremor, abnormal gait, and fatigue are the most frequent adverse effects observed during therapy with oral [oxcarbazepine](#) and oral 10-hydroxy carbamazepine and were among the effects most commonly associated with discontinuation of [oxcarbazepine](#) in clinical studies. Sedation, difficulty in concentration, and [memory impairment](#) are also described with the administration of [oxcarbazepine](#). There is some evidence that

the incidence and severity of central nervous system effects, including sedation, is less with [oxcarbazepine](#) than with [carbamazepine](#) [16][19][20][21][22][23][24][25][26][21][27][28].

2) The incidence of dizziness, drowsiness, headache, and ataxia has been similar with [oxcarbazepine](#) as compared to [carbamazepine](#) in other studies [19][22].

3) In one study, substitution of [carbamazepine](#) with [oxcarbazepine](#) in epileptics receiving polytherapy was associated with increased alertness and greater ability to concentrate [29].

### 3.3.9.L] Nystagmus

1) Incidence: adults, 2% to 26%; pediatrics, 9%[16]

2) Adults

a) [Nystagmus](#) was reported in 2% and 0% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86) , respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

b) [Nystagmus](#) was reported in 7%, 20%, 26%, and 5% of patients treated with adjunctive [oxcarbazepine](#) 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with [epilepsy](#) [16].

3) Pediatrics

a) [Nystagmus](#) was reported in 9% of patients treated with [oxcarbazepine](#) (n=171) compared with 1% of patients treated with placebo (n=139) in an adjunctive therapy trial of pediatric patients previously treated with other antiepileptic drugs [16].

b) Drug discontinuation due to [nystagmus](#) was reported in 1.1% of pediatric patients ages 4 years and above previously treated with other antiepileptic drugs (n=456) who received [oxcarbazepine](#) during adjunctive or monotherapy trials [16].

### 3.3.9.M] Seizure

1) Incidence: pediatric, 2%[16]

2) Pediatric

a) Convulsions were reported in 2% of patients treated with [oxcarbazepine](#) (n=171) compared with 1% of patients treated with placebo (n=139) in an adjunctive therapy trial of pediatric patients previously treated with other antiepileptic drugs [16].

b) Drug discontinuation due to convulsions was reported in 3.7% of pediatric patients ages 1 month to less than age 4 years (n=241) treated with [oxcarbazepine](#) during adjunctive or monotherapy trials, who had or had not been previously treated with other antiepileptic drugs [16].

### 3.3.9.N] Seizure, Aggravated

1) Incidence: adults, 2% to 5%[16]

2) Adults

a) Aggravated convulsions were reported in 5% and 2% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

3) Pediatrics

a)) In a case report, a 9-year-old female developed absence-like seizures soon after initiating [oxcarbazepine](#) therapy. The patient had been diagnosed with [benign focal epilepsy of childhood](#) with centrotemporal spikes and had a history of language delay. Her seizures were activated by drowsiness and were all generalized tonic-clonic or hemi-clonic seizures with occasional postictal Todd paralysis. Over a 6-month period, she had 3 nocturnal seizures followed by multiple nocturnal seizures over 3 days. She was then prescribed [oxcarbazepine](#) monotherapy. Soon after, she developed multiple daily episodes of eyelid fluttering with loss of awareness. A 30-minute [electroencephalogram](#) (EEG) recorded 6 seizures and benign focal epileptiform discharges of childhood (BFEDC) occurring at a rate of 9 per minute. [Oxcarbazepine](#) was then discontinued and a 24-hour EEG was performed. BFEDC decreased to 3 per minute and no seizures were recorded. The patient remained off antiepileptic medications for 6 months and did not experience a recurrence of absence-like seizures [31].

### 3.3.9.O] Somnolence

1)) Incidence: adults, 5% to 36%; pediatrics, 31% to 34.8%[16]

2)) Adults

a)) Somnolence was reported in 19% and 5% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86) respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

b)) Somnolence was reported in 20%, 28%, 36%, and 12% of patients treated with adjunctive [oxcarbazepine](#) 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with [epilepsy](#) [16].

c)) Drug discontinuation due to somnolence was reported in 3.8% of adult patients previously treated with other antiepileptic drugs in [oxcarbazepine](#) adjunctive or monotherapy trials (n=1537) [16].

d)) In a large, fixed-dose study of [oxcarbazepine](#) 2400 mg/day (target dose without dose reduction) and up to 3 concomitant antiepileptic therapies, 26% of patients developed somnolence compared with 12% treated with placebo [16].

e)) Drug discontinuation due to somnolence or cognitive adverse events was reported in 1.1% of patients treated with [oxcarbazepine](#) 2400 mg/day compared with 0% treated with [oxcarbazepine](#) 300 mg/day during two dose-controlled monotherapy trials [16].

f)) The incidence of dizziness, drowsiness, headache, and ataxia has been similar with [oxcarbazepine](#) as compared to [carbamazepine](#) in other studies [19][22].

3)) Pediatrics

a)) Somnolence was reported in 31% of patients treated with [oxcarbazepine](#) (n=171) compared with 13% treated with placebo (n=139) in an adjunctive therapy trial of pediatric patients previously treated with other antiepileptic drugs [16].

b)) Drug discontinuation due to somnolence was reported in 2.4% of pediatric patients ages 4 years and above previously treated with other antiepileptic drugs (n=456) who received [oxcarbazepine](#) during adjunctive or monotherapy trials, [16].

c)) In a large, fixed-dose study of pediatric patients (age, 3 to 17 years) treated with [oxcarbazepine](#) 30 to 46 mg/kg (based on body weight or fixed doses for predefined weight ranges), somnolence

occurred in 34.8% of patients treated with [oxcarbazepine](#) compared with 14% of patients treated with placebo [16].

### 3.3.9.P| [Status epilepticus](#)

#### 1|) Pediatrics

a|) Drug discontinuation due to [status epilepticus](#) was reported in 1.2% of pediatric patients ages 1 month to less than age 4 years (n=241) treated with [oxcarbazepine](#) during adjunctive or monotherapy trials, who had or had not been previously treated with other antiepileptic drugs [16].

### 3.3.9.Q| [Tardive dyskinesia](#)

1|) An 8-year-old girl with complex partial seizures and untreated ADHD developed [tardive dyskinesia](#) approximately 10 days after starting [oxcarbazepine](#). Prior to admission, she had 2 seizures in the past month. While hospitalized, therapy was initiated with [oxcarbazepine](#) 15 mg/kg/day for 1 week, titrated to 30 mg/kg/day thereafter. After 3 days of full-dose therapy, she presented with [trismus](#), eye deviation, protrusion of the tongue, and lateral trunk flexion. [Tardive dyskinesia](#) was diagnosed and [oxcarbazepine](#) was immediately discontinued. She was treated with a single-dose of [diazepam](#) IV and [diphenhydramine](#) orally for 2 weeks. Her symptoms resolved 3 days after [oxcarbazepine](#) was discontinued. A score of 6 on the Naranjo ADR Probability Scale showed the relationship between [oxcarbazepine](#) and occurrence of [tardive dyskinesia](#) was probable [30].

### 3.3.9.R| [Tremor](#)

1|) Incidence: adults, 3% to 16%; pediatrics, 6%[16]

#### 2|) Adults

a|) Tremor was reported in 4% of patients treated with [oxcarbazepine](#) (n=55) compared with 0% treated with placebo (n=49) in a controlled clinical trial of [oxcarbazepine](#) monotherapy among adults with no previous antiepileptic drug experience [16].

b|) Tremor was reported in 6% and 3% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

c|) Tremor was reported was reported in 3%, 8%, 16%, and 5% of patients treated with adjunctive [oxcarbazepine](#) 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with [epilepsy](#) [16].

d|) Drug discontinuation due to tremor was reported in 1.8% of adult patients previously treated with other antiepileptic drugs in [oxcarbazepine](#) adjunctive or monotherapy trials (n=1537) [16].

#### 3|) Pediatrics

a|) Tremor was reported in 6% of patients treated with [oxcarbazepine](#) (n=171) compared with 4% of patients treated with placebo (n=139) in an adjunctive therapy trial of pediatric patients previously treated with other antiepileptic drugs [16].

### 3.3.9.S| [Vertigo](#)

1|) Incidence: adults, 3% to 15%; pediatrics, 2%[16]

#### 2|) Adults

a) Vertigo was reported with [oxcarbazepine](#) doses of 2400 mg/day (n=86) and 300 mg/day (n=86) in 3% and 0% of patients, respectively, in a controlled clinical trial of patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

b) Vertigo was reported in 6%, 12%, 15%, and 2% of patients treated with adjunctive [oxcarbazepine](#) 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with [epilepsy](#) [16].

### 3) Pediatrics

a) Vertigo was reported in 2% of patients treated with [oxcarbazepine](#) (n=171) compared with 0% treated with placebo (n=139) in an adjunctive therapy trial of pediatric patients previously treated with other antiepileptic drugs [16].

## 3.3.10] Ophthalmic Effects

### 3.3.10.A] Abnormal vision

1) Incidence: adults, 2% to 14%; pediatrics, 13%[16]

#### 2) Adults

a) Abnormal vision was reported in 4% of patients treated with [oxcarbazepine](#) (n=55) compared with 0% treated with placebo (n=49) in a controlled clinical trial of [oxcarbazepine](#) monotherapy among adults with no previous antiepileptic drug experience [16].

b) Abnormal vision was reported in 14% and 2% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

c) Abnormal vision was reported in 6%, 14%, 13%, and 4% of patients treated with adjunctive [oxcarbazepine](#) 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with [epilepsy](#) [16].

d) Drug discontinuation due to abnormal vision was reported in 2.1% of adult patients previously treated with other antiepileptic drugs in [oxcarbazepine](#) adjunctive or monotherapy trials (n=1537) [16].

#### 3) Pediatrics

a) Abnormal vision was reported in 13% of patients treated with [oxcarbazepine](#) (n=171) compared with 1% of patients treated with placebo (n=139) in an adjunctive therapy trial of pediatric patients previously treated with other antiepileptic drugs [16].

### 3.3.10.B] Diplopia

1) Incidence: adults, 1% to 40%; pediatrics 17%[16]

#### 2) Adults

a) [Diplopia](#) was reported in 17% of patients treated with [oxcarbazepine](#) (n=55) compared with 1% treated with placebo (n=49) in a controlled clinical trial of [oxcarbazepine](#) monotherapy among adults with no previous antiepileptic drug experience [16].

b)) **Diplopia** was reported in 12% and 1% of patients treated with **oxcarbazepine** 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose **oxcarbazepine** from other antiepileptic drugs [16].

c)) **Diplopia** was reported in 14%, 30%, 40%, and 5% of patients treated with adjunctive **oxcarbazepine** 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with **epilepsy** [16].

d)) Drug discontinuation due to **diplopia** was reported in 5.9% of adult patients previously treated with other antiepileptic drugs in **oxcarbazepine** adjunctive or monotherapy trials (n=1537) [16].

### 3)) Pediatrics

a)) **Diplopia** was reported in 17% of patients treated with **oxcarbazepine** (n=171) compared with 1% of patients treated with placebo in an adjunctive therapy trial of pediatric patients previously treated with other antiepileptic drugs [16].

b)) Drug discontinuation due to **diplopia** was reported in 1.3% of pediatric patients ages 4 years and above previously treated with other antiepileptic drugs (n=456) who received **oxcarbazepine** during adjunctive or monotherapy [16].

#### 3.3.10.C) **Oculogyric crisis**

1)) **Oculogyric crisis**, which occurred with **carbamazepine** and ceased following its discontinuance, recurred following onset of therapy with **oxcarbazepine** in a 31-year-old male. The **oculogyric crisis** occurred as a dose-related event, with as many as 30 episodes daily at higher **oxcarbazepine** doses of 1800 mg/day. Following implantation of a vagus nerve stimulator, **oculogyric crisis** ceased, although **oxcarbazepine** therapy was continued [35].

2)) Dose-related **oculogyric crisis** has been described with the administration of **oxcarbazepine** [35].

### 3.3.11] **Otic Effects**

#### 3.3.11.A] **Infection of ear**

1)) Incidence: 2%[16]

2)) Ear infection (not otherwise specified) was reported in 2% and 0% of patients treated with **oxcarbazepine** 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose **oxcarbazepine** from other antiepileptic drugs [16].

### 3.3.12] **Psychiatric Effects**

#### 3.3.12.A] **Suicidal thoughts**

1)) Data reviewed by the US Food and Drug Administration suggest an increased risk of suicidal behavior or ideation may exist in patients receiving therapy with antiepileptic drugs (AEDs). The analysis included 199 placebo-controlled clinical studies covering 11 different AEDs used for several different indications such as **epilepsy**, selected psychiatric illnesses, and other conditions, including migraine and neuropathic pain syndromes. The analysis included 27,863 patients treated with AEDs and 16,029 patients who received placebo. Patients were age 5 years and older. There were 4 completed suicides among patients in the AED treatment groups vs none in the placebo groups. Suicidal behavior or ideation occurred in 0.43% of patients in the AED treatment groups compared with 0.22% of patients in the placebo groups. This corresponded to an estimated 2.1 per 1000 (95% confidence interval, 0.7 to 4.2) more patients in the AED treatment groups having suicidal behavior or ideation than the placebo groups. The increased risk of suicidality was noted at



1 week after starting an AED and continued at least 24 weeks. When compared with placebo, results were generally consistent among the drugs and were seen in all demographic subgroups. Patients treated for [epilepsy](#), psychiatric disorders, or other conditions were all at an increased risk for suicidality compared with placebo. Closely monitor patients treated with AEDs for emergence or worsening of depression, suicidality and other unusual changes in behavior, which may include symptoms such as anxiety, agitation, hostility, mania, and [hypomania](#) [53].

### 3.3.13] Renal Effects

#### 3.3.13.A] Urinary tract infectious disease

1) Incidence: 1% to 5%[16]

2) [Urinary tract infection](#) was reported in 5% and 1% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

### 3.3.14] Reproductive Effects

#### 3.3.14.A] Abnormal androgen

1) Antiepileptic agents have been associated with changes in serum concentrations of male reproductive hormones. When compared to healthy controls (n=41), carbamazepine-treated men with [partial epilepsy](#) (n=15) had lower serum dehydroepiandrosterone sulfate concentrations (3068 ng/mL for controls versus 1952 ng/mL for [carbamazepine](#); p less than 0.001). No statistically significant differences in dehydroepiandrosterone levels were detected between controls and [oxcarbazepine](#) treated (n=18) or [valproic acid](#) treated (n=27) men with [generalized epilepsy](#). It was also found that men in the [valproic acid](#) group had higher androstenedione levels (5.9 ng/mL) when compared to the control group (2.2 ng/mL; p less than 0.001) whereas the other arms did not. There were no statistically significant differences in serum [testosterone](#), sex hormone binding globulin, free androgen index, [luteinizing hormone](#), [follicle stimulating hormone](#), prolactin and inhibin B measurements among the 4 groups. Whether the differences in reproductive hormones are epilepsy-induced changes or antiepileptic agent-induced changes remains to be determined [46].

2) Reproductive hormone levels in men with [epilepsy](#) may be affected by use of [valproic acid](#) or [carbamazepine](#), with some effect shown by [oxcarbazepine](#) at high doses. In valproate-treated men (n=21), androstenedione levels were significantly increased compared with controls (n=25) (p less than 0.001), and more than half of the cohort taking [valproate](#) (57%) had serum concentrations of [testosterone](#), androstenedione, or dehydroepiandrosterone (DHEA) above the reference range (p less than 0.001). [Follicle stimulating hormone](#) levels were abnormally low in [valproate](#)- treated men (p less than 0.05). Among carbamazepine-treated men (n=40), serum concentrations of DHEA were low (p less than 0.001) and sex hormone-binding globulin (SHBG) levels were high (p less than 0.05). In men taking high doses of [oxcarbazepine](#) (900 mg/day or more), serum concentrations of [testosterone](#), [luteinizing hormone](#), and SHBG were high (p=0.008, p=0.02, p=0.005, respectively). The authors noted that serum [insulin](#) levels were high across all groups [47].

#### 3.3.14.B] Male infertility

1) A 30-year-old man experienced infertility following a 9-year history of [oxcarbazepine](#) therapy for the treatment of [epilepsy](#). The patient was prescribed [oxcarbazepine](#) (up to 1500 mg daily) for complex partial seizures he began experiencing at age 21 after a traumatic brain event. Following marriage at age 29, the patient and his wife tried to conceive a child for a period of 2 years without success. [Semen analysis](#) revealed a reduced sperm count (13 x 10(6)/mL), altered motility (45%), and abnormal structure

(40%). Additionally, low levels of [follicle-stimulating hormone](#), [luteinizing hormone](#), and [testosterone](#) (250 nanograms/dL) were detected. The patient took no other medications, and denied use of any recreational drugs, or alcohol. His wife was also evaluated with specific infertility diagnostic tests, but no abnormalities were found. The patient's [oxcarbazepine](#) was discontinued, and he was switched to [lamotrigine](#) (up to 150 mg daily). After a follow-up of 3 months, [semen analysis](#) results and sexual hormone levels were within the normal range. After 5 months, the patient and his wife conceived a child [54].

#### 3.3.14.C] Small testicle

1) When compared to healthy controls (n=41), [valproic acid](#) treated men with [generalized epilepsy](#) (n=27) had smaller testicular volumes (p=0.01). Within the same study however, the testicular volumes of carbamazepine-treated men with [partial epilepsy](#) (n=15) or oxcarbazepine-treated men with [partial epilepsy](#) (n=18) did not differ from controls. When further examined, valproic acid-treated men with abnormal sperm morphology had smaller testicular volumes than control whereas the testicular volumes of valproic acid-treated men with normal sperm were similar to controls [46].

#### 3.3.14.D] Teratozoospermia

1) Antiepileptic agents have been associated with changes in sperm morphology and motility. A lower frequency of morphologically normal sperm was found in carbamazepine-treated men with [partial epilepsy](#) (n=15), in valproic acid-treated men with [generalized epilepsy](#) and in oxcarbazepine-treated men with [generalized epilepsy](#) (n=18) (p less than 0.01 for [carbamazepine](#) and [valproic acid](#) and p less than 0.05 for [oxcarbazepine](#)) compared with healthy controls (n=41). A statistically significant decrease in the frequency of motile sperm was also found with all treatment groups combined when compared with the healthy controls (p less than 0.05). Within the various treatment groups, valproic acid-treated patients had a statistically significant decrease in the frequency of motile sperm than in the control group (p less than 0.05). Carbamazepine-treated men had high frequencies of abnormally low sperm concentration (p less than 0.001) and poorly motile sperm (p less than 0.05) when compared with controls [46].

### 3.3.15] Respiratory Effects

#### 3.3.15.A] [Bronchitis](#)

1) Incidence: 3%[16]

2) [Bronchitis](#) was reported in 3% and 0% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

#### 3.3.15.B] [Cough](#)

1) Incidence: 5%[16]

2) [Cough](#) was reported in 5% and 0% of patients treated with [oxcarbazepine](#) doses of 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

#### 3.3.15.C] [Epistaxis](#)

1) Incidence: 4%[16]

2) [Epistaxis](#) was reported in 4% of patients treated with [oxcarbazepine](#) (n=55) compared with 0% treated with placebo (n=49) in a controlled clinical trial of [oxcarbazepine](#) monotherapy among adults with no previous antiepileptic drug experience [16].



### 3.3.15.D] Pharyngitis

1) Incidence: 3%[16]

2) **Pharyngitis** was reported in 3% and 0% of patients treated with **oxcarbazepine** 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose **oxcarbazepine** from other antiepileptic drugs [16].

### 3.3.15.E] Pneumonia

1) Incidence: pediatrics, 2%[16]

2) Pediatrics

a) **Pneumonia** was reported in 2% of patients treated with **oxcarbazepine** (n=171) compared with 1% of patients treated with placebo (n=139) in an adjunctive therapy trial of pediatric patients previously treated with other antiepileptic drugs [16].

