PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrAPO-OXCARBAZEPINE

Oxcarbazepine Tablets

Tablets, 150 mg, 300 mg and 600 mg, oral

Apotex Standard

Antiepileptic

ATC code: N03AF02

APOTEX INC
150 Signet Drive
Toronto, Ontario
M9L 1T9

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RECENT MAJOR LABEL CHANGES

None at the time of authorization

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APO-OXCARBAZEPINE (oxcarbazepine) is indicated for:

- use as monotherapy or adjunctive therapy in the treatment of partial seizures.

1.1 Pediatrics

Pediatrics (6 to 16 years of age): APO-OXCARBAZEPINE (oxcarbazepine) is indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures.

1.2 Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical studies indicates that there are differences in the pharmacokinetic profile of oxcarbazepine in the geriatric population relative to younger adults, which may be associated with differences in safety or effectiveness. A brief discussion can be found in the appropriate sections (See 7.1.4 Geriatrics; 10.3 Pharmacokinetics, Special Populations and Conditions; 4.1 Dosing Considerations).

2 CONTRAINDICATIONS

Patients with a known hypersensitivity to oxcarbazepine or eslicarbazepine acetate or to any of the components of APO-OXCARBAZEPINE. For a complete listing, (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING)

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

HEMATOLOGIC: Although reported infrequently, serious adverse effects have been observed during the use of APO-OXCARBAZEPINE. Agranulocytosis and aplastic anemia have occurred very rarely. Leucopenia, thrombocytopenia and hepatitis have also been reported. However, in the majority of cases, leucopenia and thrombocytopenia were transient and did not signal the onset of either aplastic anemia or agranulocytosis. It is important that APO-OXCARBAZEPINE be used carefully and close clinical and frequent laboratory supervision should be maintained throughout treatment in order to detect as early as possible signs and symptoms of a possible blood dyscrasia. APO-OXCARBAZEPINE should be discontinued if any evidence of significant bone marrow depression appears (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

DERMATOLOGIC: Serious and sometimes fatal dermatologic reactions, including Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), have been reported with APO-OXCARBAZEPINE.

Human Leukocyte Antigens (HLA)-A*3101 and HLA-B*1502 may be risk factors for the development of serious cutaneous adverse drug reactions. Retrospective genome-wide

studies in Japanese and Northern European populations reported an association between severe skin reactions (SJS, TEN, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Acute Generalized Exanthematous Pustulosis (AGEP) and maculopapular rash) associated with carbamazepine use and the presence of the HLA-A*3101 allele in these patients. Similarly, in studies that included small samples of patients of Han Chinese ancestry a strong association was found between the risk of developing SJS/TEN and the presence of the HLA-B*1502 allele. The HLA-B*1502 allele is found almost exclusively in individuals with ancestry across broad areas of Asia (This provide a rough estimate of the frequency of HLA-B*1502 allele in various populations: from 2 to 12% in Han Chinese populations, about 8% in Thai populations, above 15% in the Philippines and some Malaysian populations, about 2% in Korea and 6% in India. The frequency of the HLA-B*1502 allele is negligible in persons from European descent, several African populations, indigenous peoples of the Americas, Hispanic populations sampled and in Japanese (< 1%). The estimated frequencies have limitations due to the wide allele variability that exist within ethnic groups, the difficulties in ascertaining ethnic ancestry and the likelihood of mixed ancestry)[1]. It is, therefore, recommended that physicians consider HLA-B*1502 genotyping as a screening tool in genetically at-risk populations (see 7 WARNINGS AND PRECAUTIONS, Pharmacogenomics, Ancestry and Allelic Variations in the HLA-B Gene). Until further information is available, the use of APO-OXCARBAZEPINE and other anti-epileptic drugs associated with SJS/TEN should be avoided in patients who test positive for the HLA-B*1502 allele. There are insufficient data to support a recommendation for testing the presence of HLA-A*3101 allele in patients, prior to initiating treatment with APO-OXCARBAZEPINE (see 7 WARNINGS AND PRECAUTIONS Pharmacogenomics, Ancestry and Allelic Variations in the HLA-A Gene; Ancestry and Allelic Variation in the HLA-B Gene; Important Limitations of HLA-A and HLA-B Genotyping).

Treatment recommendations for dermatological reactions: APO-OXCARBAZEPINE should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. The use of other anti-epileptic drugs associated with SJS/TEN should be avoided in patients who have shown severe dermatological reactions during APO-OXCARBAZEPINE treatment.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- **Hepatic Insufficiency**: In general, dose adjustments are not required in patients with mild to moderate hepatic impairment (see 10.3 Pharmacokinetics, Special Populations and Conditions).

- **Renal Insufficiency**: In patients with impaired renal function (creatinine clearance < 30 mL/min) APO-OXCARBAZEPINE therapy should be initiated at one-half the usual starting dose (300 mg/day) and increased slowly to achieve the desired clinical response (see 10.3 Pharmacokinetics, Special Populations and Conditions).

- **Geriatrics**: There were 52 patients over age 65 in controlled trials and 565 patients over the age of 65 in other trials. Following administration of single (300 mg) and multiple (600 mg/day) doses of oxcarbazepine to elderly volunteers (60 to 82 years of age), the maximum plasma concentrations and Area Under the Curve (AUC) values of MHD were 30% to 60% higher than in younger volunteers (18 to 32 years of age). Comparisons of creatinine clearance in young and elderly volunteers indicate that the difference was due to age related reductions in creatinine clearance. Dosage should be carefully titrated in the elderly (see 4.2 Recommended Dose and Dosage Adjustment).

4.2 Recommended Dose and Dosage Adjustment

APO-OXCARBAZEPINE (oxcarbazepine) is indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and children ages 6 to 16. All dosing should be given in a twice a day (BID) regimen.

Adult Patients

Adjunctive Therapy

Treatment with APO-OXCARBAZEPINE should be initiated with a dose of 600 mg/day, given in a BID regimen. If clinically indicated, the dose may be increased by a maximum of 600 mg/day at approximately weekly intervals; the recommended daily dose is 1200 mg/day. Daily doses above 1200 mg/day show somewhat greater effectiveness in controlled trials, but most patients were not able to tolerate the 2400 mg/day dose, primarily because of CNS effects. It is recommended that the patient be observed closely and plasma levels of the concomitant antiepileptic drugs (AEDs) be monitored during the period of APO-OXCARBAZEPINE titration, as these plasma levels may be altered, especially at APO-OXCARBAZEPINE doses greater than 1200 mg/day (see 9 DRUG INTERACTIONS).

Conversion to Monotherapy

Patients receiving concomitant AEDs may be converted to monotherapy by initiating treatment with APO-OXCARBAZEPINE at 600 mg/day (given in a BID regimen) while simultaneously initiating the reduction of the dose of the concomitant AEDs. The concomitant AEDs should be completely withdrawn over 3 to 6 weeks, while the maximum dose of APO-OXCARBAZEPINE should be reached in about 2 to 4 weeks. APO-OXCARBAZEPINE may be increased as clinically indicated by a maximum increment of 600 mg/day at approximately weekly intervals to achieve the daily dose of 2400 mg/day. A daily dose of 1200 mg/day has been shown in one study to be effective in patients in whom monotherapy has been initiated with oxcarbazepine. Patients should be observed closely during this transition phase.

Initiation of Monotherapy

Patients not currently being treated with AEDs may have monotherapy initiated with APO-OXCARBAZEPINE. In these patients, APO-OXCARBAZEPINE should be initiated at a dose of

600 mg/day (given in a BID regimen); the dose should be increased by 300 mg/day every third day to a dose of 1200 mg/day. Controlled trials in these patients examined the effectiveness of a 1200 mg/day dose; a dose of 2400 mg/day has been shown to be effective in patients converted from other AEDs to APO-OXCARBAZEPINE monotherapy (see above).

Pediatric Patients Ages 6 to 16

Adjunctive Therapy

Treatment should be initiated at a daily dose of 8 to 10 mg/kg generally not to exceed 600 mg/day, given in a BID regimen. The target maintenance dose of APO-OXCARBAZEPINE should be achieved over 2 weeks, and is dependent upon patient weight, according to the following chart:

20-29 kg:	900 mg/day
29.1-39 kg:	1200 mg/day
> 39 kg:	1800 mg/day

In the clinical trial, in which the intention was to reach these target doses, the median daily dose was 31 mg/kg with a range of 6 to 51 mg/kg.

The pharmacokinetics of oxcarbazepine are similar in older children (age >8 yrs) and adults. However, younger children (age < 8 yrs) have an increased clearance (by about 30 to 40%) compared with older children and adults. In the controlled trial, pediatric patients 8 years old and below received the highest maintenance doses.

Conversion to Monotherapy

Patients receiving concomitant antiepileptic drugs may be converted to monotherapy by initiating treatment with APO-OXCARBAZEPINE at approximately 8 to 10 mg/kg/day given in a BID regimen, while simultaneously initiating the reduction of the dose of the concomitant antiepileptic drugs. The concomitant antiepileptic drugs can be completely withdrawn over 3 to 6 weeks while APO-OXCARBAZEPINE may be increased as clinically indicated by a maximum increment of 10 mg/kg/day at approximately weekly intervals to achieve the recommended daily dose. Patients should be observed closely during this transition phase.

The recommended total daily dose of APO-OXCARBAZEPINE is shown in Table 1.

Initiation of Monotherapy

Patients not currently being treated with antiepileptic drugs may have monotherapy initiated with APO-OXCARBAZEPINE. In these patients, APO-OXCARBAZEPINE should be initiated at a dose of 8 to 10 mg/kg/day given in a BID regimen. The dose should be increased by 5 mg/kg/day every third day to the recommended daily dose shown Table 1.

Table 1 Range of Maintenance Doses of APO-OXCARBAZEPINE for Children by Weight During Monotherapy

	From	To
Weight in kg	**Dose (mg/day)**	**Dose (mg/day)**
20	600	900
25	900	1200
30	900	1200
35	900	1500
40	900	1500
45	1200	1500
50	1200	1800
55	1200	1800
60	1200	2100
65	1200	2100
70	1500	2100

Children below 2 years of age have not been studied in controlled clinical trials.

Therapeutic drug monitoring
Plasma level monitoring of oxcarbazepine or its active metabolite 10-monohydroxy derivative (MHD) is not routinely warranted. However, plasma level monitoring of MHD may be considered in order to rule out noncompliance, or in situations where an alteration in MHD clearance is to be expected, including:

- changes in renal function (see 4.1 Dosing Considerations, Renal Insufficiency)
- pregnancy (see 7.1 Special Populations and 10.3 Pharmacokinetics, Special Populations and Conditions)
- concomitant use of liver enzyme-inducing drugs (see 9 DRUG INTERACTIONS)

If any of these situations apply, the dose of APO-OXCARBAZEPINE may be adjusted (based on plasma levels measured 2 to 4 hours post dose) to maintain peak MHD plasma levels <35 mg/L.

4.4 Administration

APO-OXCARBAZEPINE can be taken with or without food.

4.5 Missed Dose

If a scheduled dose is missed, the next dose should not be doubled.

5 OVERDOSAGE

Human Overdose Experience

Isolated cases of overdose with oxcarbazepine have been reported. Patients who ingested

up to 24,000 mg recovered with symptomatic treatment. One fatality was reported with ingestion of 48,000 mg.

Signs and symptoms of overdose may include dyspnea, respiratory depression, hypotension, drowsiness, fatigue, dizziness, ataxia, tremor, abnormal coordination, convulsion, headache, loss of consciousness, coma, aggression, agitation, confusional state, hyperkinesia, dyskinesia, nausea, vomiting, diplopia, nystagmus, miosis, blurred vision, hyponatremia, QTc prolongation.

Treatment and Management

There is no specific antidote. Symptomatic and supportive treatment should be administered as appropriate. Removal of the drug by gastric lavage and/or inactivation by administering activated charcoal should be considered.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Oral	Tablets 150 mg, 300 mg, 600 mg	Colloidal silicon dioxide, crospovidone, ferric oxide yellow, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methylcellulose, polyethylene glycol and titanium dioxide.

APO-OXCARBAZEPINE (oxcarbazepine) tablets are available in the following strengths for oral use:

APO-OXCARBAZEPINE Tablets 150 mg: Each yellow, oval, biconvex, film-coated tablet, engraved “OXC” score “150” on one side, “APO” on the other side, contains 150 mg of oxcarbazepine. Available in bottles of 100.