### 3.3.15.F] Sinusitis

1) Incidence: 4%[16]

2) **Sinusitis** was reported in 4% of patients treated with **oxcarbazepine** (n=55) compared with 2% treated with placebo (n=49) in a controlled clinical trial of **oxcarbazepine** monotherapy among adults with no previous antiepileptic drug experience [16].

### 3.3.15.G] Upper respiratory infection

1) Incidence: 5% to 10%[16]

2) **Upper respiratory tract infection** was reported in 7% of patients treated with **oxcarbazepine** (n=55) compared with 0% treated with placebo (n=49) in a controlled clinical trial of **oxcarbazepine** monotherapy among adults with no previous antiepileptic drug experience [16].

3) **Upper respiratory tract infection** was reported in 10% and 5% of patients treated with **oxcarbazepine** 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose **oxcarbazepine** from other antiepileptic drugs [16].

## 3.3.16] Other

### 3.3.16.A] Angioedema

1) Rare cases of **angioedema** involving the larynx, glottis, lips, and eyelids have been reported in patients following initial or subsequent **oxcarbazepine** use and may lead to fatalities in cases with laryngeal involvement . In the event of this reaction, therapy should be discontinued and the patient should not be rechallenged with **oxcarbazepine** [55].

### 3.3.16.B] Drug withdrawal seizure

1) Rapid withdrawal of antiepileptic drugs, including **oxcarbazepine**, may result in increased seizure frequency [16].

### 3.3.16.C] Fatigue

1) Incidence: adults, 5% to 21%; pediatrics, 13%[16]

2) Adults

a) Fatigue was reported in 21% and 5% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs [16].

b) Fatigue was reported in 15%, 12%, 15%, and 7% of patients treated with adjunctive [oxcarbazepine](#) 600 mg/day (n=163), 1200 mg/day (n=171), 2400 mg/day (n=126), or placebo (n=166), respectively, during a controlled clinical trial of adults with [epilepsy](#) [16].

c) Drug discontinuation due to fatigue was reported in 2.1% of adult patients previously treated with other antiepileptic drugs in [oxcarbazepine](#) adjunctive or monotherapy trials (n=1537) [16].

### 3) Pediatrics

a) Fatigue was reported in 13% of patients treated with [oxcarbazepine](#) (n=171) compared with 9% of patients treated with placebo (n=139) in an adjunctive therapy trial of pediatric patients previously treated with other antiepileptic drugs [16].

b) Drug discontinuation due to fatigue was reported in 1.1% of pediatric patients ages 4 years and above previously treated with other antiepileptic drugs (n=456) who received [oxcarbazepine](#) during adjunctive or monotherapy trials [16].

### 3.3.16.D) Fever

1) Incidence: 3%[16]

2) Fever was reported in 3% and 0% of patients treated with [oxcarbazepine](#) 2400 mg/day (n=86) and 300 mg/day (n=86), respectively, in a controlled clinical trial of adult patients converted to either high- or low-dose [oxcarbazepine](#) from other antiepileptic drugs. Fever has been reported in post marketing surveillance of [oxcarbazepine](#) [16].

## 3.4) [Teratogenicity/Effects in Pregnancy/Breastfeeding](#)

### A) [Teratogenicity/Effects in Pregnancy](#)

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential [risk to the fetus](#).

2) Australian Drug Evaluation Committee's (ADEC) Category: D

a) Drugs which have caused, are suspected to have caused, or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) There are no adequate and well-controlled clinical studies in pregnant women. Limited data on the safety of [oxcarbazepine](#) during pregnancy demonstrates no evidence of toxicity [99][100].

Animal studies have demonstrated developmental toxicities in the offspring at oral [oxcarbazepine](#) doses similar to the maximum recommended human dose. Because [oxcarbazepine](#) is structurally similar to [carbamazepine](#), which is considered to be teratogenic in humans, it is likely that [oxcarbazepine](#) is a human teratogen. Use [oxcarbazepine](#) during pregnancy only if the potential benefit outweighs the potential [risk to the fetus](#). When use during pregnancy is required, monitor the patient for therapeutic response as plasma levels of the 10-monohydrate derivative (MHD), the active metabolite of [oxcarbazepine](#), may gradually decrease during pregnancy and return after delivery. Encourage enrollment in the North American Antiepileptic Drug (NAAED) Pregnancy Registry (1-888-233-2334) for any woman who becomes pregnant while on [oxcarbazepine](#) therapy. Information can also be found at [www.aedpregnancyregistry.org/](http://www.aedpregnancyregistry.org/) [14].

## 5) Literature Reports

**a)** In a case report of a 34-year-old woman with a 2-year history of [idiopathic epilepsy](#) (subtype partial seizures evolving to secondary generalized seizures), treatment with [oxcarbazepine](#) 600 mg twice daily before and during pregnancy resulted in a spontaneous, uncomplicated vaginal delivery of a female infant without any adverse effects. The patient began [oxcarbazepine](#) treatment after her diagnosis and was seizure-free following the first month of therapy. During week 4 of the 39-week gestation and 13 months after she started [oxcarbazepine](#), pregnancy was determined. According to the patient, there was no other drug intake, no history of smoking, alcohol or [caffeine](#) use or infections during pregnancy. Obstetrical findings, alpha-fetoprotein concentration, and three ultrasounds at weeks 22, 26, and 30 of gestation were all normal. [Oxcarbazepine](#) therapy was continued. The patient gave birth via spontaneous and uncomplicated vaginal delivery to a female infant weighing 3.4 kg and measuring 49 cm with Apgar scores of 8 and 9 at one minute and 5 minutes, respectively, and no adverse effects. There was no exacerbation of seizures following delivery [99]

**b)** No [congenital malformations](#) were reported in 9 infants born to mothers taking [oxcarbazepine](#) during the first trimester of pregnancy [100].

**c)** There are no adequate and well-controlled studies of [oxcarbazepine](#) in pregnant women. Because [oxcarbazepine](#) is structurally similar to [carbamazepine](#), which is considered to be teratogenic in humans, it is likely that [oxcarbazepine](#) is a human teratogen. In pregnant rats treated with [oxcarbazepine](#) 30, 300, or 1000 mg/kg orally throughout organogenesis, fetal malformations (craniofacial, cardiovascular, and skeletal) and variations were observed at the 300- and 1000-mg/kg doses (approximately 1.2 and 4 times the maximum recommended human dose (MRHD) on a mg/m(2) basis, respectively) while increased embryofetal death and decreased fetal body weights were observed at the 1000-mg/kg dose. Fetal structural abnormalities and other developmental toxicities were reported in the offspring of animals treated with either [oxcarbazepine](#) or its active metabolite, 10-hydroxy metabolite (MHD), during pregnancy at doses similar to the MRHD. In pregnant rabbits treated with MHD 20, 100, or 200 mg/kg during organogenesis, increased embryofetal mortality was observed at the 200-mg/kg dose (1.5 times the MRHD). In female rats treated with [oxcarbazepine](#) 25, 50, or 150 mg/kg during late gestation and during lactation, reduced body weights and altered behavior (decreased activity) were observed at the 150-mg/kg dose (0.6 times the MRHD). Rats treated with MHD 25, 75, or 250 mg/kg orally during gestation and lactation resulted in persistently reduced offspring weights at the 250-mg/kg dose (equivalent to the MRHD) [14]. In mice, a malformation incidence of 8% was reported when pregnant mice were given the highest tolerable [oxcarbazepine](#) dose of 1100 mg/kg/day on days 6 through 18 of gestation compared with a 5% incidence in those mice given no drugs [101].

## 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 when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

### 2)) Clinical Management

a)) [Oxcarbazepine](#) and its active metabolite, 10-hydroxy metabolite (MHD), are excreted in human breast milk. The milk-to-plasma concentration ratio was reported to be 0.5 for both drug and metabolite. Due to the potential for serious adverse effects in the nursing infant, a decision should be made to discontinue [oxcarbazepine](#) or discontinue nursing, taking into consideration the importance of the drug to the nursing mother [14][99].

### 3)) Literature Reports

a)) In a case report of a 34-year-old woman with a 2-year history of [idiopathic epilepsy](#) (subtype partial seizures evolving to secondary generalized seizures), treatment with [oxcarbazepine](#) 600 mg twice daily before and during pregnancy and lactation demonstrated no developmental abnormalities in the nursing infant after 4 months of breastfeeding. The patient began [oxcarbazepine](#) treatment after her diagnosis and was seizure-free following the first month of therapy. During week 4 of the 39-week gestation and 13 months after she started [oxcarbazepine](#), pregnancy was determined. [Oxcarbazepine](#) treatment was maintained throughout gestation. The patient gave birth via spontaneous and uncomplicated vaginal delivery to a female infant weighing 3.4 kg and measuring 49 cm with Apgar scores of 8 and 9 at one minute and 5 minutes, respectively, and no adverse effects. There was no exacerbation of seizures following delivery and breastfeeding was successfully initiated with concomitant [oxcarbazepine](#) treatment. During the first four months of nursing, the infant's development was normal [99].

## 3.5] Drug Interactions

### 3.5.1] Drug-Drug Combinations

#### 3.5.1.A] Bosutinib

1)) Interaction Effect: decreased bosutinib plasma concentrations

2)) Summary: [Oxcarbazepine](#) is a strong CYP3A4 inducer and bosutinib is a CYP3A4 substrate[14][94]. Although no formal studies have been conducted between bosutinib and [oxcarbazepine](#), coadministration of bosutinib with [rifampin](#) (another strong CYP3A4 inducer) resulted in reduction of bosutinib Cmax and AUC by 86% and 94%, respectively. A similar reduction in bosutinib concentrations can be expected if bosutinib is coadministered with [oxcarbazepine](#). Therefore, concomitant use of bosutinib and strong CYP3A4 inhibitors should be avoided [94].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of [oxcarbazepine](#) with bosutinib may cause a significant reduction in bosutinib exposure[94][14]. Avoid coadministration of bosutinib with strong or moderate CYP3A4 inducers [94].

7J) Probable Mechanism: induction of CYP3A4-mediated bosutinib metabolism by [oxcarbazepine](#)

### 3.5.1.BJ Carbamazepine

1J) Interaction Effect: decreased plasma concentration of the active 10-monohydroxy metabolite of [oxcarbazepine](#)

2J) Summary: Concurrent administration of [oxcarbazepine](#) and [carbamazepine](#) (CBZ) has resulted in a 40% decrease in the plasma concentration of the active 10-monohydroxy derivative (MHD) of [oxcarbazepine](#)[1]. Although the exact mechanism for this decrease is unknown, it is believed to be partially due to the potential induction of [oxcarbazepine's](#) metabolism by CBZ, which is strong inducer of cytochrome P450 enzymes [80]. Although, the clinical significance of this interaction is unknown, decreased plasma MHD concentrations may result in a potential loss of [oxcarbazepine](#) efficacy. If [oxcarbazepine](#) and [carbamazepine](#) are administered concurrently, clinical response to [oxcarbazepine](#) may need to be monitored.

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: established

6J) Clinical Management: Coadministration of [oxcarbazepine](#) and [carbamazepine](#) may result in a decreased concentration of the active 10-monohydroxy metabolite of [oxcarbazepine](#). Monitor patients for clinical response to [oxcarbazepine](#).

7J) Probable Mechanism: potential induction of cytochrome P450-mediated [oxcarbazepine](#) metabolism

8J) Literature Reports

aJ) In a randomized, double-blind, placebo-controlled trial in adults, coadministration of [carbamazepine](#) (CBZ) and [oxcarbazepine](#) resulted in decreased levels of the pharmacologically active 10-monohydroxy derivative (MHD) of [oxcarbazepine](#). Patients (n=12) being treated with a mean CBZ dose of 1025 milligrams (mg) (range 400 to 2000 mg) were administered a single 600 mg oral dose of [oxcarbazepine](#) and were randomized, a week later, to received either 300 mg [oxcarbazepine](#) three times daily or matched placebo for 3 weeks. Active controls (n=7) were untreated patients who received the single 600 mg [oxcarbazepine](#) dose and 3 weeks active treatment. Study results showed that the area under the concentration-time curve (AUC) for MHD at steady state was reduced by 40% (90% confidence interval: 17% decrease, 57% decrease) in the CBZ-treated group compared to the active controls (p less than 0.05) while AUC for CBZ did not alter significantly. Although the exact mechanism for this decrease is unknown, it was partially attributed to a potential induction of [oxcarbazepine](#) metabolism by [carbamazepine](#), a strong inducer of cytochrome P450 enzymes [80][1].

### 3.5.1.CJ Citalopram

1J) Interaction Effect: increased [citalopram](#) exposure and risk of QT interval prolongation

2J) Summary: [Citalopram](#) has been associated with dose-dependent prolongation of the QT interval[95]. In a [pharmacokinetic study](#) in patients who received [citalopram](#) 40 mg/day for 21 days, combined administration with [cimetidine](#) (a potent CYP2C19 inhibitor) 400 mg/day for 8 days resulted in an increase in [citalopram](#) AUC and Cmax of 43% and 39%, respectively. Although the interaction between [citalopram](#) (a CYP2C19 substrate) and [oxcarbazepine](#) (another CYP2C19 inhibitor) [14] has not been specifically studied, concomitant use may result in increased [citalopram](#) exposure and an increased risk of QT prolongation. If coadministration of [citalopram](#) with [oxcarbazepine](#) is required, do not exceed [citalopram](#) doses of 20 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [95].

3J) Severity: major

4J) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [citalopram](#) with [oxcarbazepine](#) may result in increased [citalopram](#) exposure and risk of QT prolongation. If coadministration of [citalopram](#) with [oxcarbazepine](#) is required, do not exceed [citalopram](#) doses of 20 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds[95].
- 7) Probable Mechanism: inhibition of CYP2C19-mediated [citalopram](#) metabolism by [oxcarbazepine](#)

#### 3.5.1.D] Clopidogrel

- 1) Interaction Effect: reduction in clinical efficacy of [clopidogrel](#)
- 2) Summary: [Clopidogrel](#) is metabolized to its active metabolite by CYP2C19. Concomitant use of CYP2C19 inhibitors, such as [oxcarbazepine](#), would be expected to result in reduced levels of the active metabolite, and therefore a reduction the clinical efficacy of [clopidogrel](#). Concomitant use of CYP2C19 inhibitors with [clopidogrel](#) is discouraged[68].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [clopidogrel](#) and [oxcarbazepine](#) is discouraged[68].
- 7) Probable Mechanism: inhibition of CYP2C19- mediated [clopidogrel](#) metabolism by [oxcarbazepine](#)

#### 3.5.1.E] Cobicistat

- 1) Interaction Effect: decreased plasma concentrations of cobicistat with reduced efficacy and possible viral resistance
- 2) Summary: Concurrent use of cobicistat, a CYP3A substrate[69], and [oxcarbazepine](#), a CYP3A inducer [14], may significantly reduce cobicistat concentrations, which may result in loss of loss of virologic response and the development of antiretroviral resistance. An alternative anticonvulsant should be considered in patients treated with cobicistat [69]. If concomitant use is necessary, monitor closely for reduced cobicistat efficacy including the potential for loss of virologic response and development of antiretroviral resistance.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution is advised with concurrent use of cobicistat and [oxcarbazepine](#) as this may lead to significantly decreased concentrations of cobicistat resulting in reduced virologic response and possible viral resistance. Consider use of an alternative anticonvulsant concomitantly with cobicistat[69]. If coadministration is necessary, monitor for reduced cobicistat efficacy including the potential for loss of virologic response and development of antiretroviral resistance.
- 7) Probable Mechanism: induction of CYP3A-mediated metabolism of cobicistat by [oxcarbazepine](#)

#### 3.5.1.F] Cyclosporine

- 1) Interaction Effect: decreased [cyclosporine](#) concentrations
- 2) Summary: [Cyclosporine](#) is extensively metabolized by CYP3A isozymes. Coadministration with [oxcarbazepine](#), a CYP3A inducer, may result in decreased [cyclosporine](#) concentrations. If concomitant therapy is required, the clinician should monitor circulating [cyclosporine](#) levels and make appropriate [cyclosporine](#) dose adjustments[96][97].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical



6) Clinical Management: Concomitant use of [cyclosporine](#) and [oxcarbazepine](#) may result in decreased [cyclosporine](#) plasma concentrations. If concurrent therapy is required, monitor circulating [cyclosporine](#) levels and make appropriate dosage adjustments as necessary[96][97]. Monitor the patient for decreased response to [cyclosporine](#).

7) Probable Mechanism: induction of CYP3A-mediated [cyclosporine](#) metabolism

### 3.5.1.G] [Desogestrel](#)

1) Interaction Effect: decreased contraceptive effectiveness

2) Summary: In studies conducted with oral contraceptives, concurrent administration of [oxcarbazepine](#) with an oral contraceptive has decreased plasma concentrations of 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#)[1]. Contraceptive effectiveness may be reduced when hormonal contraceptives (oral, transdermal, or vaginal ring) are coadministered with some drugs, such as [oxcarbazepine](#), that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Caution is advised when [oxcarbazepine](#) is administered concurrently with hormonal contraceptives [72]. Patients should be advised about using additional contraceptive methods [73].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of [oxcarbazepine](#) with hormonal contraceptives (oral, transdermal, or vaginal ring) may result in decreased contraceptive efficacy, leading to unintended pregnancy or breakthrough bleeding. Use caution if [oxcarbazepine](#) is administered concomitantly with a combination contraceptive.

7) Probable Mechanism: increased metabolism of contraceptive steroids

8) Literature Reports

a) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied in 10 healthy subjects who had taken triphasic oral contraceptives for at least three menstrual cycles. [Oxcarbazepine](#) 300 mg was administered once on day 16 of the first study cycle, twice daily on day 17, and three times daily from day 18 of the first cycle through day 18 of the second cycle. Combined use resulted in a significant decrease in the AUC for both [ethinyl estradiol](#) (3 +/- 1.2 vs 1.6 +/- 0.6 nanomoles (nmol)/hr) and [levonorgestrel](#) (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/hr) (p=0.006 for both). There was not a significant change in mean Cmax values for either [ethinyl estradiol](#) or [levonorgestrel](#). [Progesterone](#) levels were low throughout the study indicating [anovulation](#), but one subject had prolonged menstrual bleeding and two experienced breakthrough bleeding which indicates a potential loss of contraceptive efficacy [70].

b) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied on 16 healthy women 18 to 44 years of age in a randomized double-blind cross-over design. During two different menstrual cycles, each woman was given placebo or 1200 mg of [oxcarbazepine](#) in random sequence for 26 consecutive days with a one cycle washout period in between. An oral contraceptive containing 50 mcg [ethinyl estradiol](#) and 250 mcg [levonorgestrel](#) was taken for the first 21 days of each cycle. Plasma concentrations of [ethinyl estradiol](#) and [levonorgestrel](#) were measured at regular intervals on days 21 to 23 of each cycle. Compared with placebo, a 47% decrease in AUC for both [ethinyl estradiol](#) and [levonorgestrel](#) was seen during [oxcarbazepine](#) treatment. Peak plasma [ethinyl estradiol](#) concentrations decreased from 180 picograms (pg)/mL to 117 pg/mL during the placebo to [oxcarbazepine](#) cycle, respectively (p less than 0.01), and the [levonorgestrel](#) concentrations decreased from 10.2 to 7.7 nanograms/mL (p

less than 0.01). In addition, the half-lives of [ethinyl estradiol](#) and [levonorgestrel](#) decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 to 15.8 hours, respectively (p less than 0.01) [71].

c) Concurrent administration of [oxcarbazepine](#) with an oral contraceptive has affected plasma concentrations 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#). In studies conducted with oral combination contraceptives, the mean AUC values for [ethinyl estradiol](#) were reduced by 48% (90% confidence interval (CI), 22% to 65%) in one study and 52% (90% CI, 38% to 52%) in another study. The mean AUC values for [levonorgestrel](#) were reduced by 32% (90% CI, 20% to 45%) in one study and 52% (90% CI, 42% to 52%) in another study [1].