APO-OXCARBAZEPINE Tablets 300 mg: Each yellow, oval, biconvex, film-coated tablet, engraved “OXC” score “300” on one side, “APO” on the other side, contains 300 mg of oxcarbazepine. Available in bottles of 100.

APO-OXCARBAZEPINE Tablets 600 mg: Each yellow, oval, biconvex, film-coated tablet, engraved “OXC” score “600” on one side, “APO” on the other side, contains 600 mg of oxcarbazepine. Available in bottles of 100.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Serious Dermatological Reactions

Serious dermatological reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme, drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP), have been reported in both children and adults in association with the use of oxcarbazepine. The median time of onset for reported cases was 19 days. Such serious skin reactions may be life-threatening, and some patients have required hospitalization with very rare reports of fatal outcome. Recurrence of the serious skin reactions following re-challenge with oxcarbazepine has also been reported.

The reporting rate of TEN and SJS associated with oxcarbazepine use, which is generally accepted to be an underestimate due to underreporting, exceeds the background incidence rate estimates by a factor of 3- to 10-fold. Estimates of the background incidence rate for these serious skin reactions in the general population range between 0.5 to 6 cases per million-person years. Therefore, if a patient develops a skin reaction while taking APO-OXCARBAZEPINE, consideration should be given to discontinuing APO-OXCARBAZEPINE use and prescribing another antiepileptic medication.

Pharmacogenomics

Ancestry and Allelic Variation in the HLA-B Gene

In studies that included small samples of carbamazepine treated patients of Han Chinese ancestry a strong association was found between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. The HLA- B*1502 allele is found almost exclusively in individuals with ancestry across broad areas of Asia. Results of these studies suggest that the presence of the HLA-B*1502 allele may be one of the risk factors for oxcarbazepine-associated SJS/TEN in patients with Asian ancestry. Therefore, physicians should consider HLA-B*1502 genotyping as a screening tool in these patients. Until further information is available, the use of APO-OXCARBAZEPINE and other anti-epileptic drugs associated with SJS/TEN should also be avoided in patients who test positive for the HLA-B*1502 allele unless the benefits clearly outweigh the risks. Screening is not generally recommended in patients from populations in which the prevalence of HLA-B*1502 is low or in current oxcarbazepine users, as the risk of SJS/TEN is largely confined to the first few months of therapy, regardless of HLA-B*1502 status.

Ancestry and Allelic Variation in the HLA-A Gene

HLA-A*3101 may be a risk factor for the development of cutaneous adverse drug reactions such as SJS, TEN, DRESS, AGEP and maculopapular rash.

The frequency of the HLA-A*3101 allele, an inherited allelic variant of the HLA-A gene,

varies widely between ethnic populations and its frequency is about 2 to 5% in European populations and about 10% in the Japanese population. The frequency of this allele is estimated to be less than 5% in the majority of Australian, Asian, African and North American populations with some exceptions within 5 to 12%. Prevalence above 15% has been estimated in some ethnic groups in South America (Argentina and Brazil), North America (US Navajo and Sioux, and Mexico Sonora Seri) and Southern India (Tamil Nadu) and between 10% to 15% in other native ethnicities in these same regions.

HLA-A*3101 is associated with an increased risk of carbamazepine-induced cutaneous adverse drug reactions including SJS, TEN, DRESS, or less severe AGEP and maculopapular rash. However, there are insufficient data on patients treated with oxcarbazepine to support a recommendation for testing the presence of HLA-A*3101 allele in patients prior to initiating treatment with oxcarbazepine. Moreover, genetic screening is generally not recommended for any current oxcarbazepine users, as the risk of SJS/TEN, AGEP, DRESS and maculopapular rash is largely confined to the first few months of therapy, regardless of HLA-A*3101 status.

Important Limitations of HLA-A and HLA-B Genotyping

HLA-B*1502 and HLA-A*3101 genotyping as screening tools have important limitations and must never substitute for appropriate clinical vigilance and patient management. Many HLA-B*1502-positive Asian patients treated with oxcarbazepine will not develop SJS/TEN, and these reactions can still occur infrequently in HLA-B*1502-negative patients of any ethnicity. Similarly, many patients positive for HLA-A*3101 and treated with oxcarbazepine will not develop SJS, TEN, DRESS, AGEP or maculopapular rash and patients negative for HLA-A*3101 of any ethnicity can still develop these severe cutaneous adverse reactions. The role of other possible factors in the development of, and morbidity from, these severe cutaneous adverse reactions, such as antiepileptic drug (AED) dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

In addition, it should be kept in mind that oxcarbazepine treated patients who will experience SJS/TEN have this reaction within the first few months of treatment. This information may be taken into consideration when deciding whether to screen genetically at-risk patients currently on oxcarbazepine.

The identification of subjects carrying the HLA-B*1502 allele and the avoidance of carbamazepine therapy in these subjects has been shown to decrease the incidence of carbamazepine-induced SJS/TEN.

Should signs and symptoms suggest a severe skin reaction such as SJS or TEN, APO-OXCARBAZEPINE should be withdrawn at once.

Hypersensitivity

Class I (immediate) hypersensitivity reactions including rash, pruritus, urticaria, angioedema and reports of anaphylaxis have been received in the post-marketing period. Cases of

anaphylaxis and angioedema involving the larynx, glottis, lips and eyelids have been reported in patients after taking the first or subsequent doses of oxcarbazepine. The reporting rate of anaphylaxis and angioedema associated with oxcarbazepine use, which is generally accepted to be an underestimate due to underreporting, does not exceed the background incidence rate estimates. Estimates of the background incidence rate for severe anaphylaxis in the general population ranges between 50 and 300 cases per million-person years and the estimated lifetime prevalence of anaphylaxis ranges between 0.05% and 2.0% and that of angioedema ranges between 0.05% and 1%. If a patient develops these reactions after treatment with APO-OXCARBAZEPINE, the drug should be discontinued and an alternative treatment started.

Patients with a Past History of Hypersensitivity Reaction to Carbamazepine

Patients who have had hypersensitivity reactions to carbamazepine should be informed that approximately 25% to 30% of them will experience hypersensitivity reactions with oxcarbazepine. For this reason patients should be specifically questioned about any prior experience with carbamazepine, and patients with a history of hypersensitivity reactions to carbamazepine should ordinarily be treated with APO-OXCARBAZEPINE only if the potential benefit justifies the potential risk. Hypersensitivity reactions may also occur in patients without a history of hypersensitivity to carbamazepine. In general, if signs or symptoms of hypersensitivity develop, APO-OXCARBAZEPINE should be discontinued immediately.

Multi-Organ Hypersensitivity

Multi-organ hypersensitivity reactions have occurred in close temporal association (median time to detection 13 days: range 4 to 60) to the initiation of oxcarbazepine therapy in adult and pediatric patients. Although there have been a limited number of reports, many of these cases resulted in hospitalization and some were considered life threatening. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations included hemic and lymphatic system disorders (e.g., eosinophilia, thrombocytopenia, lymphadenopathy, leucopenia, neutropenia, splenomegaly), hepatobiliary disorders (e.g. hepatitis, liver function test abnormalities), renal disorders (e.g. proteinuria, nephritis, oliguria, renal failure), muscles and joints disorders (e.g. joint swelling, myalgia, arthralgia, asthenia), nervous system disorders (hepatic encephalopathy), respiratory disorders (e.g. dyspnea, pulmonary oedema, asthma, bronchospasms, interstitial lung disease), hepatorenal syndrome, pruritus, and angioedema. Because the disorder is variable in its expression, other organ system symptoms and signs, not noted here, may occur. If this reaction is suspected, APO-OXCARBAZEPINE should be discontinued and an alternative treatment started. Although there are no case reports to indicate cross sensitivity with other drugs that produce this syndrome, the experience amongst drugs associated with multi-organ hypersensitivity would indicate this to be a possibility.

General

Bone disorders

Long-term use of antiepileptics such as carbamazepine, phenobarbital, phenytoin, primidone, oxcarbazepine, lamotrigine and sodium valproate is associated with a risk of decreased bone mineral density that may lead to weakened or brittle bones.

Carcinogenesis and Mutagenesis

In 2-year carcinogenicity studies, oxcarbazepine was administered orally at doses up to 100 mg/kg/day in mice and up to 250 mg/kg in rats, and the pharmacologically active 10-hydroxy metabolite (MHD) was administered orally at doses up to 600 mg/kg/day in rats. The following dose-related increases in the incidences of liver tumors were noted: hepatocellular carcinomas in the female rats (oxcarbazepine 25 mg/kg/day), hepatocellular adenomas in mice (oxcarbazepine 70 mg/kg/day) and hepatocellular adenomas and/or carcinomas in males at 600 mg/kg/day and in females at >250 mg/kg/day with MHD. There was a marginal increase in the incidence of benign testicular interstitial cell tumors in rats at 250 mg MHD /kg/day and an increase in the incidence of granular cell aggregates or tumors in the cervix and vagina in rats at 75 mg MHD /kg/day. See 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity.

The occurrence of liver tumors was attributed to the induction of hepatic microsomal enzymes, an effect which is weak or absent in patients treated with oxcarbazepine. Interstitial cell tumors are common spontaneous tumors in aged rats and are considered to be without risk for man. The significance of granular cell tumors to therapy with oxcarbazepine is unknown, however as the tumors were microscopic in size and bland in appearance, they are considered to be of little importance in human safety assessment.

In a series of *in vitro* and *in vivo* mutagenicity studies there was no evidence of a mutagenic potential for oxcarbazepine or MHD. See 16 NON-CLINICAL TOXICOLOGY, Mutagenicity.

Cardiovascular

In clinical trials with oxcarbazepine, patients with significant cardiovascular disease or electrocardiographic abnormalities were systematically excluded. Thus, APO-OXCARBAZEPINE should be used with caution in patients with cardiac conduction abnormalities and in patients taking concomitant medications which depress atrioventricular (AV) conduction. It is recommended that APO-OXCARBAZEPINE should not be used in patients with AV block. For patients with cardiac insufficiency and secondary heart failure for whom treatment with APO-OXCARBAZEPINE is considered clinically indicated, body weight should be monitored to determine the occurrence of fluid retention. In case of fluid retention or worsening of the cardiac condition, serum sodium should be checked. If hyponatremia is observed, water restriction is an important counter-measure.

Dependence/Tolerance

Withdrawal of Anti-Epileptic Drugs (AEDs)

As with all antiepileptic drugs, APO-OXCARBAZEPINE should be withdrawn gradually to

minimize the potential of increased seizure frequency.

Abuse and Dependence Liability

The abuse potential of oxcarbazepine has not been evaluated in human studies.

Intragastric injections of oxcarbazepine to four cynomolgus monkeys demonstrated no signs of physical dependence as measured by the desire to self administer oxcarbazepine by lever pressing activity.

Driving and Operating Machinery

Adverse reactions such as dizziness, somnolence, ataxia, diplopia, blurred vision, visual disturbances, hyponatremia and depressed level of consciousness were reported with oxcarbazepine especially at the start of treatment or in connection with dose adjustments (more frequently during the up titration phase). Patients should therefore exercise due caution when driving a vehicle or operating machinery.

Endocrine and Metabolism

Hyponatremia

Clinically significant hyponatremia (sodium <125 mmol/L) can develop during APO-OXCARBAZEPINE use. In the 14 controlled epilepsy studies 2.5% of oxcarbazepine treated patients (38/1524) had a sodium of less than 125 mmol/L at some point during treatment, compared to no such patients assigned placebo or active control (carbamazepine and phenobarbital for adjunctive and monotherapy substitution studies, and phenytoin and valproate for the monotherapy initiation studies). Clinically significant hyponatremia generally occurred during the first 3 months of treatment with oxcarbazepine, although there were patients who first developed a serum sodium <125 mmol/L more than 1 year after initiation of therapy. Most patients who developed hyponatremia were asymptomatic but patients in the clinical trials were frequently monitored and some had their oxcarbazepine dose reduced, discontinued, or had their fluid intake restricted for hyponatremia. Whether or not these maneuvers prevented the occurrence of more severe events is unknown. Cases of symptomatic hyponatremia have been reported during post-marketing use. In clinical trials, patients whose treatment with oxcarbazepine was discontinued due to hyponatremia generally experienced normalization of serum sodium within a few days without additional treatment.