### 3.5.1.H] Dienogest

1) Interaction Effect: decreased contraceptive effectiveness

2) Summary: In studies conducted with oral contraceptives, concurrent administration of [oxcarbazepine](#) with an oral contraceptive has decreased plasma concentrations of 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#)[1]. Contraceptive effectiveness may be reduced when hormonal contraceptives (oral, transdermal, or vaginal ring) are coadministered with some drugs, such as [oxcarbazepine](#), that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Caution is advised when [oxcarbazepine](#) is administered concurrently with hormonal contraceptives [72]. Patients should be advised about using additional contraceptive methods [73].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of [oxcarbazepine](#) with hormonal contraceptives (oral, transdermal, or vaginal ring) may result in decreased contraceptive efficacy, leading to unintended pregnancy or breakthrough bleeding. Use caution if [oxcarbazepine](#) is administered concomitantly with a combination contraceptive.

7) Probable Mechanism: increased metabolism of contraceptive steroids

8) Literature Reports

a) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied in 10 healthy subjects who had taken triphasic oral contraceptives for at least three menstrual cycles. [Oxcarbazepine](#) 300 mg was administered once on day 16 of the first study cycle, twice daily on day 17, and three times daily from day 18 of the first cycle through day 18 of the second cycle. Combined use resulted in a significant decrease in the AUC for both [ethinyl estradiol](#) (3 +/- 1.2 vs 1.6 +/- 0.6 nanomoles (nmol)/hr) and [levonorgestrel](#) (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/hr) (p=0.006 for both). There was not a significant change in mean Cmax values for either [ethinyl estradiol](#) or [levonorgestrel](#). [Progesterone](#) levels were low throughout the study indicating [anovulation](#), but one subject had prolonged menstrual bleeding and two experienced breakthrough bleeding which indicates a potential loss of contraceptive efficacy [70].

b) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied on 16 healthy women 18 to 44 years of age in a randomized double-blind cross-over design. During two different menstrual cycles, each woman was given placebo or 1200 mg of [oxcarbazepine](#) in random sequence for 26 consecutive days with a one cycle washout period in between. An oral contraceptive containing 50 mcg [ethinyl estradiol](#) and 250 mcg [levonorgestrel](#) was taken for the first 21 days of each cycle. Plasma concentrations of [ethinyl estradiol](#) and [levonorgestrel](#) were measured at regular intervals on days 21 to 23 of each cycle. Compared with placebo, a 47% decrease in AUC for both [ethinyl estradiol](#) and [levonorgestrel](#) was seen during [oxcarbazepine](#) treatment. Peak plasma [ethinyl estradiol](#) concentrations decreased from 180



picograms (pg)/mL to 117 pg/mL during the placebo to [oxcarbazepine](#) cycle, respectively (p less than 0.01), and the [levonorgestrel](#) concentrations decreased from 10.2 to 7.7 nanograms/mL (p less than 0.01). In addition, the half-lives of [ethinyl estradiol](#) and [levonorgestrel](#) decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 to 15.8 hours, respectively (p less than 0.01) [71].

c) Concurrent administration of [oxcarbazepine](#) with an oral contraceptive has affected plasma concentrations 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#). In studies conducted with oral combination contraceptives, the mean AUC values for [ethinyl estradiol](#) were reduced by 48% (90% confidence interval (CI), 22% to 65%) in one study and 52% (90% CI, 38% to 52%) in another study. The mean AUC values for [levonorgestrel](#) were reduced by 32% (90% CI, 20% to 45%) in one study and 52% (90% CI, 42% to 52%) in another study [1].

### 3.5.1.I] [Drospirenone](#)

1) Interaction Effect: decreased contraceptive effectiveness

2) Summary: In studies conducted with oral contraceptives, concurrent administration of [oxcarbazepine](#) with an oral contraceptive has decreased plasma concentrations of 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#)[1]. Contraceptive effectiveness may be reduced when hormonal contraceptives (oral, transdermal, or vaginal ring) are coadministered with some drugs, such as [oxcarbazepine](#), that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Caution is advised when [oxcarbazepine](#) is administered concurrently with hormonal contraceptives [72]. Patients should be advised about using additional contraceptive methods [73].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of [oxcarbazepine](#) with hormonal contraceptives (oral, transdermal, or vaginal ring) may result in decreased contraceptive efficacy, leading to unintended pregnancy or breakthrough bleeding. Use caution if [oxcarbazepine](#) is administered concomitantly with a combination contraceptive.

7) Probable Mechanism: increased metabolism of contraceptive steroids

8) Literature Reports

a) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied in 10 healthy subjects who had taken triphasic oral contraceptives for at least three menstrual cycles. [Oxcarbazepine](#) 300 mg was administered once on day 16 of the first study cycle, twice daily on day 17, and three times daily from day 18 of the first cycle through day 18 of the second cycle. Combined use resulted in a significant decrease in the AUC for both [ethinyl estradiol](#) (3 +/- 1.2 vs 1.6 +/- 0.6 nanomoles (nmol)/hr) and [levonorgestrel](#) (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/hr) (p=0.006 for both). There was not a significant change in mean Cmax values for either [ethinyl estradiol](#) or [levonorgestrel](#). [Progesterone](#) levels were low throughout the study indicating [anovulation](#), but one subject had prolonged menstrual bleeding and two experienced breakthrough bleeding which indicates a potential loss of contraceptive efficacy [70].

b) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied on 16 healthy women 18 to 44 years of age in a randomized double-blind cross-over design. During two different menstrual cycles, each woman was given placebo or 1200 mg of [oxcarbazepine](#) in random sequence for 26 consecutive days with a one cycle washout period in between. An oral contraceptive containing 50 mcg [ethinyl estradiol](#) and 250 mcg [levonorgestrel](#) was taken for the first 21 days of each cycle. Plasma concentrations of [ethinyl estradiol](#) and [levonorgestrel](#) were measured at regular intervals on days 21 to 23 of each cycle. Compared

with placebo, a 47% decrease in AUC for both [ethinyl estradiol](#) and [levonorgestrel](#) was seen during [oxcarbazepine](#) treatment. Peak plasma [ethinyl estradiol](#) concentrations decreased from 180 picograms (pg)/mL to 117 pg/mL during the placebo to [oxcarbazepine](#) cycle, respectively (p less than 0.01), and the [levonorgestrel](#) concentrations decreased from 10.2 to 7.7 nanograms/mL (p less than 0.01). In addition, the half-lives of [ethinyl estradiol](#) and [levonorgestrel](#) decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 to 15.8 hours, respectively (p less than 0.01) [71].

c) Concurrent administration of [oxcarbazepine](#) with an oral contraceptive has affected plasma concentrations 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#). In studies conducted with oral combination contraceptives, the mean AUC values for [ethinyl estradiol](#) were reduced by 48% (90% confidence interval (CI), 22% to 65%) in one study and 52% (90% CI, 38% to 52%) in another study. The mean AUC values for [levonorgestrel](#) were reduced by 32% (90% CI, 20% to 45%) in one study and 52% (90% CI, 42% to 52%) in another study [1].

### 3.5.1.J] Elvitegravir

1) Interaction Effect: decreased plasma concentrations of elvitegravir with reduced efficacy and possible viral resistance

2) Summary: Concurrent use of elvitegravir, a CYP3A substrate[69], and [oxcarbazepine](#), an inducer of CYP3A4/5 [14], may significantly reduce elvitegravir concentrations, which may result in loss of virologic response and the development of antiretroviral resistance. Caution is advised with concomitant use; an alternative anticonvulsant should be considered in patients treated with elvitegravir [69]. If concomitant use is necessary, monitor closely for reduced elvitegravir efficacy including the potential for loss of virologic response and development of antiretroviral resistance.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised with concomitant use of elvitegravir and [oxcarbazepine](#), as this may lead to significantly decreased concentrations of elvitegravir resulting in reduced virologic response and possible viral resistance. Consider use of an alternative anticonvulsant concomitantly with elvitegravir[69]. If coadministration is necessary, monitor for reduced elvitegravir efficacy including the potential for loss of virologic response and development of antiretroviral resistance.

7) Probable Mechanism: induction of CYP3A-mediated metabolism of elvitegravir by [oxcarbazepine](#)

### 3.5.1.K] Enzalutamide

1) Interaction Effect: decreased enzalutamide plasma concentrations; decreased [oxcarbazepine](#) plasma concentrations

2) Summary: Although no formal studies have been conducted between [oxcarbazepine](#) and enzalutamide, [oxcarbazepine](#) is a moderate CYP3A4 inducer[14], enzalutamide is strong CYP3A4 inducer [63], and both are CYP3A4 substrates. Coadministration of [oxcarbazepine](#) and drugs that strongly induce CYP3A4 metabolism, such as enzalutamide, may decrease [oxcarbazepine](#) plasma concentrations and reduce its therapeutic effect [14]. Furthermore, [oxcarbazepine](#) may induce the CYP3A4 metabolism of enzalutamide resulting in decreased concentrations of enzalutamide, and should be avoided if possible [63].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [oxcarbazepine](#) with enzalutamide may decrease the plasma exposure of either drug. Avoid coadministration of enzalutamide with moderate CYP3A4 inducers[63], if possible, by selecting an alternate concomitant medication with no or minimal CYP3A4 induction .

7J) Probable Mechanism: induction of CYP3A4-mediated enzalutamide metabolism by [oxcarbazepine](#); induction of CYP3A4-mediated [oxcarbazepine](#) metabolism by enzalutamide

### 3.5.1.LJ [Estradiol](#) Cypionate

1J) Interaction Effect: decreased contraceptive effectiveness

2J) Summary: In studies conducted with oral contraceptives, concurrent administration of [oxcarbazepine](#) with an oral contraceptive has decreased plasma concentrations of 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#) [1]. Contraceptive effectiveness may be reduced when hormonal contraceptives (oral, transdermal, or vaginal ring) are coadministered with some drugs, such as [oxcarbazepine](#), that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Caution is advised when [oxcarbazepine](#) is administered concurrently with hormonal contraceptives [72]. Patients should be advised about using additional contraceptive methods [73].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: Concurrent use of [oxcarbazepine](#) with hormonal contraceptives (oral, transdermal, or vaginal ring) may result in decreased contraceptive efficacy, leading to unintended pregnancy or breakthrough bleeding. Use caution if [oxcarbazepine](#) is administered concomitantly with a combination contraceptive.

7J) Probable Mechanism: increased metabolism of contraceptive steroids

8J) Literature Reports

aJ) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied in 10 healthy subjects who had taken triphasic oral contraceptives for at least three menstrual cycles. [Oxcarbazepine](#) 300 mg was administered once on day 16 of the first study cycle, twice daily on day 17, and three times daily from day 18 of the first cycle through day 18 of the second cycle. Combined use resulted in a significant decrease in the AUC for both [ethinyl estradiol](#) (3 +/- 1.2 vs 1.6 +/- 0.6 nanomoles (nmol)/hr) and [levonorgestrel](#) (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/hr) (p=0.006 for both). There was not a significant change in mean Cmax values for either [ethinyl estradiol](#) or [levonorgestrel](#). [Progesterone](#) levels were low throughout the study indicating [anovulation](#), but one subject had prolonged menstrual bleeding and two experienced breakthrough bleeding which indicates a potential loss of contraceptive efficacy [70].

bJ) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied on 16 healthy women 18 to 44 years of age in a randomized double-blind cross-over design. During two different menstrual cycles, each woman was given placebo or 1200 mg of [oxcarbazepine](#) in random sequence for 26 consecutive days with a one cycle washout period in between. An oral contraceptive containing 50 mcg [ethinyl estradiol](#) and 250 mcg [levonorgestrel](#) was taken for the first 21 days of each cycle. Plasma concentrations of [ethinyl estradiol](#) and [levonorgestrel](#) were measured at regular intervals on days 21 to 23 of each cycle. Compared with placebo, a 47% decrease in AUC for both [ethinyl estradiol](#) and [levonorgestrel](#) was seen during [oxcarbazepine](#) treatment. Peak plasma [ethinyl estradiol](#) concentrations decreased from 180 picograms (pg)/mL to 117 pg/mL during the placebo to [oxcarbazepine](#) cycle, respectively (p less than 0.01), and the [levonorgestrel](#) concentrations decreased from 10.2 to 7.7 nanograms/mL (p less than 0.01). In addition, the half-lives of [ethinyl estradiol](#) and [levonorgestrel](#) decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 to 15.8 hours, respectively (p less than 0.01) [71].

cJ) Concurrent administration of [oxcarbazepine](#) with an oral contraceptive has affected plasma concentrations 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#). In studies conducted

with oral combination contraceptives, the mean AUC values for [ethinyl estradiol](#) were reduced by 48% (90% confidence interval (CI), 22% to 65%) in one study and 52% (90% CI, 38% to 52%) in another study. The mean AUC values for [levonorgestrel](#) were reduced by 32% (90% CI, 20% to 45%) in one study and 52% (90% CI, 42% to 52%) in another study [1].

### 3.5.1.M] [Estradiol Valerate](#)

- 1) Interaction Effect: decreased contraceptive effectiveness
- 2) Summary: In studies conducted with oral contraceptives, concurrent administration of [oxcarbazepine](#) with an oral contraceptive has decreased plasma concentrations of 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#)[1]. Contraceptive effectiveness may be reduced when hormonal contraceptives (oral, transdermal, or vaginal ring) are coadministered with some drugs, such as [oxcarbazepine](#), that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Caution is advised when [oxcarbazepine](#) is administered concurrently with hormonal contraceptives [72]. Patients should be advised about using additional contraceptive methods [73].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of [oxcarbazepine](#) with hormonal contraceptives (oral, transdermal, or vaginal ring) may result in decreased contraceptive efficacy, leading to unintended pregnancy or breakthrough bleeding. Use caution if [oxcarbazepine](#) is administered concomitantly with a combination contraceptive.
- 7) Probable Mechanism: increased metabolism of contraceptive steroids
- 8) Literature Reports

a) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied in 10 healthy subjects who had taken triphasic oral contraceptives for at least three menstrual cycles. [Oxcarbazepine](#) 300 mg was administered once on day 16 of the first study cycle, twice daily on day 17, and three times daily from day 18 of the first cycle through day 18 of the second cycle. Combined use resulted in a significant decrease in the AUC for both [ethinyl estradiol](#) (3 +/- 1.2 vs 1.6 +/- 0.6 nanomoles (nmol)/hr) and [levonorgestrel](#) (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/hr) (p=0.006 for both). There was not a significant change in mean Cmax values for either [ethinyl estradiol](#) or [levonorgestrel](#). [Progesterone](#) levels were low throughout the study indicating [anovulation](#), but one subject had prolonged menstrual bleeding and two experienced breakthrough bleeding which indicates a potential loss of contraceptive efficacy [70].

b) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied on 16 healthy women 18 to 44 years of age in a randomized double-blind cross-over design. During two different menstrual cycles, each woman was given placebo or 1200 mg of [oxcarbazepine](#) in random sequence for 26 consecutive days with a one cycle washout period in between. An oral contraceptive containing 50 mcg [ethinyl estradiol](#) and 250 mcg [levonorgestrel](#) was taken for the first 21 days of each cycle. Plasma concentrations of [ethinyl estradiol](#) and [levonorgestrel](#) were measured at regular intervals on days 21 to 23 of each cycle. Compared with placebo, a 47% decrease in AUC for both [ethinyl estradiol](#) and [levonorgestrel](#) was seen during [oxcarbazepine](#) treatment. Peak plasma [ethinyl estradiol](#) concentrations decreased from 180 picograms (pg)/mL to 117 pg/mL during the placebo to [oxcarbazepine](#) cycle, respectively (p less than 0.01), and the [levonorgestrel](#) concentrations decreased from 10.2 to 7.7 nanograms/mL (p less than 0.01). In addition, the half-lives of [ethinyl estradiol](#) and [levonorgestrel](#) decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 to 15.8 hours, respectively (p less than 0.01) [71].

c) Concurrent administration of [oxcarbazepine](#) with an oral contraceptive has affected plasma concentrations 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#). In studies conducted with oral combination contraceptives, the mean AUC values for [ethinyl estradiol](#) were reduced by 48% (90% confidence interval (CI), 22% to 65%) in one study and 52% (90% CI, 38% to 52%) in another study. The mean AUC values for [levonorgestrel](#) were reduced by 32% (90% CI, 20% to 45%) in one study and 52% (90% CI, 42% to 52%) in another study [1].

### 3.5.1.N] [Ethinyl Estradiol](#)

1) Interaction Effect: decreased contraceptive effectiveness

2) Summary: In studies conducted with oral contraceptives, concurrent administration of [oxcarbazepine](#) with an oral contraceptive has decreased plasma concentrations of 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#)[1]. Contraceptive effectiveness may be reduced when hormonal contraceptives (oral, transdermal, or vaginal ring) are coadministered with some drugs, such as [oxcarbazepine](#), that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Caution is advised when [oxcarbazepine](#) is administered concurrently with hormonal contraceptives [72]. Patients should be advised about using additional contraceptive methods [73].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of [oxcarbazepine](#) with hormonal contraceptives (oral, transdermal, or vaginal ring) may result in decreased contraceptive efficacy, leading to unintended pregnancy or breakthrough bleeding. Use caution if [oxcarbazepine](#) is administered concomitantly with a combination contraceptive.

7) Probable Mechanism: increased metabolism of contraceptive steroids

8) Literature Reports

a) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied in 10 healthy subjects who had taken triphasic oral contraceptives for at least three menstrual cycles. [Oxcarbazepine](#) 300 mg was administered once on day 16 of the first study cycle, twice daily on day 17, and three times daily from day 18 of the first cycle through day 18 of the second cycle. Combined use resulted in a significant decrease in the AUC for both [ethinyl estradiol](#) (3 +/- 1.2 vs 1.6 +/- 0.6 nanomoles (nmol)/hr) and [levonorgestrel](#) (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/hr) (p=0.006 for both). There was not a significant change in mean Cmax values for either [ethinyl estradiol](#) or [levonorgestrel](#). [Progesterone](#) levels were low throughout the study indicating [anovulation](#), but one subject had prolonged menstrual bleeding and two experienced breakthrough bleeding which indicates a potential loss of contraceptive efficacy [70].

b) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied on 16 healthy women 18 to 44 years of age in a randomized double-blind cross-over design. During two different menstrual cycles, each woman was given placebo or 1200 mg of [oxcarbazepine](#) in random sequence for 26 consecutive days with a one cycle washout period in between. An oral contraceptive containing 50 mcg [ethinyl estradiol](#) and 250 mcg [levonorgestrel](#) was taken for the first 21 days of each cycle. Plasma concentrations of [ethinyl estradiol](#) and [levonorgestrel](#) were measured at regular intervals on days 21 to 23 of each cycle. Compared with placebo, a 47% decrease in AUC for both [ethinyl estradiol](#) and [levonorgestrel](#) was seen during [oxcarbazepine](#) treatment. Peak plasma [ethinyl estradiol](#) concentrations decreased from 180 picograms (pg)/mL to 117 pg/mL during the placebo to [oxcarbazepine](#) cycle, respectively (p less than 0.01), and the [levonorgestrel](#) concentrations decreased from 10.2 to 7.7 nanograms/mL (p



less than 0.01). In addition, the half-lives of [ethinyl estradiol](#) and [levonorgestrel](#) decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 to 15.8 hours, respectively (p less than 0.01) [71].

c) Concurrent administration of [oxcarbazepine](#) with an oral contraceptive has affected plasma concentrations 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#). In studies conducted with oral combination contraceptives, the mean AUC values for [ethinyl estradiol](#) were reduced by 48% (90% confidence interval (CI), 22% to 65%) in one study and 52% (90% CI, 38% to 52%) in another study. The mean AUC values for [levonorgestrel](#) were reduced by 32% (90% CI, 20% to 45%) in one study and 52% (90% CI, 42% to 52%) in another study [1].

### 3.5.1.O] [Ethinodiol Diacetate](#)

1) Interaction Effect: decreased contraceptive effectiveness

2) Summary: In studies conducted with oral contraceptives, concurrent administration of [oxcarbazepine](#) with an oral contraceptive has decreased plasma concentrations of 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#)[1]. Contraceptive effectiveness may be reduced when hormonal contraceptives (oral, transdermal, or vaginal ring) are coadministered with some drugs, such as [oxcarbazepine](#), that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Caution is advised when [oxcarbazepine](#) is administered concurrently with hormonal contraceptives [72]. Patients should be advised about using additional contraceptive methods [73].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of [oxcarbazepine](#) with hormonal contraceptives (oral, transdermal, or vaginal ring) may result in decreased contraceptive efficacy, leading to unintended pregnancy or breakthrough bleeding. Use caution if [oxcarbazepine](#) is administered concomitantly with a combination contraceptive.

7) Probable Mechanism: increased metabolism of contraceptive steroids

8) Literature Reports

a) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied in 10 healthy subjects who had taken triphasic oral contraceptives for at least three menstrual cycles. [Oxcarbazepine](#) 300 mg was administered once on day 16 of the first study cycle, twice daily on day 17, and three times daily from day 18 of the first cycle through day 18 of the second cycle. Combined use resulted in a significant decrease in the AUC for both [ethinyl estradiol](#) (3 +/- 1.2 vs 1.6 +/- 0.6 nanomoles (nmol)/hr) and [levonorgestrel](#) (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/hr) (p=0.006 for both). There was not a significant change in mean Cmax values for either [ethinyl estradiol](#) or [levonorgestrel](#). [Progesterone](#) levels were low throughout the study indicating [anovulation](#), but one subject had prolonged menstrual bleeding and two experienced breakthrough bleeding which indicates a potential loss of contraceptive efficacy [70].

b) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied on 16 healthy women 18 to 44 years of age in a randomized double-blind cross-over design. During two different menstrual cycles, each woman was given placebo or 1200 mg of [oxcarbazepine](#) in random sequence for 26 consecutive days with a one cycle washout period in between. An oral contraceptive containing 50 mcg [ethinyl estradiol](#) and 250 mcg [levonorgestrel](#) was taken for the first 21 days of each cycle. Plasma concentrations of [ethinyl estradiol](#) and [levonorgestrel](#) were measured at regular intervals on days 21 to 23 of each cycle. Compared with placebo, a 47% decrease in AUC for both [ethinyl estradiol](#) and [levonorgestrel](#) was seen during [oxcarbazepine](#) treatment. Peak plasma [ethinyl estradiol](#) concentrations decreased from 180

picograms (pg)/mL to 117 pg/mL during the placebo to [oxcarbazepine](#) cycle, respectively (p less than 0.01), and the [levonorgestrel](#) concentrations decreased from 10.2 to 7.7 nanograms/mL (p less than 0.01). In addition, the half-lives of [ethinyl estradiol](#) and [levonorgestrel](#) decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 to 15.8 hours, respectively (p less than 0.01) [71].

c) Concurrent administration of [oxcarbazepine](#) with an oral contraceptive has affected plasma concentrations 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#). In studies conducted with oral combination contraceptives, the mean AUC values for [ethinyl estradiol](#) were reduced by 48% (90% confidence interval (CI), 22% to 65%) in one study and 52% (90% CI, 38% to 52%) in another study. The mean AUC values for [levonorgestrel](#) were reduced by 32% (90% CI, 20% to 45%) in one study and 52% (90% CI, 42% to 52%) in another study [1].

### 3.5.1.P] [Etonogestrel](#)

1) Interaction Effect: decreased contraceptive effectiveness

2) Summary: In studies conducted with oral contraceptives, concurrent administration of [oxcarbazepine](#) with an oral contraceptive has decreased plasma concentrations of 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#) [1]. Contraceptive effectiveness may be reduced when hormonal contraceptives (oral, transdermal, or vaginal ring) are coadministered with some drugs, such as [oxcarbazepine](#), that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Caution is advised when [oxcarbazepine](#) is administered concurrently with hormonal contraceptives [72]. Patients should be advised about using additional contraceptive methods [73].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of [oxcarbazepine](#) with hormonal contraceptives (oral, transdermal, or vaginal ring) may result in decreased contraceptive efficacy, leading to unintended pregnancy or breakthrough bleeding. Use caution if [oxcarbazepine](#) is administered concomitantly with a combination contraceptive.

7) Probable Mechanism: increased metabolism of contraceptive steroids

8) Literature Reports

a) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied in 10 healthy subjects who had taken triphasic oral contraceptives for at least three menstrual cycles. [Oxcarbazepine](#) 300 mg was administered once on day 16 of the first study cycle, twice daily on day 17, and three times daily from day 18 of the first cycle through day 18 of the second cycle. Combined use resulted in a significant decrease in the AUC for both [ethinyl estradiol](#) (3 +/- 1.2 vs 1.6 +/- 0.6 nanomoles (nmol)/hr) and [levonorgestrel](#) (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/hr) (p=0.006 for both). There was not a significant change in mean Cmax values for either [ethinyl estradiol](#) or [levonorgestrel](#). [Progesterone](#) levels were low throughout the study indicating [anovulation](#), but one subject had prolonged menstrual bleeding and two experienced breakthrough bleeding which indicates a potential loss of contraceptive efficacy [70].

b) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied on 16 healthy women 18 to 44 years of age in a randomized double-blind cross-over design. During two different menstrual cycles, each woman was given placebo or 1200 mg of [oxcarbazepine](#) in random sequence for 26 consecutive days with a one cycle washout period in between. An oral contraceptive containing 50 mcg [ethinyl estradiol](#) and 250 mcg [levonorgestrel](#) was taken for the first 21 days of each cycle. Plasma concentrations of [ethinyl estradiol](#) and [levonorgestrel](#) were measured at regular intervals on days 21 to 23 of each cycle. Compared



with placebo, a 47% decrease in AUC for both [ethinyl estradiol](#) and [levonorgestrel](#) was seen during [oxcarbazepine](#) treatment. Peak plasma [ethinyl estradiol](#) concentrations decreased from 180 picograms (pg)/mL to 117 pg/mL during the placebo to [oxcarbazepine](#) cycle, respectively (p less than 0.01), and the [levonorgestrel](#) concentrations decreased from 10.2 to 7.7 nanograms/mL (p less than 0.01). In addition, the half-lives of [ethinyl estradiol](#) and [levonorgestrel](#) decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 to 15.8 hours, respectively (p less than 0.01) [71].

c) Concurrent administration of [oxcarbazepine](#) with an oral contraceptive has affected plasma concentrations 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#). In studies conducted with oral combination contraceptives, the mean AUC values for [ethinyl estradiol](#) were reduced by 48% (90% confidence interval (CI), 22% to 65%) in one study and 52% (90% CI, 38% to 52%) in another study. The mean AUC values for [levonorgestrel](#) were reduced by 32% (90% CI, 20% to 45%) in one study and 52% (90% CI, 42% to 52%) in another study [1].

### 3.5.1.Q] Evening Primrose

- 1) Interaction Effect: reduced anticonvulsant effectiveness
- 2) Summary: Evening primrose oil contains gamolenic acid (GLA), which may reduce the effectiveness of anticonvulsants by lowering the seizure threshold[64]. Evening primrose oil is contraindicated in patients with [epilepsy](#) [65][66].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of evening primrose oil with anticonvulsants. Evening primrose oil may reduce the effectiveness of anticonvulsants by lowering the seizure threshold[64].
- 7) Probable Mechanism: evening primrose oil may reduce the seizure threshold

### 3.5.1.R] [Felodipine](#)

- 1) Interaction Effect: decreased [felodipine](#) exposure
- 2) Summary: [Oxcarbazepine](#) and its active 10-monohydroxy metabolite induce a subgroup of cytochrome P450 3A family of enzymes which are utilized in the metabolism of [felodipine](#). A small study indicated that repeated coadministration of [felodipine](#) and [oxcarbazepine](#) decreased exposure to [felodipine](#); however the reduced plasma concentrations remained within the recommended therapeutic range[74][1]. If [felodipine](#) and [oxcarbazepine](#) are coadministered, it is advisable to monitor clinical response to [felodipine](#).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Coadministration of [felodipine](#) and [oxcarbazepine](#) has resulted in decreased exposure to [felodipine](#). If [felodipine](#) and [oxcarbazepine](#) are administered concurrently, monitor clinical response to [felodipine](#).
- 7) Probable Mechanism: induction of cytochrome P450-mediated [felodipine](#) metabolism
- 8) Literature Reports

a) A [pharmacokinetic study](#) was conducted with seven healthy subjects who were given [felodipine](#) 10 mg daily for 13 days; on day 6 [oxcarbazepine](#) 600 mg was given and was increased to 450 mg twice daily from day 7 to 13. The single dose of [oxcarbazepine](#) had no effect on [felodipine](#) pharmacokinetic parameters compared with [felodipine](#) alone, but the week-long coadministration resulted in a decrease of [felodipine](#) area under the concentration-time curve (AUC) by 28% (110.2 +/- 35.9 vs 79.2 +/- 25.7; p less than 0.05) and maximum plasma concentration by 34% (9.7 +/- 3.2 vs 6.4 +/- 2 nmol/L). Similar results were obtained for the inactive [felodipine](#) pyridine metabolite.

Despite these reductions in [felodipine](#) AUC and C<sub>max</sub>, the [felodipine](#) plasma concentrations remained within the recommended therapeutic range [74].

### 3.5.1.S] Fosphenytoin

- 1) Interaction Effect: an increased risk of [phenytoin](#) toxicity (ataxia, hyperreflexia, [nystagmus](#), tremor)
- 2) Summary: [Fosphenytoin](#) is a prodrug of [phenytoin](#) and the same interactions that occur with [phenytoin](#) are expected to occur with [fosphenytoin](#)[78]. When [phenytoin](#) in doses of 250 mg to 500 mg daily was combined with [oxcarbazepine](#) in doses of 600 mg to 1800 mg daily, there was less than a 10% change in the concentration of [phenytoin](#). Additionally, concentrations of the 10-monohydroxy metabolite (MHD) of [oxcarbazepine](#), which possesses pharmacological activity, were decreased by 30%. This effect is most likely due to induction of the cytochrome P450 enzyme system by [phenytoin](#). When the same doses of [phenytoin](#) were combined with [oxcarbazepine](#) in doses greater than 1200 mg daily, there was up to a 40% increase in plasma [phenytoin](#) concentrations [79].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Patients should be monitored for [phenytoin](#) toxicity when receiving [oxcarbazepine](#) concurrently, especially when [oxcarbazepine](#) doses exceed 1200 mg daily. A decrease in the [phenytoin](#) dose may be required.
- 7) Probable Mechanism: inhibition of cytochrome P450 2C19-mediated [phenytoin](#) metabolism
- 8) Literature Reports

a) In [polypharmacy](#) studies employing add-on [oxcarbazepine](#) and [carbamazepine](#), increased serum levels of [valproic acid](#) and [phenytoin](#) were observed with patients receiving [oxcarbazepine](#). This was attributed to reduced enzyme induction [75][76]. Alternatively, dose-dependent enzyme induction has been reported by some investigators; higher doses of [oxcarbazepine](#) produced enzyme induction that was similar to [carbamazepine](#) [77]. Further studies are required to determine if [oxcarbazepine](#) will offer a significant advantage over [carbamazepine](#) with regard to enzyme induction.

### 3.5.1.T] Ginkgo

- 1) Interaction Effect: decreased anticonvulsant effectiveness
- 2) Summary: In a case report, 2 patients with [epilepsy](#) previously well controlled by [valproate](#) sodium developed a recurrence of seizures after ingesting ginkgo extract. Seizure control was regained after ginkgo was withdrawn[88]. An infant developed seizures after exposure to 4'-O-methylpyridoxine arising from ingestion of ginkgo seeds [89]. The compound 4'-O-methylpyridoxine, a neurotoxin, is found in ginkgo seeds (used as food in Japan) as well as in leaves, the ginkgo component from which commercially available extracts are derived [90]. The majority of ginkgo leaf products should not contain sufficient amounts of 4'-O-methylpyridoxine to cause seizures. However, ginkgo products are not commonly assayed to assure that 4'-O-methylpyridoxine is not contained in the commercial product. Of concern are those instances where, depending on the harvest season and the potential introduction of contamination, 4'-O-methylpyridoxine may be present in sufficient amounts to be problematic in vulnerable populations (eg, infants or those with known seizure disorders).
- 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 occur for the first time or recur in patients previously controlled by anticonvulsant medication,

inquire about the use of ginkgo seed or leaf extract. If possible, an assay should be conducted on the specific product to ascertain if 4'-O-methylpyridoxine is present.

**7))** Probable Mechanism: neurotoxin 4'-O-methylpyridoxine (found in leaves and seeds of ginkgo biloba) may cause seizures

**8))** Literature Reports

**a))** The serum of a 21-month-old patient with gin-nan food poisoning was assayed for 4'-O-methylpyridoxine levels. The serum concentration was 0.9 micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds, decreasing to 0.05 mcg/mL at 15.5 hours. The authors concluded that the 4'-O-methylpyridoxine content was responsible for the tonic/clonic convulsions and loss of consciousness observed. They further observed that infants are particularly vulnerable [85].

**b))** Four to six milligrams of the neurotoxin 4'-O-methylpyridoxine have been isolated from 2 kilograms of Ginkgo biloba leaves which is the source of commercially-available products. Highest amounts were found in seeds (85 micrograms (mcg)/seed) and leaves (5 mcg/leaf) derived from the tree at the end of July and beginning of August. The albumen of the seed can contain 105.15 mcg/gram dry weight, but this is reduced to 0.75-1.32 mcg/gram dry weight when boiled. The unprocessed seed coats contain from 5.44-7.15 mcg/gram dry weight. The neurotoxin in ginkgo leaf was detected in medications and it was even detectable in homeopathic preparations. Specifically, 8.13 mcg/mL of 4'-O-methylpyridoxine was found in Tebonin Forte(R), 9.77 mcg/mL in Rokan(R), 3.80 mcg/mL in Kaveri Forte(R), and 7.18 mcg/mL in Gingium(R). Based on recommended daily intake, this translates into a maximum daily intake of 4'-O-methylpyridoxine of 48.78 mcg, 58.62 mcg, 11.40 mcg, and 43.08 mcg for Tebonin Forte(R), Rokan(R), Kaveri Forte(R), and Gingium(R), respectively. Among the homeopathic products, Ginkgo biloba Urtinktur Hanosan(R) and Ginkgo biloba Urtinktur DHU(R) contained 0.301 mcg/mL and 0.589 mcg/mL of 4'-O-methylpyridoxine, respectively. However, the authors note that the amount contained in medicinal extracts of ginkgo leaves may be too low to be of clinical significance. Concern remains with the variance in 4'-O-methylpyridoxine content depending on the season during which the ginkgo was harvested [86].

**c))** Seizures recurred in 2 patients, both with epilepsy that was well controlled prior to ingesting ginkgo biloba (Gb). The patients (an 84-year-old woman and a 78-year-old man) had been free of seizures for at least 18 months prior to beginning therapy with Gb 120 milligrams daily to treat cognitive decline. Both patients developed seizures within 2 weeks of beginning Gb therapy, and both remained seizure-free (without changing anticonvulsant therapy) after discontinuing Gb [87].

**3.5.1.U] Ifosfamide**

**1))** Interaction Effect: increased neurotoxic and nephrotoxic effects

**2))** Summary: Ifosfamide is a substrate for CYP3A4 and CYP2B6[81], and oxcarbazepine is an inducer of CYP3A4 [14]. Concomitant administration of ifosfamide and CYP3A4 inducers may increase the metabolism of ifosfamide to its active alkylating metabolites and may increase the formation of a neurotoxic and nephrotoxic metabolite. Patients taking ifosfamide and CYP3A4 inducers, such as oxcarbazepine, should be carefully monitored for toxicity, and ifosfamide dose adjustment may be required [81].

**3))** Severity: major

**4))** Onset: unspecified

**5))** Substantiation: theoretical

6) Clinical Management: Concurrent use of ifosfamide and [oxcarbazepine](#) may increase the risk of neurotoxic and nephrotoxic side effects of ifosfamide. Patients should be carefully monitored for toxicity, and ifosfamide dose adjustment may be required[81].

7) Probable Mechanism: induction of cytochrome P450 3A4-mediated metabolism of ifosfamide to a neurotoxic and nephrotoxic metabolite

### 3.5.1.V] Ketorolac

1) Interaction Effect: reduced anticonvulsant effectiveness

2) Summary: The concomitant use of ketorolac and an anticonvulsant (such as [phenytoin](#) or [carbamazepine](#)) may cause an increased risk of seizures. Sporadic cases of seizures have been reported in patients who received ketorolac together with an antiepileptic drug[57].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing ketorolac to patients who take anticonvulsants. The concomitant use of ketorolac and an anticonvulsant (such as [phenytoin](#) or [carbamazepine](#)) may cause an increased risk of seizures[57].

7) Probable Mechanism: unknown

### 3.5.1.W] Lamotrigine

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, which is considered responsible for the [neurotoxic effects](#) of [carbamazepine](#). When [lamotrigine](#) and [oxcarbazepine](#) were administered concurrently to 14 epileptic patients, plasma concentrations of [lamotrigine](#) were decreased 28.7% compared to [lamotrigine](#) monotherapy[60]. In two patients who had received [lamotrigine](#) and [oxcarbazepine](#) concurrently, [oral ulcers](#) occurred several weeks after [oxcarbazepine](#) discontinuation or dose reduction. Induction of [lamotrigine](#) metabolism by [oxcarbazepine](#) was postulated to be the mechanism, such [oxcarbazepine](#) discontinuation or a dose reduction may have resulted in a slow increase in [lamotrigine](#) levels, thereby increasing its toxicity [58]. Concomitant use of [lamotrigine](#) and [oxcarbazepine](#) may require monitoring the patient closely for seizure control and increasing the [lamotrigine](#) dose as necessary. Conversely, in patients receiving these agents concurrently, if [oxcarbazepine](#) is discontinued or its dose is reduced, [lamotrigine](#) doses may need to be reduced. Additionally, the patient may need to be monitored over several weeks for signs/symptoms of [lamotrigine](#) toxicity.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor seizure control and anticipate a possible need to increase [lamotrigine](#) doses if [oxcarbazepine](#) is added to therapy. Conversely, if [oxcarbazepine](#) is withdrawn from therapy or if dosage is reduced, [lamotrigine](#) doses may need to be reduced and 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 [oxcarbazepine](#) discontinuation or dose reduction. In the first case, a 35-year-old woman being treated for bipolar II disorder (BD II), [hypothyroidism](#), [gastritis](#), migraines, and [asthma](#) was admitted after experiencing one week of worsening depression and two days of suicidal thoughts and treated with [oxcarbazepine](#) 600 mg/day, [topiramate](#), [fluoxetine](#),

aripiprazole, quetiapine, lithium, naproxen, pantoprazole, amoxicillin, and levothyroxine. On day 2, lamotrigine 50 mg/day was initiated and titrated up to 200 mg/day by day 6. Oxcarbazepine dose was decreased and stopped by day 5, and she was discharged on day 8 with lamotrigine 200 mg, topiramate, aripiprazole, escitalopram, naproxen, pantoprazole, levothyroxine, and hydroxyzine. On day 42 (41 days after starting lamotrigine and 39 days after stopping oxcarbazepine), she developed painful tongue ulcers. Subsequently, lamotrigine was stopped and the ulcers resolved in 4 days. In the second case, a 36-year-old man with BD II, hypertension, and GERD was admitted following a suicide attempt and prescribed oxcarbazepine 600 mg/day, phenytoin, lithium, venlafaxine, mirtazapine, metoprolol, and famotidine. Lamotrigine 50 mg/day was initiated on day 11 and titrated up to 100 mg/day by day 14. He was discharged on day 14 with lamotrigine 100 mg and oxcarbazepine 1200 mg (along with other medications); however, he reduced the oxcarbazepine dose to 600 mg/day after discharge. On day 44 (22 days after oxcarbazepine dose decrease), he developed several painful mouth sores on his lips, gums, and tongue. Both lamotrigine and oxcarbazepine were discontinued and the ulcers resolved completely [58].