In patients with pre-existing renal conditions associated with low sodium levels or in patients treated concomitantly with sodium-lowering drugs (e.g. diuretics, drugs associated with inappropriate ADH secretion), serum sodium levels should be measured prior to initiating therapy. Thereafter, serum sodium levels should be measured after approximately two weeks and then at monthly intervals for the first three months during clinical therapy, or according to clinical need. These risk factors may apply especially to elderly patients. For patients on APO-OXCARBAZEPINE therapy when starting on sodium-lowering drugs, the same approach for sodium checks should be followed. In general, if clinical symptoms

suggestive of hyponatremia (e.g., nausea, malaise, headache, lethargy, confusion, or obtundation) occur on APO-OXCARBAZEPINE therapy, serum sodium measurement may be considered. Other patients may have serum sodium assessed as part of their routine laboratory studies.

Hypothyroidism

Decreases in TT_4 and/or FT_4 (total and/or free thyroxine, respectively), usually without changes in T_3 or TSH, have been reported in pediatric and adult patients during short-term and long-term treatment with oxcarbazepine (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests; 8.5 Post Market Adverse Reactions). Although patients with oxcarbazepine-induced reductions in T_4 may remain clinically euthyroid, some patients present with symptoms of hypothyroidism. Discontinuation of oxcarbazepine treatment has been shown to be associated with a return to normal levels of T_4.

Evaluation of thyroid hormone status should be considered for patients treated with oxcarbazepine, particularly for pediatric patients, due to the potential risk of sub-clinical or clinical hypothyroidism and long-term adverse effects on development that can occur in relation to undetected changes in thyroid hormone status.

Hematologic

Very rare reports of agranulocytosis, aplastic anemia and pancytopenia have been seen in patients treated with oxcarbazepine during post-marketing experience (see 8.5 Post-Market Adverse Reactions).

Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Hepatic/Biliary/Pancreatic

Very rare cases of hepatitis and hepatic failure have been reported. Symptoms suggestive of hepatic dysfunction (nausea/vomiting, anorexia, pruritis, right upper quadrant pain, etc.) should prompt evaluation of liver function. In the event of a clinically significant liver abnormality, treatment with APO-OXCARBAZEPINE should be promptly discontinued. Caution should be exercised when treating patients with severe hepatic impairment (see 10.3 Pharmacokinetics, Special Populations and Conditions).

Monitoring and Laboratory Tests

Serum sodium levels below 125 mmol/L have been observed in patients treated with oxcarbazepine (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyponatremia). Experience from clinical trials indicates that serum sodium levels return toward normal when the oxcarbazepine dosage is reduced or discontinued, or when the patient was treated conservatively (e.g., fluid restriction).

Laboratory data from clinical trials suggest that oxcarbazepine use was associated with decreases in T_4, without changes in T_3 or TSH. Evaluation of thyroid hormone status should be considered for patients treated with oxcarbazepine, particularly for pediatric patients, due to potential risk of sub-clinical or clinical hypothyroidism and adverse effects on development that can occur in relation to undetected changes in thyroid hormone status. (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypothyroidism).

Neurologic

Use of oxcarbazepine has been associated with central nervous system related adverse events. The most significant of these can be classified into three general categories: 1) cognitive symptoms including psychomotor slowing, difficulty with concentration, and speech or language problems, 2) somnolence or fatigue, and 3) coordination abnormalities, including ataxia and gait disturbances.

Adult Patients
In one, large, fixed dose study, oxcarbazepine was added to existing AED therapy (up to three concomitant AEDs). By protocol, the dosage of the concomitant AEDs could not be reduced as oxcarbazepine was added, reduction in oxcarbazepine dosage was not allowed if intolerance developed, and patients were discontinued if unable to tolerate their highest target maintenance doses. In this trial, 65% of patients were discontinued because they could not tolerate the 2400 mg/day dose of oxcarbazepine on top of existing AEDs. The adverse events seen in this study were primarily CNS related and the risk for discontinuation was dose related.

In this trial, 7.1% of oxcarbazepine-treated patients and 4% of placebo-treated patients experienced a cognitive adverse event. The risk of discontinuation for these events was about 6.5 times greater on oxcarbazepine than on placebo. In addition, 26% of oxcarbazepine-treated patients and 12% of placebo-treated patients experienced somnolence. The risk of discontinuation for somnolence was about 10 times greater on oxcarbazepine than on placebo. Finally, 28.7% of oxcarbazepine-treated patients and 6.4% of placebo-treated patients experienced ataxia or gait disturbances. The risk for discontinuation for these events was about 7 times greater on oxcarbazepine than on placebo.

In a single placebo-controlled monotherapy trial evaluating 2400 mg/day of oxcarbazepine, no patients in either treatment group discontinued double-blind treatment because of cognitive adverse events, somnolence, ataxia, or gait disturbance.

In the two dose-controlled conversion to monotherapy trials comparing 2400 mg/day and 300 mg/day oxcarbazepine, 1.1% of patients in the 2400 mg/day group discontinued double- blind treatment because of somnolence or cognitive adverse events compared to 0% in the 300 mg/day group. In these trials, no patients discontinued because of ataxia or gait disturbances in either treatment group.

Pediatric patients

A study was conducted in pediatric patients with inadequately controlled partial seizures in which oxcarbazepine was added to existing AED therapy (up to two concomitant AEDs). By protocol, the dosage of concomitant AEDs could not be reduced as oxcarbazepine was added. Oxcarbazepine was titrated to reach a target dose ranging from 30 mg/kg to 46 mg/kg (based on a patient's body weight with fixed doses for predefined weight ranges).

Cognitive adverse events occurred in 5.8% of oxcarbazepine-treated patients (the single most common event being concentration impairment, 4 of 138 patients) and in 3.1% of patients treated with placebo. In addition, 34.8% of oxcarbazepine-treated patients and 14.0% of placebo-treated patients experienced somnolence. (No patient discontinued due to a cognitive adverse event or somnolence.). Finally, 23.2% of oxcarbazepine-treated patients and 7.0% of placebo-treated patients experienced ataxia or gait disturbances. Two (1.4%) oxcarbazepine-treated patients and 1 (0.8%) placebo-treated patient discontinued due to ataxia or gait disturbances.

Risk of seizure aggravation

Risk of seizure aggravation has been reported with oxcarbazepine. The risk is seen especially in children but may also occur in adults. In case of seizure aggravation, APO-OXCARBAZEPINE should be discontinued.

Psychiatric

Suicidal Ideation and Behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications.

All patients treated with antiepileptic drugs, irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

An FDA meta-analysis of randomized placebo controlled trials, in which antiepileptic drugs were used for various indications, has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known.

There were 43892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (antiepileptic drug or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (antiepileptic drug or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more antiepileptic

drug). Therefore, the small increased risk of suicidal ideation and behaviour reported from the meta-analysis (0.43% for patients on antiepileptic drugs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (antiepileptic drug or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and behaviour for patients with epilepsy that are taking antiepileptic drugs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct antiepileptic drug treatment in both arms.

Renal

In renally-impaired patients (creatinine clearance < 30 mL/min), the elimination half-life of MHD is prolonged with a corresponding two fold increase in AUC (see 10.3 Pharmacokinetics, Special Populations and Conditions). APO-OXCARBAZEPINE therapy should be initiated at one-half the usual starting dose and increased, if necessary, at a slower than usual rate until the desired clinical response is achieved (see 4.1 Dosing Considerations).

Reproductive Health: Female and Male Potential

There are no human data on fertility. In rats, fertility in both sexes was unaffected by oxcarbazepine or MHD at oral doses up to 150 and 450 mg/kg/day, respectively. However, disruption of estrous cyclicity and reduced numbers of corpora lutea, implantations and live embryos were observed in female animals at the highest dose of MHD. (See 16 NON-CLINICAL TOXICOLOGY, Reproductive Studies).

Women of child-bearing potential and contraceptive measures

APO-OXCARBAZEPINE may result in a failure of the therapeutic effect of hormonal contraceptive drugs containing ethinylestradiol and levonorgestrel (see 9.4 Drug-Drug Interactions). Women of child bearing potential should be advised to use highly effective contraception (preferably non-hormonal).

7.1 Special Populations

7.1.1 Pregnant Women

Offspring of epileptic mothers are known to be more prone to developmental disorders, including malformations. Data on a limited number of pregnancies indicate that oxcarbazepine may cause serious birth defects when administered during pregnancy.

Most frequently observed congenital malformations with the use of oxcarbazepine were ventricular septal defect, atrioventricular septal defect, cleft palate with cleft lip, Down's syndrome, dysplastic hip (both unilateral and bilateral), tuberous sclerosis, neural tube defects, and congenital malformation of the ear. Data related to the risk of neurodevelopmental disorders in children exposed to oxcarbazepine during pregnancy are inconclusive, and a risk cannot be excluded.

Taking these data into consideration:

- If women receiving APO-OXCARBAZEPINE become pregnant, plan to become pregnant, or if the need to initiate treatment with APO-OXCARBAZEPINE arises during pregnancy, the drug's potential benefits must carefully be weighed against its hazards, particularly during the first 3 months of pregnancy.

- As is usual clinical practice, women of childbearing potential should, whenever possible, be prescribed antiepileptic drugs as monotherapy because the incidence of congenital abnormalities in the offspring of women treated with more than one antiepileptic drug is greater than in those women receiving a single antiepileptic.

- Minimum effective doses should be given and plasma levels monitored.

- Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

- During pregnancy, effective antiepileptic treatment should not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Like many antiepileptic drugs, APO-OXCARBAZEPINE may contribute to folic acid deficiency, a possible contributory cause of foetal abnormality. Folic acid supplementation is recommended before and during pregnancy.

Due to physiological changes during pregnancy, plasma levels of the active metabolite of oxcarbazepine, the 10-monohydroxy derivative (MHD), may gradually decrease throughout pregnancy. It is recommended that clinical response should be monitored carefully in women receiving APO-OXCARBAZEPINE treatment during pregnancy and determination of changes in MHD plasma concentrations should be considered to ensure that adequate seizure control is maintained throughout pregnancy (See 4.2 Recommended Dose and Dosage Adjustment, Therapeutic drug monitoring and 10.3 Pharmacokinetics, Special Populations and Conditions). Postpartum MHD plasma levels may also be considered for monitoring, especially in the event that medication was increased during pregnancy, to minimize the risk of concentration dependent adverse events.

Newborn child

Bleeding disorders in the newborn caused by antiepileptic agents have been reported. As a precaution, vitamin K_1 should be administered as a preventive measure in the last few weeks of the woman's pregnancy and to the newborn.

7.1.2 Breast-feeding

Oxcarbazepine and its active metabolite (MHD) are excreted in human breast milk. Limited data indicate that the breastfed infants' MHD plasma concentrations correspond up to 5 % of the maternal MHD plasma concentration. A risk to the infant cannot be excluded,

therefore, a decision on whether to breastfeed while using oxcarbazepine should be considered, based on the benefit of breastfeeding and the potential risk of side effects in the infant. If breastfed the infant should be monitored for adverse effects such as drowsiness and poor weight gain.

7.1.3 Pediatrics

Pediatrics (6 to 16 years of age):

APO-OXCARBAZEPINE is indicated for use as monotherapy or as adjunctive therapy for partial seizures in patients aged 6 to 16 years old. Oxcarbazepine has been given to about 623 patients between the ages of 3 to 17 in controlled clinical trials (185 treated as monotherapy) and about 615 patients between the ages of 3 to 17 in other trials (See 8 ADVERSE REACTIONS for a description of the adverse events associated with oxcarbazepine use in this population).

7.1.4 Geriatrics

See 4.1 Dosing Considerations, Geriatrics.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Most Common Adverse Events in All Clinical Studies

Adjunctive Therapy/Monotherapy in Adults Previously Treated with other AEDs: The most commonly observed (≥ 5%) adverse experiences seen in association with oxcarbazepine and substantially more frequent than in placebo-treated patients were: dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, abnormal gait.

Approximately 23% of these 1537 adult patients discontinued treatment because of an adverse experience. The adverse experience most commonly associated with discontinuation were: dizziness (6.4%), diplopia (5.9%), ataxia (5.2%), vomiting (5.1%), nausea (4.9%), somnolence (3.8%), headache (2.9%), fatigue (2.1%), abnormal vision (2.1%), tremor (1.6%), abnormal gait (1.7%), rash (1.4%), hyponatremia (1.0%).

Monotherapy in Adults not Previously Treated with other AEDs*:* The most commonly observed (≥ 5%) adverse experiences seen in association with oxcarbazepine in these patients were similar to those in previously treated patients.