**b)** Lamotrigine serum concentrations from 222 patients receiving lamotrigine monotherapy (n = 64) or combination therapy with another antiepileptic agent were evaluated. Fourteen patients were being treated with lamotrigine and oxcarbazepine. In the lamotrigine monotherapy group, the lamotrigine concentration was 7.14 mcg/mL while the mean dose was 7.27 mg/dose/kg. The lamotrigine level-to-dose ratio (LDR) in this group calculated out to 1.07 mcg/mL/mg/kg. In the subjects receiving oxcarbazepine in addition to lamotrigine, the plasma concentration was 4.73 mcg/mL while the mean dose was 6.53 mg/dose/kg. The lamotrigine LDR in this group was 0.71 mcg/mL/mg/kg, demonstrating the inducing properties of oxcarbazepine on lamotrigine metabolism [59].

### 3.5.1.X] Levonorgestrel

- 1)** Interaction Effect: decreased contraceptive effectiveness
- 2)** Summary: In studies conducted with oral contraceptives, concurrent administration of oxcarbazepine with an oral contraceptive has decreased plasma concentrations of 2 hormonal components: ethinyl estradiol and levonorgestrel[1]. Contraceptive effectiveness may be reduced when hormonal contraceptives (oral, transdermal, or vaginal ring) are coadministered with some drugs, such as oxcarbazepine, that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Caution is advised when oxcarbazepine is administered concurrently with hormonal contraceptives [72]. Patients should be advised about using additional contraceptive methods [73].
- 3)** Severity: moderate
- 4)** Onset: delayed
- 5)** Substantiation: probable
- 6)** Clinical Management: Concurrent use of oxcarbazepine with hormonal contraceptives (oral, transdermal, or vaginal ring) may result in decreased contraceptive efficacy, leading to unintended pregnancy or breakthrough bleeding. Use caution if oxcarbazepine is administered concomitantly with a combination contraceptive.
- 7)** Probable Mechanism: increased metabolism of contraceptive steroids
- 8)** Literature Reports

**a)** The effects of oxcarbazepine on the pharmacokinetics of ethinyl estradiol and levonorgestrel were studied in 10 healthy subjects who had taken triphasic oral contraceptives for at least three menstrual cycles. Oxcarbazepine 300 mg was administered once on day 16 of the first study cycle, twice daily on day 17, and three times daily from day 18 of the first cycle through day 18 of



the second cycle. Combined use resulted in a significant decrease in the AUC for both [ethinyl estradiol](#) (3 +/- 1.2 vs 1.6 +/- 0.6 nanomoles (nmol)/hr) and [levonorgestrel](#) (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/hr) (p=0.006 for both). There was not a significant change in mean Cmax values for either [ethinyl estradiol](#) or [levonorgestrel](#). [Progesterone](#) levels were low throughout the study indicating [anovulation](#), but one subject had prolonged menstrual bleeding and two experienced breakthrough bleeding which indicates a potential loss of contraceptive efficacy [70].

**b)** The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied on 16 healthy women 18 to 44 years of age in a randomized double-blind cross-over design. During two different menstrual cycles, each woman was given placebo or 1200 mg of [oxcarbazepine](#) in random sequence for 26 consecutive days with a one cycle washout period in between. An oral contraceptive containing 50 mcg [ethinyl estradiol](#) and 250 mcg [levonorgestrel](#) was taken for the first 21 days of each cycle. Plasma concentrations of [ethinyl estradiol](#) and [levonorgestrel](#) were measured at regular intervals on days 21 to 23 of each cycle. Compared with placebo, a 47% decrease in AUC for both [ethinyl estradiol](#) and [levonorgestrel](#) was seen during [oxcarbazepine](#) treatment. Peak plasma [ethinyl estradiol](#) concentrations decreased from 180 picograms (pg)/mL to 117 pg/mL during the placebo to [oxcarbazepine](#) cycle, respectively (p less than 0.01), and the [levonorgestrel](#) concentrations decreased from 10.2 to 7.7 nanograms/mL (p less than 0.01). In addition, the half-lives of [ethinyl estradiol](#) and [levonorgestrel](#) decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 to 15.8 hours, respectively (p less than 0.01) [71].

**c)** Concurrent administration of [oxcarbazepine](#) with an oral contraceptive has affected plasma concentrations 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#). In studies conducted with oral combination contraceptives, the mean AUC values for [ethinyl estradiol](#) were reduced by 48% (90% confidence interval (CI), 22% to 65%) in one study and 52% (90% CI, 38% to 52%) in another study. The mean AUC values for [levonorgestrel](#) were reduced by 32% (90% CI, 20% to 45%) in one study and 52% (90% CI, 42% to 52%) in another study [1].

### 3.5.1.Y] [Medroxyprogesterone Acetate](#)

**1)** Interaction Effect: decreased contraceptive effectiveness

**2)** Summary: In studies conducted with oral contraceptives, concurrent administration of [oxcarbazepine](#) with an oral contraceptive has decreased plasma concentrations of 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#)[1]. Contraceptive effectiveness may be reduced when hormonal contraceptives (oral, transdermal, or vaginal ring) are coadministered with some drugs, such as [oxcarbazepine](#), that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Caution is advised when [oxcarbazepine](#) is administered concurrently with hormonal contraceptives [72]. Patients should be advised about using additional contraceptive methods [73].

**3)** Severity: moderate

**4)** Onset: delayed

**5)** Substantiation: probable

**6)** Clinical Management: Concurrent use of [oxcarbazepine](#) with hormonal contraceptives (oral, transdermal, or vaginal ring) may result in decreased contraceptive efficacy, leading to unintended pregnancy or breakthrough bleeding. Use caution if [oxcarbazepine](#) is administered concomitantly with a combination contraceptive.

**7)** Probable Mechanism: increased metabolism of contraceptive steroids

**8)** Literature Reports

**a)** The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied in 10 healthy subjects who had taken triphasic oral contraceptives for at least three

menstrual cycles. [Oxcarbazepine](#) 300 mg was administered once on day 16 of the first study cycle, twice daily on day 17, and three times daily from day 18 of the first cycle through day 18 of the second cycle. Combined use resulted in a significant decrease in the AUC for both [ethinyl estradiol](#) (3 +/- 1.2 vs 1.6 +/- 0.6 nanomoles (nmol)/hr) and [levonorgestrel](#) (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/hr) (p=0.006 for both). There was not a significant change in mean Cmax values for either [ethinyl estradiol](#) or [levonorgestrel](#). [Progesterone](#) levels were low throughout the study indicating [anovulation](#), but one subject had prolonged menstrual bleeding and two experienced breakthrough bleeding which indicates a potential loss of contraceptive efficacy [70].

**b)** The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied on 16 healthy women 18 to 44 years of age in a randomized double-blind cross-over design. During two different menstrual cycles, each woman was given placebo or 1200 mg of [oxcarbazepine](#) in random sequence for 26 consecutive days with a one cycle washout period in between. An oral contraceptive containing 50 mcg [ethinyl estradiol](#) and 250 mcg [levonorgestrel](#) was taken for the first 21 days of each cycle. Plasma concentrations of [ethinyl estradiol](#) and [levonorgestrel](#) were measured at regular intervals on days 21 to 23 of each cycle. Compared with placebo, a 47% decrease in AUC for both [ethinyl estradiol](#) and [levonorgestrel](#) was seen during [oxcarbazepine](#) treatment. Peak plasma [ethinyl estradiol](#) concentrations decreased from 180 picograms (pg)/mL to 117 pg/mL during the placebo to [oxcarbazepine](#) cycle, respectively (p less than 0.01), and the [levonorgestrel](#) concentrations decreased from 10.2 to 7.7 nanograms/mL (p less than 0.01). In addition, the half-lives of [ethinyl estradiol](#) and [levonorgestrel](#) decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 to 15.8 hours, respectively (p less than 0.01) [71].

**c)** Concurrent administration of [oxcarbazepine](#) with an oral contraceptive has affected plasma concentrations 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#). In studies conducted with oral combination contraceptives, the mean AUC values for [ethinyl estradiol](#) were reduced by 48% (90% confidence interval (CI), 22% to 65%) in one study and 52% (90% CI, 38% to 52%) in another study. The mean AUC values for [levonorgestrel](#) were reduced by 32% (90% CI, 20% to 45%) in one study and 52% (90% CI, 42% to 52%) in another study [1].

### 3.5.1.Z] [Mestranol](#)

**1)** Interaction Effect: decreased contraceptive effectiveness

**2)** Summary: In studies conducted with oral contraceptives, concurrent administration of [oxcarbazepine](#) with an oral contraceptive has decreased plasma concentrations of 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#)[1]. Contraceptive effectiveness may be reduced when hormonal contraceptives (oral, transdermal, or vaginal ring) are coadministered with some drugs, such as [oxcarbazepine](#), that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Caution is advised when [oxcarbazepine](#) is administered concurrently with hormonal contraceptives [72]. Patients should be advised about using additional contraceptive methods [73].

**3)** Severity: moderate

**4)** Onset: delayed

**5)** Substantiation: probable

**6)** Clinical Management: Concurrent use of [oxcarbazepine](#) with hormonal contraceptives (oral, transdermal, or vaginal ring) may result in decreased contraceptive efficacy, leading to unintended pregnancy or breakthrough bleeding. Use caution if [oxcarbazepine](#) is administered concomitantly with a combination contraceptive.

**7)** Probable Mechanism: increased metabolism of contraceptive steroids

**8)** Literature Reports



a) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied in 10 healthy subjects who had taken triphasic oral contraceptives for at least three menstrual cycles. [Oxcarbazepine](#) 300 mg was administered once on day 16 of the first study cycle, twice daily on day 17, and three times daily from day 18 of the first cycle through day 18 of the second cycle. Combined use resulted in a significant decrease in the AUC for both [ethinyl estradiol](#) (3 +/- 1.2 vs 1.6 +/- 0.6 nanomoles (nmol)/hr) and [levonorgestrel](#) (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/hr) (p=0.006 for both). There was not a significant change in mean Cmax values for either [ethinyl estradiol](#) or [levonorgestrel](#). [Progesterone](#) levels were low throughout the study indicating [anovulation](#), but one subject had prolonged menstrual bleeding and two experienced breakthrough bleeding which indicates a potential loss of contraceptive efficacy [70].

b) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied on 16 healthy women 18 to 44 years of age in a randomized double-blind cross-over design. During two different menstrual cycles, each woman was given placebo or 1200 mg of [oxcarbazepine](#) in random sequence for 26 consecutive days with a one cycle washout period in between. An oral contraceptive containing 50 mcg [ethinyl estradiol](#) and 250 mcg [levonorgestrel](#) was taken for the first 21 days of each cycle. Plasma concentrations of [ethinyl estradiol](#) and [levonorgestrel](#) were measured at regular intervals on days 21 to 23 of each cycle. Compared with placebo, a 47% decrease in AUC for both [ethinyl estradiol](#) and [levonorgestrel](#) was seen during [oxcarbazepine](#) treatment. Peak plasma [ethinyl estradiol](#) concentrations decreased from 180 picograms (pg)/mL to 117 pg/mL during the placebo to [oxcarbazepine](#) cycle, respectively (p less than 0.01), and the [levonorgestrel](#) concentrations decreased from 10.2 to 7.7 nanograms/mL (p less than 0.01). In addition, the half-lives of [ethinyl estradiol](#) and [levonorgestrel](#) decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 to 15.8 hours, respectively (p less than 0.01) [71].

c) Concurrent administration of [oxcarbazepine](#) with an oral contraceptive has affected plasma concentrations 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#). In studies conducted with oral combination contraceptives, the mean AUC values for [ethinyl estradiol](#) were reduced by 48% (90% confidence interval (CI), 22% to 65%) in one study and 52% (90% CI, 38% to 52%) in another study. The mean AUC values for [levonorgestrel](#) were reduced by 32% (90% CI, 20% to 45%) in one study and 52% (90% CI, 42% to 52%) in another study [1].

### 3.5.1.AA] [Naproxen](#)

- 1) Interaction Effect: reduced anticonvulsant effectiveness
- 2) Summary: As both [naproxen](#) and hydantoin anticonvulsants are bound to plasma albumin, the concomitant use of [naproxen](#) and a hydantoin anticonvulsant (such as [phenytoin](#) or [mephenytoin](#)) may cause an increased risk of seizures[67].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [naproxen](#) to patients who take a hydantoin anticonvulsant. The concomitant use of [naproxen](#) and a hydantoin may cause an increased risk of seizures[67].
- 7) Probable Mechanism: unknown

### 3.5.1.AB] [Nimodipine](#)

- 1) Interaction Effect: reduced [nimodipine](#) plasma concentrations and lack of [nimodipine](#) efficacy

2)) Summary: Decreased plasma levels and reduced antihypertensive efficacy of [nimodipine](#), a CYP3A4 substrate, may occur during coadministration with a CYP3A4 inducer (eg, [oxcarbazepine](#))[92]. In a [pharmacokinetic study](#), the AUC of [felodipine](#) was reduced by 28% in the presence of [oxcarbazepine](#) (a CYP3A4 inducer), compared with [felodipine](#) monotherapy [14]. Patients receiving concomitant therapy of [nimodipine](#) and [oxcarbazepine](#) should be monitored closely for lack of antihypertensive response to [nimodipine](#), and increased [nimodipine](#) dosage may be necessary [92].

3)) Severity: moderate

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Caution is advised with concomitant use of [nimodipine](#) and CYP3A4 inducers such as [oxcarbazepine](#), as this may lead to decreased [nimodipine](#) plasma levels and reduced antihypertensive efficacy. If concurrent therapy is indicated, monitor patients closely for lack of antihypertensive response to [nimodipine](#). Increased [nimodipine](#) dosages may be necessary[92].

7)) Probable Mechanism: induction of CYP3A4-mediated metabolism of [nimodipine](#) by [oxcarbazepine](#)

8)) Literature Reports

a)) [Oxcarbazepine](#) and its active 10-monohydroxy metabolite (MHD) have been shown to induce CYP3A4, and to reduce the systemic exposure of nondihydropyridine [calcium](#) channel blockers. In a [pharmacokinetic study](#), repeated coadministration of [oxcarbazepine](#) lowered the AUC of [felodipine](#) by 28% (90% CI 20% to 33%) compared with [felodipine](#) monotherapy [14].

### 3.5.1.AC] [Norelgestromin](#)

1)) Interaction Effect: decreased contraceptive effectiveness

2)) Summary: In studies conducted with oral contraceptives, concurrent administration of [oxcarbazepine](#) with an oral contraceptive has decreased plasma concentrations of 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#)[1]. Contraceptive effectiveness may be reduced when hormonal contraceptives (oral, transdermal, or vaginal ring) are coadministered with some drugs, such as [oxcarbazepine](#), that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Caution is advised when [oxcarbazepine](#) is administered concurrently with hormonal contraceptives [72]. Patients should be advised about using additional contraceptive methods [73].

3)) Severity: moderate

4)) Onset: delayed

5)) Substantiation: probable

6)) Clinical Management: Concurrent use of [oxcarbazepine](#) with hormonal contraceptives (oral, transdermal, or vaginal ring) may result in decreased contraceptive efficacy, leading to unintended pregnancy or breakthrough bleeding. Use caution if [oxcarbazepine](#) is administered concomitantly with a combination contraceptive.

7)) Probable Mechanism: increased metabolism of contraceptive steroids

8)) Literature Reports

a)) The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied in 10 healthy subjects who had taken triphasic oral contraceptives for at least three menstrual cycles. [Oxcarbazepine](#) 300 mg was administered once on day 16 of the first study cycle, twice daily on day 17, and three times daily from day 18 of the first cycle through day 18 of the second cycle. Combined use resulted in a significant decrease in the AUC for both [ethinyl estradiol](#) (3 +/- 1.2 vs 1.6 +/- 0.6 nanomoles (nmol)/hr) and [levonorgestrel](#) (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/hr) (p=0.006 for both). There was not a significant change in mean Cmax values for either [ethinyl estradiol](#) or [levonorgestrel](#). [Progesterone](#) levels were low throughout the study

indicating [anovulation](#), but one subject had prolonged menstrual bleeding and two experienced breakthrough bleeding which indicates a potential loss of contraceptive efficacy [70].

**b)** The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied on 16 healthy women 18 to 44 years of age in a randomized double-blind cross-over design. During two different menstrual cycles, each woman was given placebo or 1200 mg of [oxcarbazepine](#) in random sequence for 26 consecutive days with a one cycle washout period in between. An oral contraceptive containing 50 mcg [ethinyl estradiol](#) and 250 mcg [levonorgestrel](#) was taken for the first 21 days of each cycle. Plasma concentrations of [ethinyl estradiol](#) and [levonorgestrel](#) were measured at regular intervals on days 21 to 23 of each cycle. Compared with placebo, a 47% decrease in AUC for both [ethinyl estradiol](#) and [levonorgestrel](#) was seen during [oxcarbazepine](#) treatment. Peak plasma [ethinyl estradiol](#) concentrations decreased from 180 picograms (pg)/mL to 117 pg/mL during the placebo to [oxcarbazepine](#) cycle, respectively (p less than 0.01), and the [levonorgestrel](#) concentrations decreased from 10.2 to 7.7 nanograms/mL (p less than 0.01). In addition, the half-lives of [ethinyl estradiol](#) and [levonorgestrel](#) decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 to 15.8 hours, respectively (p less than 0.01) [71].

**c)** Concurrent administration of [oxcarbazepine](#) with an oral contraceptive has affected plasma concentrations 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#). In studies conducted with oral combination contraceptives, the mean AUC values for [ethinyl estradiol](#) were reduced by 48% (90% confidence interval (CI), 22% to 65%) in one study and 52% (90% CI, 38% to 52%) in another study. The mean AUC values for [levonorgestrel](#) were reduced by 32% (90% CI, 20% to 45%) in one study and 52% (90% CI, 42% to 52%) in another study [1].

### 3.5.1.AD] [Norethindrone](#)

**1)** Interaction Effect: decreased contraceptive effectiveness

**2)** Summary: In studies conducted with oral contraceptives, concurrent administration of [oxcarbazepine](#) with an oral contraceptive has decreased plasma concentrations of 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#)[1]. Contraceptive effectiveness may be reduced when hormonal contraceptives (oral, transdermal, or vaginal ring) are coadministered with some drugs, such as [oxcarbazepine](#), that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Caution is advised when [oxcarbazepine](#) is administered concurrently with hormonal contraceptives [72]. Patients should be advised about using additional contraceptive methods [73].

**3)** Severity: moderate

**4)** Onset: delayed

**5)** Substantiation: probable

**6)** Clinical Management: Concurrent use of [oxcarbazepine](#) with hormonal contraceptives (oral, transdermal, or vaginal ring) may result in decreased contraceptive efficacy, leading to unintended pregnancy or breakthrough bleeding. Use caution if [oxcarbazepine](#) is administered concomitantly with a combination contraceptive.

**7)** Probable Mechanism: increased metabolism of contraceptive steroids

**8)** Literature Reports

**a)** The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied in 10 healthy subjects who had taken triphasic oral contraceptives for at least three menstrual cycles. [Oxcarbazepine](#) 300 mg was administered once on day 16 of the first study cycle, twice daily on day 17, and three times daily from day 18 of the first cycle through day 18 of the second cycle. Combined use resulted in a significant decrease in the AUC for both [ethinyl estradiol](#) (3 +/- 1.2 vs 1.6 +/- 0.6 nanomoles (nmol)/hr) and [levonorgestrel](#) (29.3 +/- 94.6 vs 189.5

+/- 71.7 nmol/hr) (p=0.006 for both). There was not a significant change in mean Cmax values for either [ethinyl estradiol](#) or [levonorgestrel](#). [Progesterone](#) levels were low throughout the study indicating [anovulation](#), but one subject had prolonged menstrual bleeding and two experienced breakthrough bleeding which indicates a potential loss of contraceptive efficacy [70].