Approximately 9% of these 295 adult patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated with discontinuation were: dizziness (1.7%), nausea (1.7%), rash (1.7%), headache (1.4%).

Adjunctive Therapy in Pediatric Patients Previously Treated with other AEDs*:* The most commonly observed (≥ 5%) adverse experiences seen in association with oxcarbazepine in these patients were similar to those seen in adults.

Approximately 11% of these 456 pediatric patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated with discontinuation were: somnolence (2.4%), vomiting (2.0%), ataxia (1.8%), diplopia (1.3%), dizziness (1.3%), fatigue (1.1%), nystagmus (1.1%).

Monotherapy in Pediatric Patients not Previously Treated with other AEDs: The most commonly observed (≥ 5%) adverse experiences seen in association with oxcarbazepine in these patients were similar to those in adults.

Approximately 9.2% of 152 pediatric patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated (≥ 1%) with discontinuation were rash (5.3%) and maculopapular rash (1.3%).

Incidence in Controlled Clinical Studies: The prescriber should be aware that the figures in Tables 3, 4, 5, 6 and 7 cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studies.

Controlled Clinical Studies of Adjunctive Therapy/Monotherapy in Adults Previously Treated with other AEDs*:* Table 3 lists treatment-emergent signs and symptoms that occurred in at least 2% of adult patients with epilepsy treated with oxcarbazepine or placebo as adjunctive treatment and were numerically more common in the patients treated with any dose of oxcarbazepine. Table 4 lists treatment-emergent signs and symptoms in patients converted from other AEDs to either high dose oxcarbazepine or low dose (300 mg) oxcarbazepine. Note that in some of these monotherapy studies patients who dropped out during a preliminary tolerability phase are not included in the tables.

Table 3 Treatment-Emergent Adverse Event Incidence in a Controlled Clinical Study of Adjunctive Therapy in Adults (events in at least 2% of patients treated with 2400 mg/day of oxcarbazepine and numerically more frequent than in the placebo group)

	Oxcarbazepine Dosage (mg/day)			
Body system/Adverse event	**OXC 600 N=163 %**	**OXC 1200 N=171 %**	**OXC 2400 N=126 %**	**Placebo N=166 %**
Body as a Whole				
Fatigue	15	12	15	7
Asthenia	6	3	6	5
Edema Legs	2	1	2	1
Weight Increase	1	2	2	1
Feeling abnormal	0	1	2	0
Cardiovascular System				
Hypotension	0	1	2	0
Digestive System				
Nausea	15	25	29	10
Vomiting	13	25	36	5
Pain abdominal	10	13	11	5
Diarrhea	5	6	7	6
Dyspepsia	5	5	6	2
Constipation	2	2	6	4
Gastritis	2	1	2	1
Metabolic & Nutritional Disorders				
Hyponatremia	3	1	2	1
Musculoskeletal System				
Muscle weakness	1	2	2	0
Sprains & strains	0	2	2	1
Nervous System				
Headache	32	28	26	23
Dizziness	26	32	49	13
Somnolence	20	28	36	12
Ataxia	9	17	31	5
Nystagmus	7	20	26	5
Gait abnormal	5	10	17	1
Insomnia	4	2	3	1
Tremor	3	8	16	5
Nervousness	2	4	2	1
Agitation	1	1	2	1
Coordination abnormal	1	3	2	1
EEG Abnormal	0	0	2	0
Speech disorder	1	1	3	0
Confusion	1	1	2	1
Cranial injury	1	0	2	1

Body system/Adverse event	Oxcarbazepine Dosage (mg/day)			
	OXC 600 N=163 %	OXC 1200 N=171 %	OXC 2400 N=126 %	Placebo N=166 %
Dysmetria	1	2	3	0
Thinking abnormal	0	2	4	0
Respiratory System				
Rhinitis	2	4	5	4
Skin & Appendages				
Acne	1	2	2	0
Special Senses				
Diplopia	14	30	40	5
Vertigo	6	12	15	2
Vision abnormal	6	14	13	4
Accommodation abnormal	0	0	2	0

Table 4 Treatment-Emergent Adverse Event Incidence in Controlled Clinical Studies of Monotherapy in Adults Previously Treated with Other AEDs (events in at least 2% of patients treated with 2400 mg/day of oxcarbazepine and numerically more frequent than in the low dose control group)

Body system/Adverse event	Oxcarbazepine Dosage (mg/day)	
	2400 N=86 %	300 N=86 %
Body as a Whole - General Disorder		
Fatigue	21	5
Fever	3	0
Allergy	2	0
Edema Generalized	2	1
Pain Chest	2	0
Digestive System		
Nausea	22	7
Vomiting	15	5
Diarrhea	7	5
Dyspepsia	6	1
Anorexia	5	3
Pain Abdominal	5	3
Mouth Dry	3	0
Hemorrhage Rectum	2	0
Toothache	2	1
Hemic & Lymphatic System		
Lymphadenopathy	2	0
Infections & Infestations		
Infection Viral	7	5
Infection	2	0

	Oxcarbazepine Dosage (mg/day)	
Body system/Adverse event	**2400 N=86 %**	**300 N=86 %**
Metabolic & Nutritional Disorders		
Hyponatremia	5	0
Thirst	2	0
Nervous System		
Headache	31	15
Dizziness	28	8
Somnolence	19	5
Anxiety	7	5
Ataxia	7	1
Confusion	7	0
Nervousness	7	0
Insomnia	6	3
Tremor	6	3
Amnesia	5	1
Convulsions Aggravated	5	2
Emotional Lability	3	2
Hypoesthesia	3	1
Coordination abnormal	2	1
Nystagmus	2	0
Speech disorder	2	0
Respiratory System		
Upper respiratory tract infection	10	5
Coughing	5	0
Bronchitis	3	0
Pharyngitis	3	0
Skin & Appendages		
Hot Flushes	2	1
Purpura	2	0
Special Senses		
Vision abnormal	14	2
Diplopia	12	1
Taste Perversion	5	0
Vertigo	3	0
Ear Ache	2	1
Ear Infection	2	0
Urogenital & Reproductive System		
Urinary Tract Infection	5	1
Micturition Frequency	2	1
Vaginitis	2	0

Controlled Clinical Study of Monotherapy in Adults Not Previously Treated with other AEDs: Table 5 lists treatment-emergent signs and symptoms in a controlled clinical study of monotherapy in adults not previously treated with other AEDs that occurred in at least 2% of adult patients with epilepsy treated with oxcarbazepine or placebo and were numerically more common in the patients treated with oxcarbazepine.

Table 5 Treatment-Emergent Adverse Event Incidence in a Controlled Clinical Study of Monotherapy in Adults not Previously Treated with Other AEDs (events in at least 2% of patients treated with oxcarbazepine and numerically more frequent than in the placebo group)

Body System/Adverse Event	Oxcarbazepine N=55 %	Placebo N=49 %
Body as a Whole		
Falling Down	4	0
Digestive System		
Nausea	16	12
Diarrhea	7	2
Vomiting	7	6
Constipation	5	0
Dyspepsia	5	4
Musculoskeletal System		
Back Pain	4	2
Nervous System		
Dizziness	22	6
Headache	13	10
Ataxia	5	0
Nervousness	5	2
Amnesia	4	2
Coordination Abnormal	4	2
Tremor	4	0
Respiratory System		
Upper Respiratory Tract Infection	7	0
Epistaxis	4	0
Infection Chest	4	0
Sinusitis	4	2
Skin & Appendages		
Rash	4	2
Special Senses		
Vision abnormal	4	0

Controlled Clinical Studies of Adjunctive Therapy/Monotherapy in Pediatric Patients Previously Treated with other AEDs: Table 6 lists treatment-emergent signs and symptoms that occurred in at least 2% of pediatric patients with epilepsy treated with oxcarbazepine or placebo as adjunctive treatment and were numerically more common in the patients

treated with oxcarbazepine.

Table 6 Treatment-Emergent Adverse Event incidence in Controlled Clinical Studies of Adjunctive Therapy in Pediatric Patients Previously Treated with Other AEDs (events in at least 2% of patients treated with oxcarbazepine and numerically more frequent than in the placebo group)

Body System/Adverse Event	Oxcarbazepine N = 171 %	Placebo N = 139 %
Body as a Whole		
Fatigue	13	9
Allergy	2	0
Asthenia	2	1
Digestive System		
Vomiting	33	14
Nausea	19	5
Constipation	4	1
Dyspepsia	2	0
Nervous System		
Headache	31	19
Somnolence	31	13
Dizziness	28	8
Ataxia	13	4
Nystagmus	9	1
Emotional Lability	8	4
Gait Abnormal	8	3
Tremor	6	4
Speech Disorder	3	1
Concentration Impaired	2	1
Convulsions	2	1
Muscle Contractions Involuntary	2	1
Respiratory System		
Rhinitis	10	9
Pneumonia	2	1
Skin & Appendages		
Bruising	4	2
Sweating increased	3	0
Special Senses		
Diplopia	17	1
Vision Abnormal	13	1
Vertigo	2	0

Controlled Clinical Studies of Monotherapy in Pediatric Patients Not Previously Treated with other AEDs: Table 7 lists treatment-emergent signs and symptoms regardless of relationship to study drug, in controlled clinical studies of monotherapy in pediatric patients

not previously treated with other AEDs. The signs and symptoms listed are the ones that occurred in at least 2% of pediatric patients with epilepsy treated with oxcarbazepine or placebo and were numerically more frequent in the patients treated with oxcarbazepine.

Table 7 Treatment-Emergent Adverse Event Incidence Regardless of Relationship to Study Drug, in Controlled Clinical Studies of Monotherapy in Pediatric Patients Not Previously Treated with Other AEDs (events in at least 2% of patients treated with oxcarbazepine and numerically more frequent than in the placebo group)

Body System/Adverse Event	Oxcarbazepine N = 129 %	Placebo N = 17 %
Body as a Whole		
Fever	14.7	5.9
Chest Pain	3.9	0
Cardiovascular System		
Syncope	3.9	0
Digestive System		
Abdominal Pain	7.8	5.9
Vomiting	7.8	5.9
Anorexia	6.2	5.9
Diarrhea	4.7	0
Gum Hyperplasia	2.3	0
Infections & Infestations		
Viral Infection	18.6	17.6
Parasitic Infection	6.2	0
Musculoskeletal System		
Arthralgia	3.1	0
Leg Pain	3.1	0
Nervous System		
Headache	45.0	17.6
Somnolence	25.6	0
Dizziness	15.5	0
Apathy	9.3	0
Learning Difficulties NOS	3.9	0
Aggressive Reaction	3.1	0
Respiratory System		
Upper Respiratory Tract Infection	7.8	5.9
Epistaxis	3.9	0
Rhinitis	2.3	0
Skin & Appendages		
Acne	6.2	0
Pruritus	4.7	0
Impetigo	2.3	0
Urogenital & Reproductive System		

Body System/Adverse Event	Oxcarbazepine N = 129 %	Placebo N = 17 %
Dysmenorrhea	2.3	0

8.3 Less Common Clinical Trial Adverse Reactions

Other Events Observed in Association with the Administration of Oxcarbazepine

In the paragraphs that follow, the adverse events other than those in the preceding tables or text, that occurred in a total of 565 children and 1574 adults exposed to oxcarbazepine and that are reasonably likely to be related to drug use are presented. Events common in the population, events reflecting chronic illness and event likely to reflect concomitant illness are omitted particularly if minor. They are listed in order of decreasing frequency. Because the reports cite events observed in open label and uncontrolled trials, the role of oxcarbazepine in their causation cannot be reliably determined.

Body as a Whole: Fever, malaise, pain chest precordial, rigors, weight decrease.

Cardiovascular System: bradycardia, cardiac failure, cerebral hemorrhage, hypertension, hypotension postural, palpitation, syncope, tachycardia.

Digestive System: appetite increased, blood in stool, cholelithiasis, colitis, duodenal ulcer, dysphagia, enteritis, eructation, esophagitis, flatulence, gastric ulcer, gingival bleeding, gum hyperplasia, hematemesis, hemorrhage rectum, hemorrhoids, hiccup, mouth dry, pain biliary, pain right hypochondrium, retching, sialoadenitis, stomatitis, stomatitis ulcerative.

Hemic and Lymphatic System: Leucopenia, thrombocytopenia.

Laboratory Abnormalities: blood uric acid increased, gamma - glutamyl transferase (GGT) increased, hyperglycemia, hypocalcemia, hypoglycemia, hypokalemia, liver enzymes elevated, serum transaminase increased.