**b)** The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied on 16 healthy women 18 to 44 years of age in a randomized double-blind cross-over design. During two different menstrual cycles, each woman was given placebo or 1200 mg of [oxcarbazepine](#) in random sequence for 26 consecutive days with a one cycle washout period in between. An oral contraceptive containing 50 mcg [ethinyl estradiol](#) and 250 mcg [levonorgestrel](#) was taken for the first 21 days of each cycle. Plasma concentrations of [ethinyl estradiol](#) and [levonorgestrel](#) were measured at regular intervals on days 21 to 23 of each cycle. Compared with placebo, a 47% decrease in AUC for both [ethinyl estradiol](#) and [levonorgestrel](#) was seen during [oxcarbazepine](#) treatment. Peak plasma [ethinyl estradiol](#) concentrations decreased from 180 picograms (pg)/mL to 117 pg/mL during the placebo to [oxcarbazepine](#) cycle, respectively (p less than 0.01), and the [levonorgestrel](#) concentrations decreased from 10.2 to 7.7 nanograms/mL (p less than 0.01). In addition, the half-lives of [ethinyl estradiol](#) and [levonorgestrel](#) decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 to 15.8 hours, respectively (p less than 0.01) [71].

**c)** Concurrent administration of [oxcarbazepine](#) with an oral contraceptive has affected plasma concentrations 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#). In studies conducted with oral combination contraceptives, the mean AUC values for [ethinyl estradiol](#) were reduced by 48% (90% confidence interval (CI), 22% to 65%) in one study and 52% (90% CI, 38% to 52%) in another study. The mean AUC values for [levonorgestrel](#) were reduced by 32% (90% CI, 20% to 45%) in one study and 52% (90% CI, 42% to 52%) in another study [1].

### 3.5.1.AE] [Norgestimate](#)

**1)** Interaction Effect: decreased contraceptive effectiveness

**2)** Summary: In studies conducted with oral contraceptives, concurrent administration of [oxcarbazepine](#) with an oral contraceptive has decreased plasma concentrations of 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#)[1]. Contraceptive effectiveness may be reduced when hormonal contraceptives (oral, transdermal, or vaginal ring) are coadministered with some drugs, such as [oxcarbazepine](#), that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Caution is advised when [oxcarbazepine](#) is administered concurrently with hormonal contraceptives [72]. Patients should be advised about using additional contraceptive methods [73].

**3)** Severity: moderate

**4)** Onset: delayed

**5)** Substantiation: probable

**6)** Clinical Management: Concurrent use of [oxcarbazepine](#) with hormonal contraceptives (oral, transdermal, or vaginal ring) may result in decreased contraceptive efficacy, leading to unintended pregnancy or breakthrough bleeding. Use caution if [oxcarbazepine](#) is administered concomitantly with a combination contraceptive.

**7)** Probable Mechanism: increased metabolism of contraceptive steroids

**8)** Literature Reports

**a)** The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied in 10 healthy subjects who had taken triphasic oral contraceptives for at least three menstrual cycles. [Oxcarbazepine](#) 300 mg was administered once on day 16 of the first study cycle, twice daily on day 17, and three times daily from day 18 of the first cycle through day 18 of

the second cycle. Combined use resulted in a significant decrease in the AUC for both [ethinyl estradiol](#) (3 +/- 1.2 vs 1.6 +/- 0.6 nanomoles (nmol)/hr) and [levonorgestrel](#) (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/hr) (p=0.006 for both). There was not a significant change in mean Cmax values for either [ethinyl estradiol](#) or [levonorgestrel](#). [Progesterone](#) levels were low throughout the study indicating [anovulation](#), but one subject had prolonged menstrual bleeding and two experienced breakthrough bleeding which indicates a potential loss of contraceptive efficacy [70].

**b))** The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied on 16 healthy women 18 to 44 years of age in a randomized double-blind cross-over design. During two different menstrual cycles, each woman was given placebo or 1200 mg of [oxcarbazepine](#) in random sequence for 26 consecutive days with a one cycle washout period in between. An oral contraceptive containing 50 mcg [ethinyl estradiol](#) and 250 mcg [levonorgestrel](#) was taken for the first 21 days of each cycle. Plasma concentrations of [ethinyl estradiol](#) and [levonorgestrel](#) were measured at regular intervals on days 21 to 23 of each cycle. Compared with placebo, a 47% decrease in AUC for both [ethinyl estradiol](#) and [levonorgestrel](#) was seen during [oxcarbazepine](#) treatment. Peak plasma [ethinyl estradiol](#) concentrations decreased from 180 picograms (pg)/mL to 117 pg/mL during the placebo to [oxcarbazepine](#) cycle, respectively (p less than 0.01), and the [levonorgestrel](#) concentrations decreased from 10.2 to 7.7 nanograms/mL (p less than 0.01). In addition, the half-lives of [ethinyl estradiol](#) and [levonorgestrel](#) decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 to 15.8 hours, respectively (p less than 0.01) [71].

**c))** Concurrent administration of [oxcarbazepine](#) with an oral contraceptive has affected plasma concentrations 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#). In studies conducted with oral combination contraceptives, the mean AUC values for [ethinyl estradiol](#) were reduced by 48% (90% confidence interval (CI), 22% to 65%) in one study and 52% (90% CI, 38% to 52%) in another study. The mean AUC values for [levonorgestrel](#) were reduced by 32% (90% CI, 20% to 45%) in one study and 52% (90% CI, 42% to 52%) in another study [1].

### 3.5.1.AF] [Norgestrel](#)

**1))** Interaction Effect: decreased contraceptive effectiveness

**2))** Summary: In studies conducted with oral contraceptives, concurrent administration of [oxcarbazepine](#) with an oral contraceptive has decreased plasma concentrations of 2 hormonal components: [ethinyl estradiol](#) and [levonorgestrel](#)[1]. Contraceptive effectiveness may be reduced when hormonal contraceptives (oral, transdermal, or vaginal ring) are coadministered with some drugs, such as [oxcarbazepine](#), that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Caution is advised when [oxcarbazepine](#) is administered concurrently with hormonal contraceptives [72]. Patients should be advised about using additional contraceptive methods [73].

**3))** Severity: moderate

**4))** Onset: delayed

**5))** Substantiation: probable

**6))** Clinical Management: Concurrent use of [oxcarbazepine](#) with hormonal contraceptives (oral, transdermal, or vaginal ring) may result in decreased contraceptive efficacy, leading to unintended pregnancy or breakthrough bleeding. Use caution if [oxcarbazepine](#) is administered concomitantly with a combination contraceptive.

**7))** Probable Mechanism: increased metabolism of contraceptive steroids

**8))** Literature Reports

**a))** The effects of [oxcarbazepine](#) on the pharmacokinetics of [ethinyl estradiol](#) and [levonorgestrel](#) were studied in 10 healthy subjects who had taken triphasic oral contraceptives for at least three



menstrual cycles. **Oxcarbazepine** 300 mg was administered once on day 16 of the first study cycle, twice daily on day 17, and three times daily from day 18 of the first cycle through day 18 of the second cycle. Combined use resulted in a significant decrease in the AUC for both **ethinyl estradiol** (3 +/- 1.2 vs 1.6 +/- 0.6 nanomoles (nmol)/hr) and **levonorgestrel** (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/hr) (p=0.006 for both). There was not a significant change in mean Cmax values for either **ethinyl estradiol** or **levonorgestrel**. **Progesterone** levels were low throughout the study indicating **anovulation**, but one subject had prolonged menstrual bleeding and two experienced breakthrough bleeding which indicates a potential loss of contraceptive efficacy [70].

**b)** The effects of **oxcarbazepine** on the pharmacokinetics of **ethinyl estradiol** and **levonorgestrel** were studied on 16 healthy women 18 to 44 years of age in a randomized double-blind cross-over design. During two different menstrual cycles, each woman was given placebo or 1200 mg of **oxcarbazepine** in random sequence for 26 consecutive days with a one cycle washout period in between. An oral contraceptive containing 50 mcg **ethinyl estradiol** and 250 mcg **levonorgestrel** was taken for the first 21 days of each cycle. Plasma concentrations of **ethinyl estradiol** and **levonorgestrel** were measured at regular intervals on days 21 to 23 of each cycle. Compared with placebo, a 47% decrease in AUC for both **ethinyl estradiol** and **levonorgestrel** was seen during **oxcarbazepine** treatment. Peak plasma **ethinyl estradiol** concentrations decreased from 180 picograms (pg)/mL to 117 pg/mL during the placebo to **oxcarbazepine** cycle, respectively (p less than 0.01), and the **levonorgestrel** concentrations decreased from 10.2 to 7.7 nanograms/mL (p less than 0.01). In addition, the half-lives of **ethinyl estradiol** and **levonorgestrel** decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 to 15.8 hours, respectively (p less than 0.01) [71].

**c)** Concurrent administration of **oxcarbazepine** with an oral contraceptive has affected plasma concentrations 2 hormonal components: **ethinyl estradiol** and **levonorgestrel**. In studies conducted with oral combination contraceptives, the mean AUC values for **ethinyl estradiol** were reduced by 48% (90% confidence interval (CI), 22% to 65%) in one study and 52% (90% CI, 38% to 52%) in another study. The mean AUC values for **levonorgestrel** were reduced by 32% (90% CI, 20% to 45%) in one study and 52% (90% CI, 42% to 52%) in another study [1].

### 3.5.1.AG] **Phenobarbital**

**1)** Interaction Effect: decreased concentration of the active 10-monohydroxy metabolite of **oxcarbazepine** and potential loss of **oxcarbazepine** efficacy

**2)** Summary: Concurrent administration of **oxcarbazepine** (600 to 1,800 milligrams (mg)/day) in patients receiving treatment with **phenobarbital** (100 to 150 mg/day) resulted in a 25% decrease (90% confidence interval (CI), 12% decrease to 51% decrease) in the plasma concentration of **oxcarbazepine's** 10-monohydroxy derivative (MHD) and a 14% increase (90% confidence interval (CI), 2% increase to 24% increase) in the **phenobarbital** concentration[1]. Although the clinical significance of this interaction is unknown, MHD is the pharmacologically active metabolite of **oxcarbazepine** and decreased plasma MHD concentrations may result in potential loss of **oxcarbazepine** efficacy. If **oxcarbazepine** and **phenobarbital** are administered concurrently, clinical response to **oxcarbazepine** may need to be monitored.

**3)** Severity: moderate

**4)** Onset: delayed

**5)** Substantiation: probable

**6)** Clinical Management: Coadministration of **oxcarbazepine** and **phenobarbital** has resulted in decreased concentrations of the active 10-monohydroxy metabolite of **oxcarbazepine**. Monitor patients for clinical response to **oxcarbazepine**.

**7)** Probable Mechanism: potential induction of cytochrome P450-mediated **oxcarbazepine** metabolism

### 3.5.1.AH] Phenytoin

- 1J) Interaction Effect: an increased risk of [phenytoin](#) toxicity (ataxia, hyperreflexia, [nystagmus](#), tremor)
- 2J) Summary: Coadministration of [phenytoin](#) and [oxcarbazepine](#) (600 to 1800 milligrams (mg)/day) resulted in decreased levels of the pharmacologically active 10-monohydroxy derivative (MHD) of [oxcarbazepine](#) while [oxcarbazepine](#) doses above 1200 to 2400 mg/day resulted in increased levels of [phenytoin](#) plasma concentrations. Patients should be monitored for signs of [phenytoin](#) toxicity (ataxia, hyperreflexia, [nystagmus](#), tremor) when receiving [oxcarbazepine](#) concurrently, especially when [oxcarbazepine](#) doses exceed 1200 mg daily. A decrease in the [phenytoin](#) dose may be required[1].
- 3J) Severity: moderate
- 4J) Onset: delayed
- 5J) Substantiation: probable
- 6J) Clinical Management: Concurrent administration of [oxcarbazepine](#) and [phenytoin](#) have resulted in increased plasma levels of [phenytoin](#). Monitor patients for signs of [phenytoin](#) toxicity (ataxia, hyperreflexia, [nystagmus](#), tremor) when receiving [oxcarbazepine](#) concurrently, especially when [oxcarbazepine](#) doses exceed 1200 mg daily. A decrease in the [phenytoin](#) dose may be required.
- 7J) Probable Mechanism: potential inhibition of cytochrome P450 -mediated [phenytoin](#) metabolism
- 8J) Literature Reports

aJ) Administration of [phenytoin](#) in doses of 250 to 500 milligrams (mg) daily in patients concurrently receiving [oxcarbazepine](#) in doses of 600 to 1800 mg daily resulted in a less than 10% change in the concentration of [phenytoin](#). However, concentrations of the active 10-monohydroxy derivative (MHD) of [oxcarbazepine](#) were decreased by 30% (90% confidence interval (CI): 3% decrease to 48% decrease). When the same doses of [phenytoin](#) were combined with [oxcarbazepine](#) in doses greater than 1200 to 2400 mg daily, there was up to a 40% increase (90% CI: 12% increase to 60% increase) in [phenytoin](#) plasma concentrations [1].

bJ) In [polypharmacy](#) studies employing add-on [oxcarbazepine](#) and [carbamazepine](#), increased serum levels of [valproic acid](#) and [phenytoin](#) were observed with patients receiving [oxcarbazepine](#). This was attributed to reduced enzyme induction [75][83]. Alternatively, dose-dependent enzyme induction has been reported by some investigators; higher doses of [oxcarbazepine](#) produced enzyme induction that was similar to [carbamazepine](#) [84]. Further studies are required to determine if [oxcarbazepine](#) will offer a significant advantage over [carbamazepine](#) with regard to enzyme induction.

### 3.5.1.AI] Rilpivirine

- 1J) Interaction Effect: reduced rilpivirine plasma concentrations and risk of diminished therapeutic effect of rilpivirine
- 2J) Summary: Rilpivirine is primarily metabolized by CYP3A isozymes and concomitant use with drugs that induce CYP3A, such as [oxcarbazepine](#), may lead to decreased rilpivirine plasma concentrations and possible loss of virologic response or drug resistance development. Therefore, concomitant use of [oxcarbazepine](#) and rilpivirine is contraindicated[61].
- 3J) Severity: contraindicated
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant use of [oxcarbazepine](#) and rilpivirine is contraindicated as it may lead to decreased rilpivirine plasma concentrations, loss of virologic response, and possible resistance development[61].
- 7J) Probable Mechanism: induction of CYP3A-mediated rilpivirine metabolism



### 3.5.1.AJ] Selegiline

- 1J) Interaction Effect: an increase in [selegiline](#) plasma concentration
- 2J) Summary: In subjects who had received [carbamazepine](#) 400 mg/day for 14 days, slightly increased levels of [selegiline](#) and its metabolites were seen after a single application of [selegiline](#) transdermal patch 6 mg/24 hr. Changes in the [selegiline](#) plasma levels were nearly 2-fold and variable across the subject population[93]. Although not studied with [oxcarbazepine](#), a similar interaction would be expected. Concomitant use of [oxcarbazepine](#) and [selegiline](#) is contraindicated. It is recommended that [selegiline](#) be discontinued for a minimum of 14 days prior to initiation of [oxcarbazepine](#) when necessary [93].
- 3J) Severity: contraindicated
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant use of [oxcarbazepine](#) and [selegiline](#) is contraindicated. [Selegiline](#) should be discontinued for a minimum of 14 days before [oxcarbazepine](#) therapy is initiated[93].
- 7J) Probable Mechanism: unknown

### 3.5.1.AK] Simvastatin

- 1J) Interaction Effect: reduced [simvastatin](#) exposure
- 2J) Summary: [Oxcarbazepine](#) is a molecular derivative of [carbamazepine](#) and shares a similar ability to induce cytochrome P450/3A4. Theoretically, [oxcarbazepine](#) may be expected to induce the metabolism of [simvastatin](#), a cytochrome P450/3A4 substrate. In a controlled study, the concurrent administration of [carbamazepine](#) with [simvastatin](#) significantly reduced maximum serum concentration, serum half-life, and area under the concentration-time curve for both [simvastatin](#) and its active metabolite [simvastatin](#) acid[62].
- 3J) Severity: moderate
- 4J) Onset: delayed
- 5J) Substantiation: probable
- 6J) Clinical Management: Monitor cholesterol levels in patients receiving concomitant therapy with [oxcarbazepine](#) and [simvastatin](#). [Simvastatin](#) dose may need to be adjusted.
- 7J) Probable Mechanism: induction of CYP3A4-mediated first-pass metabolism of [simvastatin](#) by [oxcarbazepine](#)
- 8J) Literature Reports

aJ) Concurrent administration of [simvastatin](#) with [carbamazepine](#) (an anticonvulsant chemically related to [oxcarbazepine](#)) significantly reduced [simvastatin](#) exposure. In a randomized, crossover study with a 2-week wash out period, healthy subjects (n=12) received either no drug or [carbamazepine](#) 200 milligrams (mg) once daily for 2 days, after which the active drug group received [carbamazepine](#) 300 mg twice daily for the next 12 days. On day 15 (12 hours after the last [carbamazepine](#) dose), subjects fasted for 2 hours prior to receiving a single dose of [simvastatin](#) 80 mg. Serial blood samples were obtained immediately prior to and for 24 hours after [simvastatin](#) administration. [Carbamazepine](#) co-administration significantly reduced the mean maximum serum concentration for both [simvastatin](#) and its active metabolite [simvastatin](#) acid (from 18.7 nanograms/milliliter (ng/mL) to 6.0 ng/mL and from 3.5 ng/mL to 1.1 ng/mL, respectively; p less than 0.01, both values). [Simvastatin](#) and [simvastatin](#) acid mean areas under the concentration-time curves (AUC, 0-infinity) declined from 88.8 ng/mL x hour to 22.6 ng/mL x hour and from 33.5 ng/mL x hour to 6.8 ng/mL x hour, respectively (p less than 0.001, both values). Concurrent administration with [carbamazepine](#) also significantly reduced [simvastatin](#) acid serum mean half-life (from 5.9 hours to 3.7 hours, p less than 0.01) [62].

### 3.5.1.AL] Tolvaptan

- 1) Interaction Effect: decreased tolvaptan plasma concentrations
- 2) Summary: Concomitant use of tolvaptan (primarily metabolized by CYP3A) and [oxcarbazepine](#) (a CYP3A inducer) may reduce tolvaptan exposure and should be avoided. If concomitant use is required, tolvaptan dose increases may be necessary to achieve the same clinical effect[56].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [oxcarbazepine](#) and tolvaptan should be avoided due to a risk of reduced plasma concentrations of tolvaptan. If concomitant use is required, the dose of tolvaptan may need to be increased to achieve the same clinical effect[56].
- 7) Probable Mechanism: induction of CYP3A-mediated tolvaptan metabolism by [oxcarbazepine](#)

### 3.5.1.AM] Ulipristal Acetate

- 1) Interaction Effect: decreased ulipristal acetate plasma concentrations
- 2) Summary: Studies to evaluate drug interactions with ulipristal acetate have not been performed. Because ulipristal acetate is metabolized by CYP3A4, concomitant use of [oxcarbazepine](#), a CYP3A4 inducer, and ulipristal acetate may result in decreased plasma concentrations of ulipristal acetate, thereby decreasing its effectiveness[91].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [oxcarbazepine](#) and ulipristal acetate may result in decreased plasma concentrations of ulipristal acetate which may reduce its effectiveness[91].
- 7) Probable Mechanism: induction of CYP3A4-mediated ulipristal acetate metabolism by [oxcarbazepine](#)

### 3.5.1.AN] Valproic Acid

- 1) Interaction Effect: decreased plasma concentration of the active 10-monohydroxy metabolite of [oxcarbazepine](#)
- 2) Summary: Concurrent administration of [oxcarbazepine](#) (600 to 1,800 milligrams (mg)/day) in patients receiving treatment with [valproic acid](#) (400 to 2,800 mg/day) resulted in a 18% decrease (90% confidence interval, 13% decrease to 40% decrease) in the plasma concentration of [oxcarbazepine's](#) 10-monohydroxy derivative (MHD) and a less than 10% change in the [valproic acid](#) concentration[1]. Although, the clinical significance of this interaction is unknown, decreased plasma MHD concentrations may result in a potential loss of [oxcarbazepine](#) efficacy. If [oxcarbazepine](#) and [valproic acid](#) are administered concurrently, clinical response to [oxcarbazepine](#) may need to be monitored.
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Coadministration of [oxcarbazepine](#) and [valproic acid](#) may result in a decreased concentration of the active 10-monohydroxy metabolite of [oxcarbazepine](#). Monitor patients for clinical response to [oxcarbazepine](#).
- 7) Probable Mechanism: unknown

### 3.5.1.AO] Verapamil

- 1) Interaction Effect: decreased plasma levels of the active 10-monohydroxy metabolite of [oxcarbazepine](#) and potential loss of [oxcarbazepine](#) efficacy
- 2) Summary: Concurrent administration of [oxcarbazepine](#) (OCBZ) and [verapamil](#) has resulted in a 20% decrease in the plasma concentration of 10-monohydroxy derivative (MHD)[1][82]. Although the clinical significance of this interaction is unknown, MHD is the active metabolite of OCBZ and decreased plasma MHD concentrations may result in potential loss of OCBZ efficacy. If OCBZ and [verapamil](#) are administered concurrently, clinical response to OCBZ may need to be monitored.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: established
- 6) Clinical Management: Coadministration of [oxcarbazepine](#) and [verapamil](#) may result in decreased plasma levels of the active 10-monohydroxy metabolite of [oxcarbazepine](#). Although the clinical significance of this interaction is unknown, if [oxcarbazepine](#) and [verapamil](#) are coadministered, monitor clinical response to [oxcarbazepine](#).
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concurrent administration of [oxcarbazepine](#) (OCBZ) and [verapamil](#) resulted in decreased plasma concentration of the 10-monohydroxy derivative (MHD), the active metabolite of OCBZ. In healthy volunteers (n=10), upon titration of OCBZ to 900 milligrams/day (mg/day), [verapamil](#) (240 mg/day) was administered for 1 week. The area under the concentration-time curve (AUC) of MHD decreased by 20%; however, AUC was unchanged for OCBZ. The mechanism for this decrease in MHD plasma concentration and its clinical significance are unknown [82].