Musculoskeletal System: hypertonia muscle.

Nervous System: Aggressive reaction, amnesia, anguish, anxiety, apathy, aphasia, aura, convulsions aggravated, delirium, delusion, depressed level of consciousness, dysphonia, dystonia, emotional lability, euphoria, extra pyramidal disorder, feeling drunk, hemiplegia, hyperkinesia, hyperreflexia, hypoesthesia, hypokinesia, hyporeflexia, hypotonia, hysteria, libido decreased, libido increased, manic reaction, migraine, muscle contractions involuntary, nervousness, neuralgia, oculogyric crisis, panic disorder, paralysis, paroniria, personality disorder, psychoses, ptosis, stupor, tetany.

Respiratory System: asthma, dyspnea, epistaxis, laryngismus, pleurisy.

Skin and Appendages: acne, alopecia, angioedema, bruising, dermatitis contact, eczema, facial rash, flushing, folliculitis, heat rash, hot flushes, photosensitivity reaction, pruritis

genital, psoriasis, purpura, rash erythematous, rash maculopapular, vitiligo.

Special Senses: Accommodation abnormal, cataract, conjunctival hemorrhage, edema eye, hemianopia, mydriasis, otitis externa, photophobia, scotoma, taste perversion, tinnitus, xerophthalmia.

Surgical and Medical Procedures: procedure dental oral, procedure female reproductive, procedure musculoskeletal, procedure skin.

Urogenital and Reproductive System: Dysuria, hematuria, intermenstrual bleeding, leukorrhea, menorrhagia, micturition frequency, pain renal, pain urinary tract, polyuria, priapism, renal calculus.

Other: System lupus erythematosus.

8.5 Post-Market Adverse Reactions

The following adverse events not seen in controlled clinical trials have been observed in named patient programs or post-marketing experience.

Blood and Lymphatic System Disorders: bone marrow depression, agranulocytosis, aplastic anemia, pancytopenia, neutropenia (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Hematologic).

Gastrointestinal Disorders: pancreatitis and/or lipase and/or amylase increase.

Immune System Disorders: multi-organ hypersensitivity disorders characterized by features such as rash, fever, lymphadenopathy, abnormal liver function tests, eosinophilia and arthralgia (see 7 WARNING AND PRECAUTIONS, Multi-Organ Hypersensitivity), anaphylactic reactions (see 7 WARNING AND PRECAUTIONS, Hypersensitivity).

Injury, poisoning and procedural complications: Fall.

Metabolism and Nutrition Disorders: folic acid deficiency, abnormal thyroid function tests (decreased total T_4 and/or free T_4), hypothyroidism (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypothyroidism), inappropriate ADH secretion-like syndrome.

Musculoskeletal, Connective Tissue and Bone Disorders: There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with oxcarbazepine. The mechanism by which oxcarbazepine affects bone metabolism has not been identified.

Nervous system disorders: Speech disorders (including dysarthria); more frequent during up titration of oxcarbazepine dose.

Skin and Subcutaneous Disorders: Urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX,

Dermatologic and 7 WARNINGS AND PRECAUTIONS, Serious Dermatological Reactions), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Enzyme Inhibition

Oxcarbazepine and MHD inhibit the cytochrome P450 CYP2C19. Therefore, interactions could arise when co- administering high doses (e.g. 2,400 mg/day) of oxcarbazepine with drugs that are metabolised by CYP2C19 (e.g. phenobarbital, phenytoin, see below). In some patients treated with oxcarbazepine and drugs metabolized via CYP2C19 dose reduction of the co-administered drugs might be necessary. In human liver microsomes, oxcarbazepine and MHD have little or no capacity to function as inhibitors for the following enzymes: CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP4A9 and CYP4A11.

Enzyme Induction

Oxcarbazepine and MHD induce *in vitro* and *in vivo*, cytochromes CYP3A4 and CYP3A5 responsible for the metabolism of dihydropyridine calcium antagonists, oral contraceptives, and AEDs (e.g. carbamazepine) resulting in a lower plasma concentration of these medicinal products (see below). A decrease in plasma concentrations may also be observed for other drugs mainly metabolized by CYP3A4 and CYP3A5, for example immunosuppressants (e.g. cyclosporine).

In vitro, oxcarbazepine and MHD are weak inducer of UDP-glucuronyl transferase (UDPGT) and, therefore, *in vivo* they are unlikely to have an effect on drugs which are mainly eliminated by conjugation through the UDP-glucuronyl transferases (e.g. valproic acid, lamotrigine). Even in view of the weak induction potential of oxcarbazepine and MHD, a higher dose of concomitantly used drugs which are metabolized via CYP3A4 or via conjugation (UDPGT) may be necessary. In the case of discontinuation of APO-OXCARBAZEPINE therapy, a dose reduction of the concomitant medication may be necessary. Induction studies conducted with human hepatocytes confirmed oxcarbazepine and MHD as weak inducers of isoenzymes of the 2B and 3A4 CYP sub-family. The induction potential of oxcarbazepine/MHD on other CYP isoenzymes is not known.

9.3 Drug-Behavioural Interactions

Alcohol may increase the sedative effects of oxcarbazepine.

9.4 Drug-Drug Interactions

Antiepileptic Drugs (AED) and Enzyme Inducing Drugs

Potential interactions between oxcarbazepine and other AEDs were assessed in clinical

studies. The effect of these interactions on mean AUCs and C_{min} are summarized in Table 8:

Table 8 Summary of AED Interactions with oxcarbazepine

AED Co-administered	Dose of AED (mg/day)	Oxcarbazepine dose (mg/day)	Influence of oxcarbazepine on AED Concentration (Mean Change, 90% Confidence Interval)	Influence of AED on MHD Concentration (Mean change, 90% Confidence Interval)
Carbamazepine	400 to 1200	900	nc[1]	40% decrease [CI: 17% decrease, 57% decrease]
Phenobarbital	100 to 150	600 to 1800	14% increase [CI: 2% increase, 24% increase]	25% decrease [CI:12% decrease, 51% decrease]
Phenytoin	250 to 500	600 to 1800 > 1200-2400	nc[1,2] up to 40% increase[3] [CI: 12% increase, 60% increase]	30% decrease [CI: 3% decrease, 48% decrease]
Valproic acid	400 to 2800	600 to 1800	nc[1]	18% decrease [CI: 13% decrease, 40% decrease]

[1] nc denotes a mean change of less than 10%
[2] Pediatrics
[3] Mean increase in adults at high oxcarbazepine doses

In vivo, plasma levels of phenytoin increased by up to 40% when oxcarbazepine was given at doses above 1200 mg/day. Therefore, when using doses of APO-OXCARBAZEPINE greater than 1200 mg/day during adjunctive therapy, a decrease in the dose of phenytoin may be required (see 4.2 Recommended Dose and Dosage Adjustment). The increase in the phenobarbital level, however, is small (15%) when given with oxcarbazepine.

Strong inducers of cytochrome P450 enzymes and/or UDP-glucuronyl transferase (UGT) (e.g. rifampicin, carbamazepine, phenytoin and phenobarbital) have been shown to decrease the MHD plasma/serum levels (29% to 49%).

No autoinduction has been observed with oxcarbazepine.

Hormonal Contraceptives

Co-administration of oxcarbazepine with an oral contraceptive has been shown to influence the plasma concentrations of the two hormonal components, ethinylestradiol (EE) and levonorgestrel (LNG). The mean AUC values of EE were decreased by 48% [90% CI: 22 to 65] in one study and 52% [90% CI: 38 to 52] in another study. The mean AUC values of LNG were decreased by 32% [90% CI: 20 to 45] in one study and 52% [90% CI: 42 to 52] in another study. Therefore, concurrent use of APO-OXCARBAZEPINE with hormonal contraceptives

may render these contraceptives ineffective. Studies with other oral or implant contraceptives have not been conducted.

Calcium Antagonists

After repeated co-administration of oxcarbazepine, the AUC of felodipine was lowered by 28% [90% CI: 20 to 33]. Verapamil produced a decrease of 20% [90% CI: 18 to 27] in the plasma levels of MHD.

Other Drug Interactions

Cimetidine and erythromycin had no effect on the pharmacokinetics of MHD. Results with warfarin show no evidence of interaction with either single or repeated doses of oxcarbazepine.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

There are no known interactions of oxcarbazepine with commonly used laboratory tests.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The pharmacological activity of oxcarbazepine is primarily exerted through the 10-monohydroxy metabolite (MHD) of oxcarbazepine (see 10.3 Pharmacokinetics, Metabolism and Elimination). The precise mechanism by which oxcarbazepine and MHD exert their antiseizure effect is unknown; however, *in vitro* electrophysiological studies indicate that they produce blockade of voltage- sensitive sodium channels, resulting in stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses. These actions are thought to be important in the prevention of seizure spread in the intact brain. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may contribute to the anticonvulsant effects of the drug. No significant interactions of oxcarbazepine or MHD with brain neurotransmitter or modulator receptor sites have been demonstrated.

10.2 Pharmacodynamics

Oxcarbazepine and its active metabolite (MHD) exhibit anticonvulsant properties in animal seizure models. They protected rodents against electrically induced tonic extension seizures

and, to a lesser degree, chemically induced clonic seizures, and abolished or reduced the frequency of chronically recurring focal seizures in Rhesus monkeys with aluminum implants. No development of tolerance (i.e., attenuation of anticonvulsive activity) was observed in the maximal electroshock test when mice and rats were treated daily for 5 days and 4 weeks, respectively, with oxcarbazepine or MHD.

10.3 Pharmacokinetics

Absorption: Following oral administration of oxcarbazepine tablets, oxcarbazepine is completely absorbed and extensively metabolized to its pharmacologically active 10-monohydroxy metabolite (MHD). The half-life of the parent is about 2 hours, while the half-life of MHD is about 9 hours, so that MHD is responsible for most antiepileptic activity.

After single dose administration of oxcarbazepine tablets to healthy male volunteers under fasted conditions, the median time to reach maximum plasma concentration (t_{max}) was 4.5 (range 3 to 13 hours).

In a mass balance study in people, only 2% of total radioactivity in plasma was due to unchanged oxcarbazepine, with approximately 70% present as MHD, and the remainder attributable to minor metabolites. Food has no effect on the rate and extent of absorption of oxcarbazepine.

Steady-state plasma concentrations of MHD are reached within 2 to 3 days in patients when oxcarbazepine is given twice a day. At steady-state the pharmacokinetics of MHD are linear and show dose proportionality over the dose range of 300 to 2400 mg/day.

Distribution: The apparent volume of distribution of MHD is 49 L.

Approximately 40% of MHD is bound to serum proteins, predominantly to albumin. Binding is independent of the serum concentration within the therapeutically relevant range. Oxcarbazepine and MHD do not bind to alpha-1-acid glycoprotein.

Metabolism: Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to its 10-monohydroxy metabolite, MHD, which is primarily responsible for the pharmacological effect of oxcarbazepine. MHD is metabolized further by conjugation with glucuronic acid. Minor amounts (4% of the dose) are oxidized to the pharmacologically inactive 10,11-dihydroxy metabolite (DHD).

Elimination: Oxcarbazepine is cleared from the body mostly in the form of metabolites which are predominantly excreted by the kidneys. More than 95% of the dose appears in the urine, with less than 1% as unchanged oxcarbazepine. Fecal excretion accounts for less than 4% of the administered dose. Approximately 80% of the dose is excreted in the urine either as glucuronides of MHD (49%) or as unchanged MHD (27%); the inactive DHD accounts for approximately 3% and conjugates of MHD and oxcarbazepine account for 13% of the dose.

Special Populations and Conditions

- **Pediatrics:** After a single-dose administration of 5 or 15 mg/kg of oxcarbazepine, the dose-adjusted AUC values of MHD were 30% to 40% lower in children below the age of 8 years than in children above 8 years of age. The clearance in children greater than 8 years old approaches that of adults.

- **Geriatrics:** Following administration of single (300 mg) and multiple (600 mg/day) doses of oxcarbazepine to elderly volunteers (60 to 82 years of age), the maximum plasma concentrations and AUC values of MHD were 30% to 60% higher than in younger volunteers (18 to 32 years of age). Comparisons of creatinine clearance in young and elderly volunteers indicate that the difference was due to age- related reductions in creatinine clearance.

- **Sex:** No gender related pharmacokinetic differences have been observed in children, adults, or the elderly.

- **Pregnancy and Breast-feeding:** Due to physiological changes during pregnancy, MHD plasma levels may gradually decrease throughout pregnancy (see 7.1.1 Pregnant Women).

- **Genetic Polymorphism:** (See 7 WARNINGS AND PRECAUTIONS, Ancestry and Allelic Variation in the HLA-A Gene, Ancestry and Allelic Variation in the HLA-B Gene)

- **Ethnic origin:** No specific studies have been conducted to assess what effect, if any, race may have on the disposition of oxcarbazepine.

- **Hepatic Insufficiency:** The pharmacokinetics and metabolism of oxcarbazepine and MHD were evaluated in healthy volunteers and hepatically-impaired subjects after a single 900 mg oral dose. Mild-to-moderate hepatic impairment did not affect the pharmacokinetics of oxcarbazepine and MHD. No dose adjustment for APO-OXCARBAZEPINE is recommended in patients with mild-to-moderate hepatic impairment. The pharmacokinetics of oxcarbazepine and MHD have not been evaluated in severe hepatic impairment.

- **Renal Insufficiency:** There is a linear correlation between creatinine clearance and the renal clearance of MHD. When oxcarbazepine is administered as a single 300 mg dose in renally impaired patients (creatinine clearance <30 mL/min), the elimination half-life of MHD is prolonged to 19 hours, with a two fold increase in AUC. Dose adjustment for APO-OXCARBAZEPINE is recommended in these patients (see 7 WARNINGS AND PRECAUTIONS, Renal and 4.1 Dosing Considerations).

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15°C-30°C.

Keep APO-OXCARBAZEPINE out of the reach and sight of children.

There is no specific instruction for disposal.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

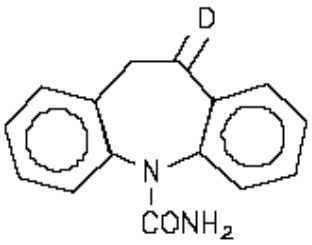
Drug Substance

Proper name: Oxcarbazepine

Chemical name: 10,11-Dihydro-10-oxo-5H-dibenz [*b,f*]azepine-5-carboxamide

Molecular formula and molecular mass: $C_{15}H_{12}N_2O_2$ (252.27 g/mol)

Structural formula:



Physicochemical properties:

Physical Form: White to faintly orange powder.

Solubility: and: Slightly soluble in chloroform, dichloromethane, acetone, methanol; practically insoluble in ethanol, ether, and water.

pKa and PH values: pKa = 13.73 ± 0.20 (Calculated using ACD Labs, vers. 6.0)
5.43 (1% solution in water)

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

14.1 Trial Design and Study Demographics

The effectiveness of oxcarbazepine as adjunctive and monotherapy for partial seizures in adults, and as adjunctive therapy in children aged 6 to 16 was established in 6 multicenter randomized, double-blind controlled trials.

The effectiveness of oxcarbazepine as monotherapy for partial seizures in children aged 6 to 16 was determined from data obtained in the studies described, as well as by pharmacokinetic/pharmacodynamic considerations.

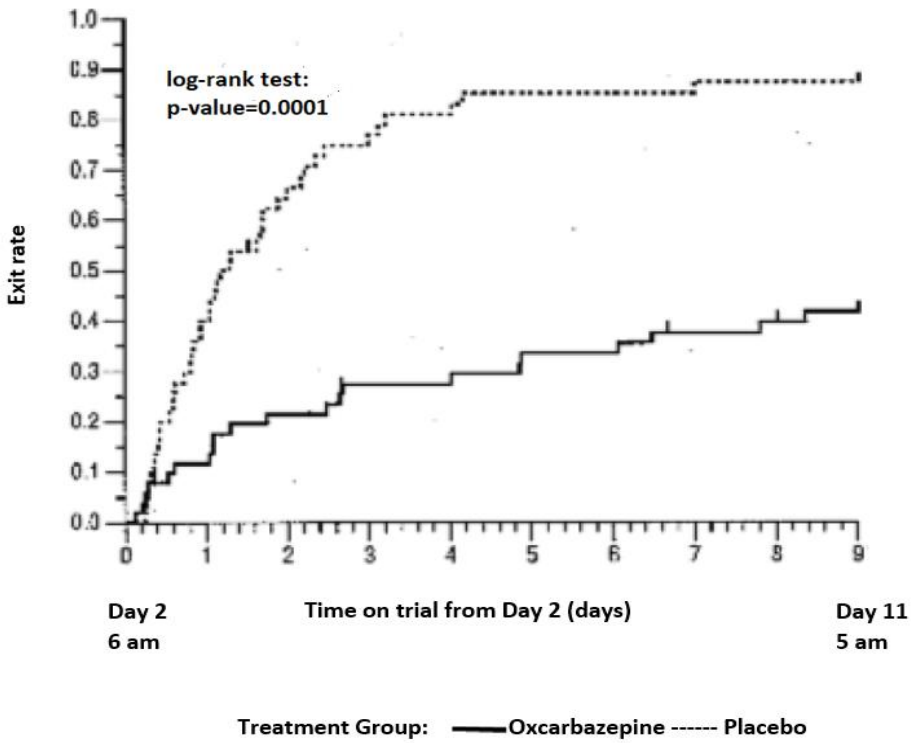
14.2 Study Results

Oxcarbazepine Monotherapy Trials

Four randomized, double-blind, multicenter trials demonstrated the efficacy of oxcarbazepine as monotherapy. Two trials compared oxcarbazepine to placebo and two trials used a randomized withdrawal design to compare a high dose (2400 mg) with a low dose (300 mg) of oxcarbazepine, after substituting oxcarbazepine 2400 mg/day for one or more antiepileptic drugs (AEDs). All doses were administered on a BID schedule.

One placebo-controlled trial was conducted in 102 patients (11 to 62 years of age) with refractory partial seizures who had completed an inpatient evaluation for epilepsy surgery. Patients had been withdrawn from all AEDs and were required to have 2 to 10 partial seizures within 48 hours prior to randomization. Patients were randomized to receive either placebo or oxcarbazepine given as 1500 mg/day on Day 1 and 2400 mg/day thereafter for an additional 9 days, or until one of the following three exit criteria occurred: 1) the occurrence of a fourth partial seizure, excluding Day 1, 2) two new-onset secondarily generalized seizures, where such seizures were not seen in the 1-year period prior to randomization, or 3) occurrence of serial seizures or status epilepticus. The primary measure of effectiveness was a between group comparison of the time to meet exit criteria. There was a statistically significant difference in favor of oxcarbazepine (see Figure 1), p=0.0001.

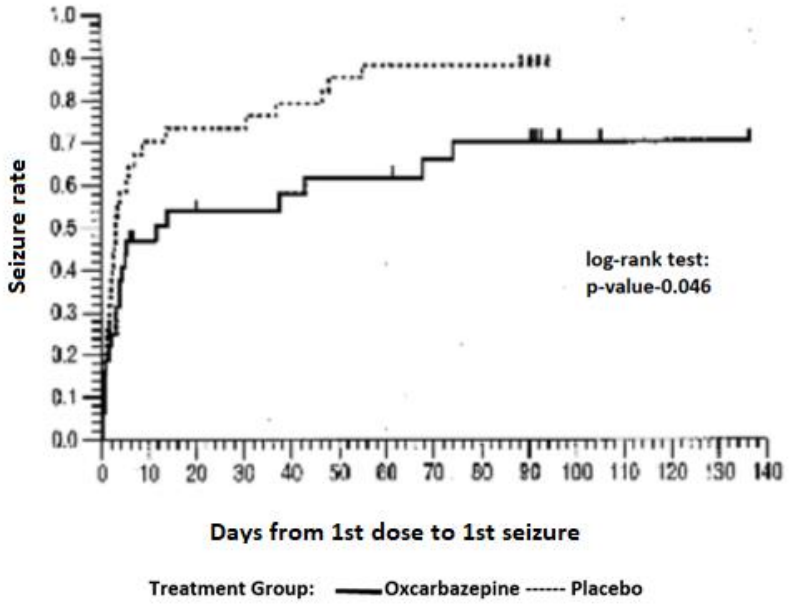
Figure 1 Kaplan-Meier Estimates of Exit Rate by Treatment Group



The second placebo-controlled trial was conducted in 67 untreated patients (8 to 69 years of

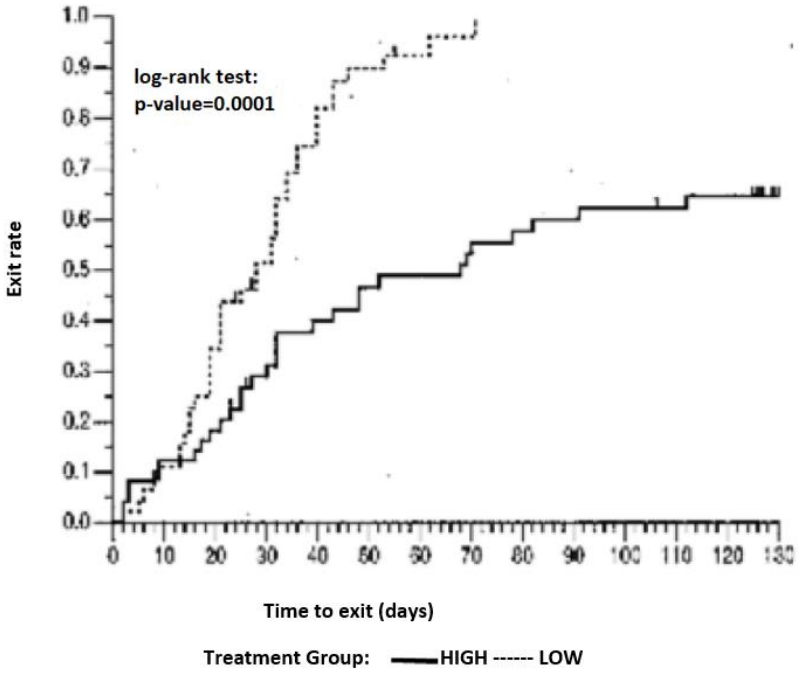
age) with newly-diagnosed and recent-onset partial seizures. Patients were randomized to placebo or oxcarbazepine, initiated at 300 mg BID and titrated to 1200 mg/day (given as 600 mg BID) in 6 days, followed by maintenance treatment for 84 days. The primary measure of effectiveness was a between group comparison of the time to first seizure. The difference between the two treatments was statistically significant in favor of oxcarbazepine (see Figure 2), p=0.046.

Figure 2 Kaplan-Meier Estimates of First Seizure Event Rate by Treatment Group



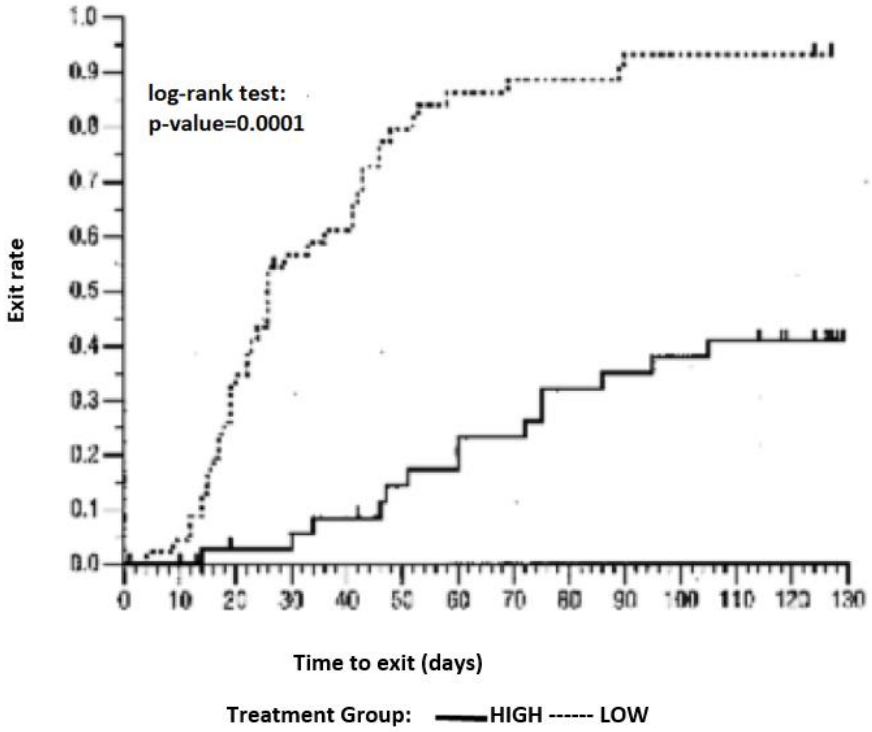
A third trial substituted oxcarbazepine monotherapy at 2400 mg/day for carbamazepine in 143 patients (12 to 65 years of age) whose partial seizures were inadequately controlled on carbamazepine (CBZ) monotherapy at a stable dose of 800 to 1600 mg/day, and maintained this oxcarbazepine dose for 56 days (baseline phase). Patients who were able to tolerate titration of oxcarbazepine to 2400 mg/day during simultaneous carbamazepine withdrawal were randomly assigned to either 300 mg/day of oxcarbazepine or 2400 mg/day oxcarbazepine. Patients were observed for 126 days or until one of the following 4 exit criteria occurred: 1) a doubling of the 28-day seizure frequency compared to baseline, 2) a two fold increase in the highest consecutive 2-day seizure frequency during baseline, 3) a single generalized seizure if none had occurred during baseline, or 4) a prolonged generalized seizure. The primary measure of effectiveness was a between group comparison of the time to meet exit criteria. The difference between the curves was statistically significant in favor of the oxcarbazepine 2400 mg/day group (see Figure 3), p=0.0001.