## 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) In patients with [epilepsy](#), therapeutic serum levels have not been adequately established.

b) In women who plan on becoming pregnant, obtaining concentrations of [oxcarbazepine](#) and mono-hydroxy-carbazepine (MHD) before becoming pregnant and during the pregnancy may be beneficial. Although therapeutic concentrations have not been established, prepregnancy concentrations in an optimally-treated woman provide a reference concentration for comparison to concentrations during pregnancy, when concentrations decrease due to changes in the pharmacokinetic characteristics of [oxcarbazepine](#). Possible sampling times could be once monthly, with less sampling in patients with mild and stable [epilepsy](#), and every 3 to 4 days for 2 weeks after delivery in patients who had their dosage adjusted during pregnancy [13].

c) In patients with [trigeminal neuralgia](#), therapeutic serum concentrations of the active metabolite of [oxcarbazepine](#) (10-hydroxy-carbazepine) have ranged from 50 to 110 micromoles/L [27].

## 2) Physical Findings

### a) [Epilepsy](#)

1) Control of partial seizures is indicative of efficacy.

2) Monitor therapeutic response during pregnancy and through the postpartum period as physiological changes during pregnancy may gradually decrease plasma levels of 10-monohydroxy derivative (MHD), the active metabolite of oxcarbazepine [14].

### b) [Trigeminal Neuralgia](#)

1) A reduction or elimination of pain is indicative of a therapeutic response.

## B) Toxic

### 1) Laboratory Parameters

a) Monitor serum sodium during maintenance treatment, particularly among patients receiving concurrent medications known to decrease serum sodium levels [14].

### 2) Physical Findings

a) Monitor patient for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior [14].

## 4.2] Patient Instructions

### A) [Oxcarbazepine](#) (By mouth)

#### [Oxcarbazepine](#)

Used alone or together with other medicines to treat seizures caused by [epilepsy](#) in adults and children 2 years of age and older.

When This Medicine Should Not Be Used:

You should not use this medicine if you have had an [allergic reaction](#) to [oxcarbazepine](#).

How to Use This Medicine:

Liquid, Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for 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.

Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup.

Shake the oral liquid well just before using. You can take the medicine directly from the oral syringe, or you can mix the medicine in a glass with a small amount of water. If you mix the medicine, drink the mixture right away. Do not save any mixture to use later.

If you use any type of medicine to control your seizures, keep using it as directed by your doctor. Do not stop taking it without first checking with your doctor. If you will be switching to [oxcarbazepine](#) only, your doctor may want you to gradually reduce the amount of the other medicine you are taking for 3 to 6 weeks before stopping it completely.

This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your doctor or pharmacist if you have any questions. Ask your pharmacist for the Medication Guide if you do not have one.

#### 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, wait until then to 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. Store the oral liquid in the original container. Use the liquid within 7 weeks after opening the bottle for the first time. Throw away any unused liquid.

Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any outdated medicine or medicine no longer needed.

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 herbal products.

Make sure your doctor knows if you are also using any other medicines to control seizures. Seizure medicine includes [carbamazepine](#) ([Tegretol](#)®), [phenobarbital](#), [phenytoin](#) ([Dilantin](#)®), or [valproic acid](#) ([Depakote](#)®). Tell your doctor if you also use [felodipine](#) ([Plendil](#)®), [verapamil](#) ([Calan](#)®, [Covera](#)®, [Isoptin](#)®), or [birth control pills](#).

Do not drink alcohol while you are using this medicine.

#### Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you have [kidney disease](#), depression, low sodium in the blood, or if you have had an [allergic reaction](#) to [carbamazepine](#) ([Tegretol](#)®).

Tell your doctor if you become pregnant while taking this medicine. Your doctor may need you to be monitored carefully during your pregnancy and after giving birth. Also, your doctor may want you to join the North American Antiepileptic Drug Pregnancy Registry, which is used by pregnant patients who are taking this medicine.

[Hyponatremia](#) (low sodium in the blood) may occur while you are taking this medicine. Check with your doctor right away if you or your child develop confusion, decreased urine output, dizziness, fast or irregular heartbeat, headache, muscle pain or cramps, nausea or vomiting, weakness, or swelling of the face, ankles, or hands while taking this medicine.

This medicine may cause a serious type of [allergic reaction](#) called [anaphylaxis](#). [Anaphylaxis](#) can be life-threatening and requires immediate medical attention. Stop using this medicine and call your doctor right away if you or your child have itching, hives, hoarseness, trouble breathing, trouble swallowing, or any swelling of your face, eyes, lips, or tongue while you are using this medicine.

This medicine can cause a serious reaction called [angioedema](#). Stop using this medicine and tell your doctor right away if you or your child start to have swelling of your face, lips, tongue, throat, arms, or legs, or if you are having trouble swallowing or breathing.

Serious skin reactions can occur with this medicine. Stop using this medicine and check with your doctor right away if you or your child have blistering, [peeling](#), or loosening of the skin; red [skin lesions](#); severe acne or skin rash; sores or [ulcers on the skin](#); or fever or chills while you are using this medicine.

If you or your child develop any unusual or strange thoughts and behavior while taking this medicine, be sure to discuss it with your doctor. Other changes might be confusion, worsening of depression, hallucinations (seeing, hearing, or feeling things that are not there), suicidal thoughts, and unusual excitement, nervousness, or irritability.

This medicine may make you dizzy, drowsy, lightheaded, clumsy, unsteady, or less alert. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert or able to think or see well.

Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your dose before stopping it completely. Stopping the medicine suddenly may cause your seizures to return or to occur more often.

This medicine may cause serious [allergic reactions](#) that may affect several parts of the body (e.g., liver or kidneys). Check with your doctor right away if you or your child have more than one of the following symptoms: fever, dark-colored urine, headache, rash, itching, extra fluid around the face, stomach pain, unusual tiredness, or yellow eyes or skin.

This medicine lowers the number of some [types of blood](#) cells in your body. Because of this, you may bleed or get infections more easily. To help with these problems, avoid being near people who are sick or have infections. Wash your hands often. Stay away from rough sports or other situations where you could be bruised, cut, or injured. Brush and floss your teeth gently. Be careful when using sharp objects, including razors and fingernail clippers.

[Birth control pills](#) may not work while you are using [oxcarbazepine](#). To keep from getting pregnant, use another form of birth control. Other forms include [condoms](#), diaphragms, or contraceptive foams or jellies. Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments. Blood tests will also be needed to check for unwanted effects.

#### 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, chest tightness, trouble breathing
- Blistering, [peeling](#), or red skin rash.
- Blurred vision or any changes in vision.
- Change in how much or how often you urinate.
- Chills, [cough](#), runny or stuffy nose, sore throat, and body aches.
- Confusion, weakness, and muscle twitching.
- Fast, slow, or pounding heartbeat.
- Feeling depressed, irritable, nervous, or restless.
- Fever with rash, or swollen glands in your neck.
- Nausea, vomiting, loss of appetite, or pain in your upper stomach.
- Rapid eye movements (especially in children).
- Seizures or tremors.
- Trouble walking, speaking, or controlling body movements.
- Uncontrollable shaking.
- Unusual behavior or thoughts of hurting oneself.
- Unusual bleeding, bruising, or weakness.
- Yellowing of your skin or the whites of your eyes.

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

- Feeling of constant movement of self or surroundings.

Headache or dizziness.  
 Joint pain.  
 Mild nausea, vomiting, belching, gas, indigestion, or stomach pain.  
 Mild skin rash.  
 Sleepiness or unusual drowsiness.  
 Trouble sleeping.

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

#### 4.3] Place In Therapy

A) Oxcarbazepine appears to be as effective as carbamazepine in the treatment of epilepsy and slightly better tolerated. It should be considered an alternative in epileptic patients unable to tolerate carbamazepine, including those with hypersensitivity, although caution is advised in these patients.

B) In the treatment of trigeminal neuralgia, oxcarbazepine has been effective in patients unresponsive to, or intolerant of, carbamazepine, which is currently the drug of choice. The superiority of oxcarbazepine over carbamazepine has been suggested, but these studies employed small numbers of patients and were not adequately controlled.

C) Dose-dependent enzyme induction has been reported by some investigators, with higher doses of oxcarbazepine producing effects similar to carbamazepine [126]. As the optimal dose of oxcarbazepine remains undefined, further studies will also be needed to determine if the drug will offer a significant advantage in regard to enzyme induction and autoinduction.

D) Hyponatremia is a concern with oxcarbazepine therapy, and may limit its use as an anticonvulsant and antineuralgic. The use of oxcarbazepine in diabetes insipidus has also been suggested, although data is not available for this indication [40].

#### 4.4] Mechanism of Action / Pharmacology

##### A) MECHANISM OF ACTION

1) Oxcarbazepine, an anticonvulsant, is the 10-keto derivative of carbamazepine. Chemically, oxcarbazepine is 10,11-dihydro-10-oxo-5H-dibenz(b,f)azepine 5-carboxamide [1][112][105]. The metabolite 10-hydroxy-carbazepine is primarily responsible for the pharmacological activity of oxcarbazepine. However, the exact mechanism of action for its antiseizure effect is unknown. In vitro electrophysiological studies suggest that drug-induced blockage of voltage-sensitive sodium channels may prevent repetitive neuronal firing and results in the stabilization of hyperexcited neural membranes and the diminution of synaptic impulse propagation. Increased potassium conductance and high-voltage calcium channel modulation may also play a role [1].

2) Animal studies have demonstrated that the mechanism of action of oxcarbazepine is similar to that of carbamazepine, which is inhibition of seizure propagation via reduction of posttetanic potentiation of synaptic transmission [115][112][105]. The spectrum of antiepileptic activity of each agent is also similar [115][112]. Antineuralgic properties of oxcarbazepine have also been demonstrated [116][102].

##### B) REVIEW ARTICLES

1) Dosages and formulations of antiepileptic drugs used to treat pediatric epilepsy have been reviewed [117].

2) The pharmacology and therapeutic use of oxcarbazepine has been reviewed [118][119][120][121][122].

3) A review of newer antiepileptic medications, including a summary of clinical experience and recommendations for use, has been published [123].



4)) The pharmacokinetic interaction profile of [oxcarbazepine](#) and its importance clinically has been reviewed [124].

## 4.5] Therapeutic Uses

### 4.5.A] Migraine; Prophylaxis

See Drug Consult reference: MIGRAINE -- RECOMMENDATIONS FOR PROPHYLAXIS IN ADULTS

### 4.5.B] Partial seizure, monotherapy

FDA Labeled Indication

#### 1)) Overview

FDA Approval: Adult, yes; Pediatric, [yes \( 4 years and older\)](#)

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 for use as monotherapy in the treatment of partial seizures in adults and children 4 years and older [1]

In an observational study (n=673; mean age 42.5 years) of adult male patients with [partial epilepsy](#), [oxcarbazepine](#) improved sexual dysfunction in patients with preexisting sexual function disorders at baseline [7].

#### 3)) Adult:

a)) [Oxcarbazepine](#) (OXC) was an effective monotherapeutic substitute when selected to replace antiepileptic drugs (AED) used to maintain patients with medication-refractory [partial epilepsy](#), in a randomized, double-blind, multicenter clinical trial that compared two doses of [oxcarbazepine](#) (OXC 300 milligrams (mg)/day and OXC 2400 mg/day). Patients with a history of 2 to 40 seizures per 28-day period received either OXC 300 mg/day (n=46), or OXC 2400 mg/day (n=41) throughout a 126-day blinded treatment phase; all prior AED's were tapered and discontinued by day 43. Patients receiving 2400 mg/day were titrated from an initial dose of 1200 mg up to the target dose in 600 mg weekly increments; those patients unable to tolerate the maximum dose were adjusted to either 2100 mg or 1800 mg daily. Efficacy was measured by the number of patients meeting one of 4 protocol-defined exit criteria (primary variable) and the time required to meet one of the exit criteria (secondary variable). The number of patients meeting one of the 4 exit criteria was significantly lower for the OXC 2400 mg cohort compared with the OXC 300 mg cohort (41.2% versus 93.3%; p less than 0.0001), while significantly greater time was required by the OXC 2400 mg group to meet an exit criterion compared with the OXC 300 mg group (p=0.0001). The intent-to-treat analysis revealed at least a 50% reduction in seizure incidence in 42% of OXC 2400 mg-treated patients (12% rendered seizure-free) compared with 7% of patients receiving OXC 300 mg (none seizure-free). Dizziness, headache, somnolence, nausea, and vomiting were the adverse events most frequently reported; most were transient, and mild or moderate in severity [8].

**b)** Oxcarbazepine, 2400 milligrams/day (mg/day) in 2 divided doses, was effective as monotherapy for the treatment of refractory partial seizures in 102 patients (from 11 to 62 years of age) in a placebo-controlled, double-blind trial. The primary efficacy variable was time to meet one of the exit criteria, defined as: completion of the 10-day treatment phase; 4 partial seizures; 2 new-onset secondarily generalized seizures; serial seizures; or status epilepticus. This variable was statistically significant in favor of oxcarbazepine ( $p=0.0001$ ; by day 2.5 of the study period, 75% of the placebo-treated patients had met one of the exit criteria versus (vs) 25% of the patients treated with oxcarbazepine. The secondary efficacy variable was the percentage of patients to meet one of the exit criteria and was also statistically significantly lower ( $p$  less than 0.0001) for the patients treated with oxcarbazepine (47%) vs 84% for the placebo-treated group [9].

**c)** Oxcarbazepine initiated at 600 milligrams/day, titrated to 1200 milligrams/day (both dosages in 2 daily divided doses), and maintained at the higher dose for 84 days was statistically significantly superior to placebo ( $p=0.046$ ) in previously untreated patients ( $n=67$ ; 8 to 69 years of age). The primary efficacy measure was a comparison of time to first seizure [10].

**d)** In 2 trials comparing oxcarbazepine in daily doses of 300 or 2400 milligrams (mg) in patients previously treated with carbamazepine or other antiepileptic drugs, the higher dose of oxcarbazepine was statistically significantly superior to the lower dose ( $p=0.0001$ ). Primary efficacy measures differed between the 2 studies; they were time to meet exit criteria in 1 study and percentage of patients meeting exit criteria in the other [10].

**e)** Seizure frequency decreased in 32% to 48% of patients treated with oxcarbazepine in a multicenter trial conducted over 10 years in 947 patients [2]. Patients were diagnosed with simple partial or complex partial seizures with or without secondary generalization and primary generalized seizures. Median daily doses employed were 30 milligrams/kilogram/day in children and 18 milligrams/kilogram/day in adults, usually given in 2 or 3 divided doses. One-third of patients experienced adverse reactions such as dizziness, sedation, fatigue or hyponatremia. Oxcarbazepine was used as monotherapy in 63% of the patients and as part of polytherapy in 37%.

**f)** Similar decreases in seizure frequency were seen in a double-blind study, of oxcarbazepine and carbamazepine in 16 epileptic patients inadequately controlled on at least 1 anticonvulsant (other than carbamazepine) [11]. Each patient had experienced at least 1 tonic-clonic or complex partial seizure/month. Oxcarbazepine or carbamazepine were added sequentially in randomized fashion during a 1-month titration period; therapy was continued for an additional 3 months. Mean doses were 1111.5 and 788.5 milligrams daily for oxcarbazepine and carbamazepine, respectively. Concomitant anticonvulsants were continued throughout the study. Seizure frequency was reduced by 90% during therapy with both agents, with 28% of all patients becoming seizure-free. Adverse effects were less in patients treated with oxcarbazepine. Increases in serum levels of valproic acid, phenytoin, and primidone were observed in the oxcarbazepine group, presumably secondary to a lesser degree of enzyme induction as compared to carbamazepine.

# 1) Sexual Dysfunction Improvement in Male Patients with Epilepsy

**a)** In an observational study ( $n=673$ ; mean age 42.5 years) of adult male patients with partial epilepsy, oxcarbazepine improved sexual dysfunction in patients with preexisting sexual function disorders at baseline. Patients received oxcarbazepine monotherapy either as initial treatment or were changed from other antiepileptic drug (AED) pretreatment to oxcarbazepine monotherapy; doses were titrated to the optimal therapeutic dose. The patients were assessed regarding their sexual

dysfunction at baseline, and again 12 weeks later at the final examination. Seizure occurrence, global ratings of efficacy, and tolerability were also assessed. At baseline, sexual dysfunction was reported in 228 (34%) patients, with 27 patients receiving no antiepileptic pretreatment, 168 patients receiving enzyme-inducing AEDs as pretreatment, and 33 patients receiving non-enzyme inducing AEDs as pretreatment. Sexual dysfunction improvement was reported in 79.4% (n=181/228) of patients with preexisting sexual function disorders after 3 months of treatment with oxcarbazepine, with no impairment reported in 10.1% (n=23/228) of patients at final assessment. The improvements were most significant in patients receiving enzyme-inducing AED pretreatment. Seizure occurrence per 28 days decreased during the retrospective period from a mean of 1.8 +/- 4.9 (95% CI, 1.43 to 2.17) to 0.4 +/- 1.8 (95% CI, 0.26 to 0.54) after 3 months of therapy. Carbamazepine-treated patients (n=313) were excluded from results; however, in the patients who reported sexual dysfunction (n=147) with carbamazepine, 110 (75%) patients improved when switched to oxcarbazepine [7].

#### 4) Pediatric:

**a)** An open-label study (n=92) failed to demonstrate the effectiveness of [oxcarbazepine](#) monotherapy for children (1 month to 16 years of age) with inadequately-controlled or new-onset partial seizures; however, based on pharmacokinetic and pharmacodynamic parameters, [oxcarbazepine](#) monotherapy was approved for children 4 years and older. Hospitalized children were randomized to either [oxcarbazepine](#) 10 milligrams/kilogram/day (mg/kg/day) or were titrated up to 40 to 60 mg/kg/day within 3 days while withdrawing the previous antiepileptic drugs on the second day of [oxcarbazepine](#) therapy. From day 3 to day 5, seizures were monitored by continuous video-electroencephalogram monitoring. The primary efficacy outcome was either completed the 5 day treatment or met one of the 2 exit criteria. The exit criteria were: 1) 3 study specific seizures (ie, electrographic partial seizures with a behavioral correlate) 2) a prolonged study specific seizure. Most children from both dose groups completed the 5-day study without exiting. The between group comparison of the time to meet exit criteria was not statistically significant (p=0.904 for the difference between the curves). The manufacturer states the results were uninterpretable because of study limitations (no placebo, short treatment and assessment period, and inadequate washout period) [1].