Figure 3 Kaplan-Meier Estimates of Exit Rate by Treatment Group



Another monotherapy substitution trial was conducted in 87 patients (11 to 66 years of age) whose seizures were inadequately controlled on 1 or 2 AEDs. Patients were randomized to either oxcarbazepine 2400 mg/day or 300 mg/day and their standard AED regimen(s) were eliminated over the first 6 weeks of double-blind therapy. Double-blind treatment continued for another 84 days (total double-blind treatment of 126 days) or until one of the 4 exit criteria described for the previous study occurred. The primary measure of effectiveness was a between group comparison of the percentage of patients meeting exit criteria. The results were statistically significant in favor of the oxcarbazepine 2400 mg/day group (14/34; 41.2%) compared to the oxcarbazepine 300 mg/day group (42/45; 93.3%) ($p<0.0001$). The time to meeting one of the exit criteria was also statistically significant in favor of the oxcarbazepine 2400 mg/day group (see Figure 4), p=0.0001.

Figure 4 Kaplan-Meier Estimates of Exit Rate by Treatment Group



Oxcarbazepine Adjunctive Therapy Trials

The effectiveness of oxcarbazepine as an adjunctive therapy for partial seizures was established in two multicenter, randomized, double-blind, placebo-controlled trials, one in 692 patients (15 to 66 years of age) and one in 264 pediatric patients (3 to 17 years of age). Patients in these trials were on 1 to 3 concomitant AEDs. In both of the trials, patients were stabilized on optimum dosages of their concomitant AEDs during an 8-week baseline phase. Patients who experienced at least 8 (minimum of 1 to 4 per month) partial seizures during the baseline phase were randomly assigned to placebo or to a specific dose of oxcarbazepine in addition to their other AEDs.

In these studies, the dose was increased over a 2-week period until either the assigned dose was reached, or intolerance prevented increases. Patients then entered a 14 (pediatrics) or 24 week (adults) maintenance period.

In the adult trial, patients received fixed doses of 600, 1200 or 2400 mg/day. In the pediatric trial, patients received maintenance doses in the range of 30 to 46 mg/kg/day, depending on baseline weight. The primary measure of effectiveness in both trials was a between group comparison of the percentage change in partial seizure frequency in the double-blind Treatment Phase relative to Baseline Phase. This comparison was statistically significant in favor of oxcarbazepine at all doses tested in both trials (p=0.0001 for all doses for both trials). The number of patients randomized to each dose, the median baseline seizure rate, and the median percentage seizure rate reduction for each trial are shown in Table 9. It is important to note that in the high dose group in the study in adults, over 65% of patients discontinued treatment because of adverse events; only 46 (27%) of the patients in this

group completed the 28-week study (see 8 ADVERSE REACTIONS), an outcome not seen in the monotherapy studies.

Table 9 Summary of Percentage Change in Partial Seizure Frequency from Baseline for Placebo-controlled Adjunctive Therapy Trials

Trial	Treatment Group	N	Baseline Median Seizure Rate†	Median % Reduction
1 (pediatrics)	Oxcarbazepine	136	12.5	34.8[1]
	Placebo	128	13.1	9.4
2 (adults)	Oxcarbazepine 2400 mg/day	174	10	49.9[1]
	Oxcarbazepine 1200 mg/day	177	9.8	40.2[1]
	Oxcarbazepine 600 mg/day	168	9.6	26.4[1]
	placebo	173	8.6	7.6

[1]p=0.0001; †=# per 28 days

Subset analyses of the antiepileptic efficacy of oxcarbazepine with regard to gender in these trials revealed no important differences in response between men and women. Because there were very few patients over the age of 65 in controlled trials, the effect of the drug in the elderly has not been adequately assessed.

14.3 Comparative Bioavailability Studies

A randomized, two-treatment, two-period, single oral dose (1 x 600 mg), crossover comparative bioavailability study of APO-OXCARBAZEPINE tablets, 600 mg (Apotex Inc.) and TRILEPTAL® tablets, 600 mg (Novartis Pharmaceuticals Inc.), was conducted in healthy, adult male subjects under fasting conditions. Comparative bioavailability data from 25 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Oxcarbazepine (1 x 600 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng·h/mL)	9394.04 9768.06 (28)	9224.90 9583.51 (28)	101.8	96.6 – 107.4
AUC_I (ng·h/mL)	10081.23 10462.48 (27)	9861.50 10240.97 (28)	102.2	96.9 – 107.8
C_{max} (ng/mL)	2182.67 2407.84 (45)	2314.48 2520.77 (43)	94.3	82.7 – 107.6

Oxcarbazepine (1 x 600 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
T_{max}[3] (h)	1.98 (49)	1.76 (58)		
$T_{½}$[3] (h)	11.56 (23)	11.74 (26)		

[1] APO-OXCARBAZEPINE (oxcarbazepine) tablets, 600 mg (Apotex Inc.)
[2] TRILEPTAL® (oxcarbazepine) tablets, 600 mg (Novartis Pharmaceuticals Inc., Canada)
[3] Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Detailed pharmacology

The clinical effects of established and new AEDs are achieved by their actions at neurotransmitter receptors or on ion channels. The main targeted mediators of neuronal excitability are $GABA_A$ receptor channels, voltage-dependent sodium channels and T-type calcium channels. In humans, oxcarbazepine is rapidly and almost completely reduced to the pharmacologically active 10-monohydroxy derivative (10-hydroxy-10, 11-dihydro-10-oxo-5H- dibenz[b,f]azepine-5-carboxamide; GP 47779; MHD) without epoxide formation.

There are three possible anticonvulsant mechanisms of action reported for oxcarbazepine and/or MHD:

- blockade of voltage-dependent sodium channels,
- decrease of high-voltage activated calcium currents and
- interaction with potassium channels.

The first, blockade of voltage-dependent sodium channels in the brain, is regarded as being the most plausible mechanism. At therapeutic concentrations, both oxcarbazepine and MHD limited sustained high frequency repetitive firing (SRF) of sodium-dependent action potentials of cultured mouse neurones. This effect, also seen with carbamazepine, phenytoin and lamotrigine, could contribute to blocking the spread of seizure activity from an epileptic focus. Both oxcarbazepine and MHD displayed similar activity in this model, with Half maximal effective concentration EC_{50s} of 5×10^{-8} and 2×10^{-8} M, respectively.

The following *in vitro* studies demonstrated anticonvulsant effects:

- MHD and oxcarbazepine limited SRF of action potentials of cultured neurones,
- MHD and lamotrigine decreased the field potential amplitude in rat neocortical slices at concentrations of 3×10^{-6} to 2×10^{-4} M in the presence or absence of magnesium. Therefore, and contrary to felbamate which was effective only in magnesium free solution, this effect was not mediated by NMDA.
- MHD in concentrations ranging from 3×10^{-6} to 10^{-4} M inhibited glutaminergic excitatory postsynaptic potentials (intracellular studies using striatal neurons in corticostriatal slices) and oxcarbazepine inhibited the veratridine-stimulated release of glutamate and other transmitters (rat brain slices; Half maximal inhibitory concentration $IC_{50} = 4 \times 10^{-5}$ M).

MHD is a racemic mixture, consisting of the S(+)[CGP 13751] and R(-)[CGP 13698] enantiomers. Formation of MHD is stereospecific with the two enantiomers formed in humans in a ratio of 80% (S-MHD) to 20% (R-MHD). MHD, R(-) and S(+) had similar anticonvulsant profiles and potencies in the maximal electroshock (MES), pentylenetetrazole (PTZ), picrotoxin and strychnine tests, when administered orally or i.v. Generally, none of the three compounds appeared superior to the others with regard to their anticonvulsant profile irrespective of the route of administration. The enantiomers R(-) and S(+) were tested for anticonvulsant activity in an *in vitro* system that minimized the possibility of metabolic reactions including oxidation to oxcarbazepine. Epileptiform discharges induced by penicillin in rat hippocampal slices were suppressed equally well and in a concentration-dependent manner (10^{-4} to 5×10^{-4} M) by MHD, R(-) and S(+). These findings strongly support the conclusions drawn from *in vivo* tests, that the racemate and each of the enantiomers have a similar anticonvulsant profile. Overall, the *in vitro* and *in vivo* pharmacological data indicate that the therapeutic profiles of these compounds would be similar in clinical use.

The two most widely used, reliable and reproducible *in vivo* tests in rodents for the prediction of clinical antiepileptic activity, the maximal electroshock and the pentylenetetrazole test, were applied to oxcarbazepine and MHD. In addition, the picrotoxin and strychnine tests, kindling evolution and cat and monkey models for partial seizures were used to provide supporting evidence for the anticonvulsant profile of oxcarbazepine and MHD.

The maximal electroshock (MES) test evaluates the ability of drugs to prevent electrically induced tonic hindlimb extension seizures in rodents. Efficacy in this model has been shown to correlate with ability to prevent partial and generalized tonic-clonic seizures in man, and it is stated that this model evaluates the capacity of a drug to prevent seizure spread. Drugs that are mainly active in the MES test, e.g., carbamazepine, phenytoin and lamotrigine, often also interact with voltage-dependent sodium channels.

In the MES test in rodents, orally administered oxcarbazepine and MHD were potent and efficacious compared to standard and new antiepileptic drugs in clinical use. The duration of anticonvulsant action lasts for about 8h. Oxcarbazepine and MHD did not show tolerance towards their anticonvulsant effect in the MES test in mice and rats.

The pentylenetetrazole (PTZ) test generally evaluates the ability of potential antiepileptic drugs to prevent clonic seizures and may also correlate with activity against absence seizures. Such seizures were blocked by both oxcarbazepine and MHD at ED_{50s} of 30 to 52 mg/kg p.o. (i.e., higher ED_{50s} when compared with the MES test).

In rats of 7, 12, 18, 25 and 90 days of age, oxcarbazepine and MHD (5 to 60 mg/kg i.p.) did not affect the incidence of clonic seizures induced by PTZ (100 mg/kg s.c.), but suppressed tonic seizures in all age groups. This parallels the findings in the MES test and indicates that the anticonvulsant properties of oxcarbazepine and MHD are comparable in developing, juvenile and adult animals.

Unlike other AEDs such as carbamazepine, phenytoin, phenobarbitone, primidone, valproic acid, and diazepam, which are metabolized by the cytochrome P450 oxidase system, oxcarbazepine undergoes primarily reductive biotransformation. Therefore, oxcarbazepine has a decreased propensity to induce oxidative enzymes and a reduced potential for drug-drug interactions.

Toxicology

Acute Toxicity

Acute toxicity studies were performed with oxcarbazepine (GP 47680) and its major human metabolite (GP 47779). The results indicate that GP 47680 and GP 47779 were practically non- toxic when given by single-dose administration to mice, rats, hamsters, rabbits or dogs.