**b)** [Oxcarbazepine](#) initiated at 600 milligrams/day, titrated to 1200 milligrams/day (both dosages in 2 daily divided doses), and maintained at the higher dose for 84 days was statistically significantly superior to placebo (p=0.046) in previously untreated patients (n=67; 8 to 69 years of age). The primary efficacy measure was a comparison of time to first seizure [1].

**c)** [Oxcarbazepine](#), 2400 milligrams/day (mg/day) in 2 divided doses, was effective as monotherapy for the treatment of refractory partial seizures in 102 patients (from 11 to 62 years of age) in a placebo-controlled, double-blind trial. The primary efficacy variable was time to meet one of the exit criteria, defined as: completion of the 10-day treatment phase; 4 partial seizures; 2 new-onset secondarily generalized seizures; serial seizures; or [status epilepticus](#). This variable was statistically significant in favor of [oxcarbazepine](#) (p=0.0001; by day 2.5 of the study period, 75% of the placebo-treated patients had met one of the exit criteria versus (vs) 25% of the patients treated with [oxcarbazepine](#). The secondary efficacy variable was the percentage of patients to meet one of the exit criteria and was also statistically significantly lower (p less than 0.0001) for the patients treated with [oxcarbazepine](#) (47%) vs 84% for the placebo-treated group [9].

**d)** [Oxcarbazepine](#) was found to be useful in both adjunctive use and monotherapy in children with seizures during a chart review. Children (mean age 3.9 years, range 0.6 to 6.9 years) had either

localization-related seizures (n=44) or [generalized epilepsy](#) (n=9) with the main seizure types being complex partial (n=37), simple partial (n=4), epileptic spasm (n=9), and generalized tonic-clonic (n=3). In 13 children, an overnight change was made from [carbamazepine](#) to [oxcarbazepine](#) at 1.5 times their previous [carbamazepine](#) dose. The other children were titrated up to 30 milligrams/kilogram/day (mg/kg/day) over 1 to 3 weeks. Out of the children with localization-related seizures, 12 of 44 became seizure-free while 16 achieved a 50% reduction in seizures. No child with generalized seizures became seizure-free, but 5 of 9 had a 50% reduction in seizures. In children who had previously had a poor response to [carbamazepine](#), 4 of 30 children become seizure-free while 13 had a reduction in seizures of at least 50%. Of the 23 children receiving monotherapy, 10 became seizure-free, and 7 had a 50% reduction in seizures. The mean effective dose for children achieving at least a 50% decrease in seizures was 47 mg/kg/day. [Hyponatremia](#) occurred in 7 of the 53 children [6].

#### 4.5.C] Partial seizure; 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 for use as adjunctive therapy in the treatment of partial seizures in adults and children 2 years and older [1]

No evidence that [oxcarbazepine](#) was effective in children less than 2 years of age (n=75) in an open-label, multicenter, rater-blind, randomized, parallel-group study [1]

During adjunctive therapy studies, median reductions in partial seizure frequencies from baseline were 26% to 50% for [oxcarbazepine](#) and 8% for placebo in adults, and 35% for [oxcarbazepine](#) and 9% for placebo in children [1]

No important differences in response due to gender were identified during adjunctive therapy trials [1]

##### 3) Adult:

a) Efficacy for [oxcarbazepine](#) as adjunctive therapy for partial seizures in adults was demonstrated in a multicenter, double-blind, placebo-controlled trial (n=692; 15 to 66 years of age). Patients who experienced 1 to 4 partial seizures per month during the baseline phase were randomized to receive placebo or fixed [oxcarbazepine](#) doses of 600, 1200, or 2400 milligrams/day (mg/day) in conjunction with 1 to 3 other antiepileptic drugs. A comparison between treatment groups of the percentage change in partial seizure frequency was the primary measure of efficacy and all doses of [oxcarbazepine](#) were statistically significantly superior to placebo (p=0.0001). In the high dose group, however, over 65% of patients discontinued treatment due to adverse events [1].

b) Seizure frequency decreased in 32% to 48% of patients treated with [oxcarbazepine](#) in a multicenter trial conducted over 10 years in 947 patients [2]. Patients were diagnosed with simple partial or complex partial seizures with or without secondary generalization and primary generalized seizures. Median daily doses employed were 30 milligrams/kilogram/day in children and 18 milligrams/kilogram/day in adults, usually given in 2 or 3 divided doses. One-third of patients experienced adverse reactions such

as dizziness, sedation, fatigue or [hyponatremia](#). [Oxcarbazepine](#) was used as monotherapy in 63% of the patients and as part of polytherapy in 37%.

#### 4) Pediatric:

**a)** Efficacy for [oxcarbazepine](#) as adjunctive therapy for inadequately-controlled partial seizures in children was demonstrated in a multicenter, rater-blind, randomized, parallel-group, open-label trial (n=128; 1 month to less than 4 years of age). Inclusion criteria were at least 2 study specific seizures (ie, partial seizures identified on electrograph with a behavioral correlate) during the 72 hour baseline period. Children were randomized to either 10 milligrams/kilogram/day (mg/kg/day) or were titrated up to 60 mg/kg/day within 26 days. After 9 days on their randomized target dose, seizures were monitored by continuous video-electroencephalogram monitoring during the last 72 hours of the maintenance period. A between group comparison of the change in seizure frequency per 24 hours compared to the seizure frequency at baseline was statistically better (results and p value not provided) in the 60 mg/kg/day group vs 10 mg/kg/day group. No evidence that [oxcarbazepine](#) was effective in children less than 2 years of age (n=75) [1].

**b)** [Oxcarbazepine](#) (OXC) was safe and effective when used as an adjunctive antiepileptic agent in the treatment of partial seizures in children, in a randomized, double-blind, parallel-group study. Pediatric patients (ages 3 to 17 years) with inadequately controlled partial seizures treated with one or two antiepileptic drugs (AED) were assigned to receive 98-day regimens of either OXC (titrated to dose range of 30 to 46 milligrams (mg)/kilogram (kg)/day) two times a day (n=138) or placebo (n=129) in addition to their pre-established AED regimen. Patients in the OXC group experienced a baseline median partial seizure frequency of 12 per 28-day period; the median OXC dose administered was 31.4 mg/kg/day. The addition of OXC to the preexisting AED regimen produced a significantly greater median percent reduction from baseline in 28-day partial seizure frequency compared with placebo (35% versus 9%, respectively; p=0.0001). Forty-one percent of patients OXC-group patients recorded a seizure frequency reduction from baseline of 50% or more per 28-day period compared with 22% of patients receiving placebo (p=0.0005), and 5 OXC-group patients were seizure-free throughout the double-blind treatment period, compared with 1 patient receiving placebo. OXC-treated patients also experienced a significantly greater median percentage reduction in the occurrence of secondarily generalized seizures compared with patients receiving placebo (78% versus 33%, respectively; p=0.0012). The frequency of adverse events was similar between groups; somnolence, headache, dizziness, nausea and vomiting were most commonly reported, with the majority being considered mild to moderate in severity [1][3].

**c)** [Oxcarbazepine](#), in a mean dose of 56.7 milligrams/kilogram/day (mg/kg/day), was found to be efficacious for adjunctive therapy in [epilepsy](#) in a retrospective chart review of 46 children and adolescents (mean age 10.3 years; range 1.3 to 17.9 years). [Oxcarbazepine](#) doses ranged from 19 to 123 mg/kg twice a day, [valproic acid](#) was the most common co-medication (32 of 46 patients) and no patients were maintained on more than one other drug besides [oxcarbazepine](#). After follow-up for 1 year, [oxcarbazepine](#) was found to be of some benefit in 50% of the patients. Specifically, 2 children experienced an exacerbation of seizures and 17 children exhibited no change, but 4 children became seizure-free, 18 experienced a 75% to 99% reduction in seizures, and 1 had a 50% to 74% reduction in seizures; 4 patients were lost to follow-up. Adverse effects tended to occur in patients with blood serum concentrations of 35 to 40 mg/L 10-hydroxy-carbazepine, the active metabolite of [oxcarbazepine](#) [4].

**d)** In a small study (n=40) in children with intellectual disability and [intractable epilepsy](#), seizure frequency was reduced by at least 50% in 48% (19) of patients treated with [oxcarbazepine](#) 49 milligrams/kilogram/day (mg/kg/day) (mean maximum dosage), given in 2 or 3 divided doses. Nine of the children received [oxcarbazepine](#) as monotherapy and 31 received it concomitantly with other antiepileptic drugs



regimens including vigabatrin, benzodiazepines, valproate, lamotrigine, phenytoin, and acetazolamide. Oxcarbazepine therapy was initiated using several strategies. Oxcarbazepine was initiated in 10 children as an overnight change from carbamazepine (at 1.5 times the carbamazepine dosage). In the remaining children who weighed under 40 kg, the oxcarbazepine dose was titrated over 1 to 3 weeks to 30 mg/kg/day and then increased as necessary. For the other children weighing over 40 kg, oxcarbazepine was initiated at 20 mg/kg/day and titrated according to response. A greater than 50% response was reported in 14 of 28 children (50%) with localization-related epilepsy and 5 of 12 children (42%) with generalized epilepsy. Oxcarbazepine dose reduction or discontinuation occurred in 8 children due to adverse effects and at least one adverse effect was reported in 40% of patients. Hyponatremia occurred in 24% [5].

e) Oxcarbazepine was found to be useful in both adjunctive use and monotherapy in children with seizures during a chart review. Children (mean age 3.9 years, range 0.6 to 6.9 years) had either localization-related seizures (n=44) or generalized epilepsy (n=9) with the main seizure types being complex partial (n=37), simple partial (n=4), epileptic spasm (n=9), and generalized tonic-clonic (n=3). In 13 children, an overnight change was made from carbamazepine to oxcarbazepine at 1.5 times their previous carbamazepine dose. The other children were titrated up to 30 milligrams/kilogram/day (mg/kg/day) over 1 to 3 weeks. Out of the children with localization-related seizures, 12 of 44 became seizure-free while 16 achieved a 50% reduction in seizures. No child with generalized seizures became seizure-free, but 5 of 9 had a 50% reduction in seizures. In children who had previously had a poor response to carbamazepine, 4 of 30 children become seizure-free while 13 had a reduction in seizures of at least 50%. Of the 30 children receiving polytherapy, 2 became seizure free and seizure reduction occurred in 14. The mean effective dose for children achieving at least a 50% decrease in seizures was 47 mg/kg/day. Hyponatremia occurred in 7 of the 53 children [6].

#### 4.6] Comparative Efficacy / Evaluation With Other Therapies

##### 4.6.A] Carbamazepine

##### 4.6.A.1] Epilepsy

a) SUMMARY: Oxcarbazepine appears to be as effective as carbamazepine in the treatment of epilepsy; severe adverse effects have occurred to a lesser degree with oxcarbazepine in some studies. Further studies are needed to investigate its enzyme-inducing effects, particularly at higher doses.

b) Oxcarbazepine is similar in efficacy to carbamazepine as monotherapy or add-on therapy in epileptic patients [134][135]; (Bulau et al, 1987)[129][136][128][137][132][138]. There is some evidence of efficacy in patients unresponsive to carbamazepine. Doses associated with therapeutic equivalency in some studies have been 200 mg carbamazepine and 300 to 400 mg oxcarbazepine [129], however the ratio has been closer to 1:1 in others (Bulau et al, 1987).

c) Oxcarbazepine is at least as effective as carbamazepine in patients receiving polytherapy, and oxcarbazepine may be better tolerated in some patients. The efficacy of oxcarbazepine and carbamazepine was compared in 48 epileptic inpatients poorly controlled on polytherapy, including carbamazepine, in a double-blind, crossover study [129]. The types of seizures were generalized (9 patients), partial (10 patients), or both generalized and partial (29 patients); all patients had at least 2 seizures/week despite therapy with 2 to 4 antiepileptic agents. Patients were randomly allocated to oxcarbazepine 300 mg/day or carbamazepine 200 mg/day. Following a titration period, where the dose of each was increased to achieve optimal seizure control, therapy was continued for 12 weeks (steady-state) in each trial period. As compared to carbamazepine, therapy with oxcarbazepine reduced the total number of seizures by 9%; tonic-clonic and tonic seizures were further reduced by 20% and 31%, respectively. In 5 patients, a shift from complex partial to simple partial seizures or atypical absence seizures was observed during oxcarbazepine therapy. Other differences reported during oxcarbazepine therapy were an increase in alertness and greater ability to concentrate in 5 patients and remission of carbamazepine related allergic



skin reactions in 2. Serum levels of [valproic acid](#) and [phenytoin](#) were higher in [oxcarbazepine](#) treated patients, and serum sodium concentration were lower. Other adverse effects were similar with each agent. d)) In a double-blind study, the efficacy of [oxcarbazepine](#) and [carbamazepine](#) in 16 epileptic patients inadequately controlled on at least 1 anticonvulsant (other than [carbamazepine](#)) was evaluated (Bulau et al, 1987). Each patient had experienced at least 1 tonic-clonic or complex partial seizure per month. [Oxcarbazepine](#) or [carbamazepine](#) were added sequentially in randomized fashion during a 1 month titration period; therapy was continued for an additional 3 months. Mean doses were 1111.5 and 788.5 mg daily for [oxcarbazepine](#) and [carbamazepine](#), respectively. Concomitant anticonvulsants were continued throughout. Seizure frequency was reduced by 90% during therapy with both agents, with 28% of all patients becoming seizure-free. Adverse effects were less in [oxcarbazepine](#) treated patients. Increases in serum levels of [valproic acid](#), [phenytoin](#), and [primidone](#) were observed in the [oxcarbazepine](#) group, presumably secondary to a lesser degree of enzyme induction as compared to [carbamazepine](#).

#### 4.6.A.2] Trigeminal neuralgia

a)) [Oxcarbazepine](#) and its 10-hydroxy-metabolite (10-hydroxy-carbazepine; 10,11-dihydro-10-hydroxy [carbamazepine](#)) were compared with [carbamazepine](#) in 24 patients with [trigeminal neuralgia](#) [142]. All patients had either [idiopathic trigeminal neuralgia](#) or other idiopathic [facial neuralgias](#) for at least 2 weeks. Fourteen patients had been treated previously with [carbamazepine](#). [Oxcarbazepine](#) was administered to 13 of the 24 patients for a mean of 11 months (mean maximal doses of 1100 milligrams daily), resulting in an adequate clinical response in 10 and a moderate response in 3. Symptom recurrence, however, was seen in 1 patient after 6 months of treatment. Eleven patients were treated with the 10-hydroxy-metabolite of [oxcarbazepine](#) (GP 47779) for a mean of 3.5 months (mean maximal dose, 1100 milligrams daily), with 7 achieving alleviation of symptoms and 4 noticing definite improvement. However, recurrence of symptoms occurred in 2 patients after 3 weeks and 2 months of treatment, respectively. In the 14 patients treated previously with [carbamazepine](#), therapy with either [oxcarbazepine](#) or its metabolite was reported to be more effective than [carbamazepine](#) in 12; efficacy was considered equivalent in 1 and worse in another. These overall results suggest the potential superiority of [oxcarbazepine](#) over [carbamazepine](#) in [trigeminal neuralgia](#). However, placebo-controlled trials are required to confirm these findings.

#### 4.6.A.3]) Efficacy

a)) The primary difference between [oxcarbazepine](#) and [carbamazepine](#) is in regard to pharmacokinetic properties, which in turn affect the propensity of these agents to elicit adverse effects. Following absorption, [oxcarbazepine](#) is rapidly and extensively converted via reduction to 10-hydroxy-carbazepine, the active metabolite, which is excreted in the urine as the glucuronide conjugate. A portion of the 10-hydroxy-metabolite is hydroxylated to isomeric 10,11-diols, the trans-diol predominating [139][140][130].

b)) In contrast, [carbamazepine](#) is oxidized to the active [carbamazepine](#)-10,11-epoxide; a portion of this metabolite is also converted to the inactive 10,11-diol [141][130][132]. The 10,11-epoxide metabolite of [carbamazepine](#) is responsible for dose-dependent adverse effects [132][130]. Because an epoxide is not produced during [oxcarbazepine](#) metabolism, this drug is expected to be better tolerated than [carbamazepine](#) [132].

#### 4.6.A.4]) Adverse Effects

a)) A trend toward a lower incidence of severe adverse effects has been observed with [oxcarbazepine](#) as compared to [carbamazepine](#) in some studies (Bulau et al, 1987)[128][129], which at times reached statistical significance [128].

b)) [Oxcarbazepine](#) appears less likely than [carbamazepine](#) to influence oxidative processes, as the metabolism of [oxcarbazepine](#) is facilitated primarily by reduction. Studies have reported that

oxcarbazepine lacks autoinducing properties, unlike carbamazepine, a feature which may decrease the incidence of breakthrough seizures [130][131][132].

c) In some studies, oxcarbazepine has not influenced antipyrene kinetics, suggesting an advantage with regard to drug interactions [130]. However, dose-dependent enzyme induction has been reported by other investigators, with higher doses producing effects similar to carbamazepine [133]. As the optimal dose of oxcarbazepine remains undefined, further studies will be needed to determine if the drug will offer a significant advantage in regard to enzyme induction and autoinduction.

#### 4.6.B] Haloperidol

##### 4.6.B.1] Bipolar disorder

a) Oxcarbazepine has been compared with haloperidol in 42 patients with acute mania; mean doses used were 2400 mg/day and 42 mg/day respectively. Although the response to oxcarbazepine was slower, by the end of the second week of treatment, results were similar in both treatment groups. Haloperidol-treated patients had a significantly higher incidence of adverse effects [143].

#### 4.6.C] Lithium

##### 4.6.C.1] Bipolar disorder

a) In a review of the results of a double-blind multicenter trial comparing oxcarbazepine with lithium in 58 acutely manic patients, oxcarbazepine was found to be equally effective but with a higher incidence of side effects. Onset was somewhat slower with oxcarbazepine [144].

b) Conversely, a 3-year randomized study of oxcarbazepine vs lithium prophylaxis in 18 patients with bipolar disorder demonstrated no clear responders in the oxcarbazepine-treated group. A reduction in relapses was clearly seen in the lithium-treated group. This study was flawed by poor patient selection and the treatment of lithium nonresponders with oxcarbazepine (Wildegrube, 1990).

#### 4.6.D] Surgical procedure

##### 4.6.D.1] Trigeminal neuralgia

a) Oxcarbazepine was initially efficacious for relieving pain of intractable trigeminal neuralgia, but eventually surgery was necessary in most patients. Fifteen patients who had not found relief of trigeminal neuralgia pain or had experienced adverse reactions with carbamazepine, phenytoin, and baclofen, either as monotherapy or in combination, were transferred from their current medication to oxcarbazepine and followed for 13 years. Over a period of 3 days, oxcarbazepine 300 milligrams (mg) was substituted for each 200 mg dose of carbamazepine or 100 mg dose of phenytoin. Patients were free to discontinue medication during remissions. Eight patients used oxcarbazepine continuously, and 7 stopped during remissions for periods of 2 to 7 months and, in one case, for 26 months. The mean daily dose was 17.9 mg/kilogram (range 3.9 to 46.5 mg/kg). The mean duration of treatment was 4 years (range 2.4 months to 10.8 years). Oxcarbazepine gave pain relief, but eventual surgery was considered necessary in 12 of the 13 surviving patients. Surgery was immediately successful in 8 of those patients but had to be repeated in 3 patients because of pain recurrence or complete failure. Repeat surgery was successful in the 2 with pain recurrence, but the one whose initial surgery completely failed required medication for pain relief after the second surgery. Three of the patients who underwent surgery had numbness and one had deafness as a consequence. The mean time for recurrence of pain after oxcarbazepine treatment was 10 months (median 7 months); the mean time for recurrence after surgery was 28 months. At the time of this report, 8 patients continued to be pain free. Most patients felt they should have had surgery earlier [127].

## 6.0] References

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