Acute oral toxicity

Species	Route	N/dose	Dose (mg/kg)	LD50
GP 47680 (Synthesis 1)				
Mice	oral gavage	5M/5F	100, 300, 1000, 3000, 4500 or 6000 in 2% CMC or at 5000 in acacia	in CMC: 5000 (3900-6500) In acacia: > 5000
Mice	oral gavage	5M/5F	0.1, 1, 10, 100, 300, 1000, 2000, 3000 or 6000 in 0.5% CMC-Na	> 6000
Rats	oral gavage	5M/5F	100, 300, 1000, 3000, 4500 or 6000 in 2% CMC	> 6000
Rats	oral gavage	1 to 5 M/ 1 to 5 F	100, 300, 1000, 3000, 4500 or 6000 in 2% CMC or at 5000 in acacia	In 2% CMC: > 6000 In acacia: > 5000
Rats	oral gavage	5M/5F	0.1, 1, 10, 100, 300, 1000, 3000 or 6000 in O.5% CMC-Na	> 6000
Rats	oral gavage	5M/5F	0 or 1800 as a 6% suspension in syrup	> 1800
Hamsters	oral gavage	5M/5F	3000 or 6000 in 0.5% CMC-Na	> 6000
Rabbits	oral gavage	3M/3F	5000 in acacia	> 5000
Beagle dogs	oral gavage	1F	0, 600 or 1200 as a 6% suspension in syrup	
Mice	i.p.	5M/5F	0.1, 1, 10, 100, 1000, 3000, 4000, 4500, 5000 or 6000 in 0.5% CMC-Na	4310 (4070-4560)
Rats	i.p.	5M/5F	0.1, 1, 10, 100, 1000, 3000, 4000 or 6000 in 0.5% CMC-Na	4130 (3600-4740)
GP 47779 (Synthesis 1)				
Mice	oral gavage	5M/5F	10, 100, 300, 600, 1000, 2000 or 3000 in 0.7% CMC	1240 (960-1600)
Rats	oral gavage	5M/5F	10, 100, 300, 600, 1000, 3000, 4500 or 6000 in 0.7% CMC	4520 (3620-5630)
Neonatal rats	oral gavage	10	10, 100, 150, 200, 250, 300, 600, 1000 or 3000 in 0.7% CMC	205 (183-229)
Hamster	oral gavage	5M/5F	10, 30, 100, 300, 600, 1000, 3000 or 6000 in 0.7% CMC	> 6000
Dogs	oral capsule	1M/1F	30, 100, 300 or 1000	Doses ≥ 100 were emetic
Rabbits	i.v.	2M/2F	3, 10, 30, 60, 100, 200 or 300 in PEG 400	100 to 200 (M) 100 to 300 (F)
Dogs	i.v.	1M/1F	3, 10, 30, 100 or 200 in PEG 400	> 200
Mice	i.p.	10M/10 F	10, 30, 100, 150, 200, 250, 300, 350, 400, 600 or 800 in 0.7% CMC	338 (320-358)
Rats	i.p.	10M/10 F	10, 100, 300, 400, 500, 600, 700, 1000, 3000 or 6000 in 0.7% CMC	484 (448-524)

Sub-Acute and Chronic Toxicity

Sub-acute and chronic toxicity studies were performed with oxcarbazepine (GP 47680) and its major human metabolite (GP 47779). In chronic toxicity studies in rats and dogs, the only significant effects were sedation, ataxia, tremors and lack of body weight gain at higher doses. These represented exaggerated pharmacological effects and they are manifested in patients as ataxia, headache, dizziness and somnolence. Other findings were encountered in animals at high doses, but are not considered relevant for patients. The most important of these was hepatic microsomal enzyme induction and consequent hepatotoxicity. As enzyme induction is not a feature of oxcarbazepine therapy, liver toxicity is not a relevant safety issue for patients.

Evidence of nephrotoxicity was noted in the repeated dose toxicity rat studies but not in dog or mice studies.

Immunostimulatory tests in mice showed that MHD (and to a lesser extent oxcarbazepine) can induce delayed hypersensitivity.

The synthesis of GP 47680 was altered during the course of development. Since the impurity profile and particle size of the material synthesized by the new method differed from those of batches prepared using the original synthesis, pivotal toxicity studies were repeated to ascertain whether these differences altered the toxic properties of the end product. The results (not presented here) indicate that material from both synthetic processes have similar toxicity profiles.

In general the toxicity tests conducted with GP 47779 produced qualitatively similar alterations to those that occurred with GP 47680.

Special studies employing GP 47680 (primary dermal irritation, primary ocular irritation) and GP 47779 (intravenous irritation, intraarterial in rabbit and an *in vitro* hemolysis test in dogs) showed no significant adverse effects.

Species	Route	Dose mg/kg/d	N/dose	Duration	Findings
GP 47680 Synthesis 1					
Mice	oral, feed	0, 600, 1800 or 6000 ppm	5M/5F	3 months	≥ 600 ppm: ↑ alanine aminotransferase and aspartate aminotransferase activities (F); and hepatocellular hypertrophy and hepatocyte necrosis (M). ≥ 1800 ppm: ↑ cholesterol, total protein, and total globulin (M); ↑ absolute and relative liver weights (M,F); and hepatocellular hypertrophy and hepatocyte necrosis (F). 6000 ppm: ↑ alanine aminotransferase activity (M); ↑ cholesterol and total protein (F); ↑ absolute and relative spleen weights (F); and fatty change in the centrilobular region of the liver and nuclear inclusion bodies (M,F). Most changes dose-dependent in severity and/or incidence. Toxicological changes restricted to the liver.
weanling rats	oral gavage	0, 300, 600 or 1000 in 0.5% CMC-Na	10M/10F	10 days	≥ 300: Inhibition of spontaneous motility, sedation, and ataxia; and macroscopic evidence of single or multiple ulcerations/erosions of the gastric mucosa. ≥ 600: Muscular hypotonia, stiff movements, dyspnea, and piloerection; and ↓ body weight gain. 1000: ↓ blood glucose. No histopathologic organ/tissue changes were evident. With the exception of decreased body weight gains in the mid- and high-dose M, all changes were reversible.

Species	Route	Dose mg/kg/d	N/dose	Duration	Findings
Rats	Oral gavage	0, 100, 300, 1000 or 3000 in 0.5% CMC-Na	10M/10 F	90 days	100 mg/kg: Asymptomatic. ≥ 300: Hair loss (F); ↑ absolute and relative liver weights (M,F); grossly enlarged livers (M,F); and microscopic evidence of slight to marked hepatocellular hypertrophy, and cytoplasmic eosinophilic droplets in occasional hepatocytes (M,F). ≥ 1000: Ataxia, muscle weakness, sedation, reduction of spontaneous motility, and rough fur (M,F); and ↓terminal body weight (M,F). 3000: Salivation (M,F); and microscopic evidence of occasional monocellular necrosis of hepatocytes (M,F). All changes reversible by the end of the follow-up period.
Rats	Oral Feed	0, 100, 300 or 1000	10-25 M/ 10-25F	6 months	≥100 mg/kg: Fluctuations in food consumption (M,F); ↓ mean body weight (F); ↑ BUN (M,F); ↑ ALAT activity (M); ↓ alkaline phosphatase (M); ↑ absolute and relative liver weights (M,F); ↑ relative kidney weights (F); grossly enlarged livers (M); microscopic evidence of liver changes characterized by hypertrophy (F); microscopic evidence of kidney changes characterized by hyaline droplet and cast formation within dilated cortical tubules (M). ≥300 mg/kg: ↑ relative kidney weights (M); ↓ absolute adrenal weights (F); grossly enlarged kidneys (F); microscopic evidence of liver changes characterized by nuclear pyknosis (M, F-300 mg/kg only), and cloudy swelling and hypertrophy (M); microscopic evidence of kidney changes characterized by epithelial hyperplasia and endogenous pigment in the proximal convoluted tubules (M), and hyaline droplet and cast

Species	Route	Dose mg/kg/d	N/dose	Duration	Findings
					formation within dilated cortical tubules (F). 1000 mg/kg: ↓ mean body weight (M); ↑ absolute and relative adrenal weights (M); ↑ relative adrenal weight (recovery F); grossly enlarged livers (F); microscopic evidence of liver changes characterized by endogenous pigment in the Kupffer cells (M) and hepatocytes (F), and vacuolar degeneration (F); microscopic evidence of kidney changes characterized by glomerular fibrosis and vacuolar epithelial degeneration of cortical tubules (M), and epithelial hyperplasia and endogenous pigment in the proximal convoluted tubules (F). With the exception of increases in BUN, relative adrenal weight (females), relative liver weights and the presence of hyaline casts (both sexes), hyaline droplets within dilated tubules (males), and epithelial hyperplasia in the proximal convoluted tubules (males) at 1000 mg/kg, all changes were reversible by the end of the recovery period.
Dogs	Oral Gelatin Capsules	600	2M/2F	10 days	Stiff movements, exaggerated gait (steppage), and slight sedation and mydriasis; ↓ body weight and food consumption; ↑ alanine aminotransferase activity, aspartate aminotransferase activity and alkaline phosphatase; ↓ hemoglobin, erythrocytes, and slight leukocytosis; and ↑ absolute and relative liver weights. No treatment-related gross or microscopic organ/ tissue changes were evident.
Dogs	Oral Gelatin Capsules	0, 60, 200, 200 or 600	3M/3F	3 months	≥60 mg/kg: ↑ liver weights (M,F). ≥200 mg/kg: Microscopic evidence of an ↑ in hemosiderin in the Kupffer cells of the liver (M,F).

Species	Route	Dose mg/kg/d	N/dose	Duration	Findings
					600 mg/kg: Various occurrences of emesis (M,F); ↑ alanine aminotransferase and aspartate aminotransferase activities (M); microscopic evidence of an ↑ in hemosiderin in the kidney (M,F). There were no treatment-related changes in any of the recovery animals.
Dogs	Oral Gelatin Capsule	0, 60, 200 or 600 →400*	8M/8F	6/12 months	≤200 mg/kg: Asymptomatic. 600→400 mg/kg: ↓ food consumption (F); slower body weight gain (F); and slight atrophy of thymic tissue in interim-sacrifice animals (F).

*The high-dose level was reduced to 400 mg/kg after 33 days of dosing due to reductions in food consumption

Species	Route	Dose mg/kg/d	N/dose	Duration	Findings
GP 47779 (synthesis 1)					
Rats	oral gavage	0, 200, 600 or 2000 in 2% CMC	10-15M/ 10-15F	3 months	≥ 200 mg/kg: ↑ mean absolute and relative liver weights; and microscopic evidence of centrilobular hepatocellular hypertrophy. ≥ 600 mg/kg: Sedation, lethargy, abnormal stance when moved, and distention of the abdomen with tenseness of the musculature; retardation in growth rates; and microscopic evidence of occasional necrotic hepatocytes. 2000 mg/kg: ↓ food consumption; ↑ alanine aminotransferase activity and slight thrombocytopenia; and microscopic evidence of excess pigment in the liver cells. All changes at least partially reversible by end of recovery period. Hepatic changes attributed to occurrence of enzyme induction.

Species	Route	Dose mg/kg/d	N/dose	Duration	Findings
Rats	Oral feed	0, 52, 164 or 549 (M) or 0, 57, 187 or 606 (F)	30M/30F	6 months	≥ 52/57 mg/kg: Dose-related ↓ in mean body weight gain and food consumption; and ↑ mean thrombin time. ≥ 187 mg/kg: ↑ mean alanine aminotransferase and alkaline phosphatase (F). No treatment-related gross or microscopic organ/tissue changes All treatment-related clinical changes reversible by end of recovery
Dogs	Oral Capsules	0, 60, 200 or 600→400 *	3M/3F	3 months	60 mg/kg: Asymptomatic. Transient muscle tremors in 1F only; depression in growth rates of 2 dogs. ≥ 200 mg/kg: Ataxia, lethargy, muscle or whole body tremors, salivation, and vomiting; ↓ food intake and/or body weight; mild to marked anemia in individual animals; microscopic evidence of extramedullary hemopoiesis of the spleen & hemosiderin in renal proximal convoluted epithelium. 600→400 mg/kg: ↑ serum Na and ↓ serum K and albumin in individual animals; ↓ absolute and relative heart weights; gross evidence of lack of body fat, distended or enlarged gallbladders, enlarged spleen, and atrophic & hemorrhagic thymus; microscopic evidence of centrilobular hepatocellular changes, marked extramedullary hemopoiesis in the spleen, thymic atrophy, moderate increases in pigment granules in the convoluted epithelium of the kidney, & ↓ spermatogenesis. All changes reversible during recovery period.

Species	Route	Dose mg/kg/d	N/dose	Duration	Findings
Dogs	Oral Capsule	0, 30, 100 or 300→200**	8M/8F	6-12 months	≥ 30 mg/kg: Ataxia and tremors; and ↑ serum Na ≥ 100 mg/kg: Emesis, salivation, depression, decreased activity, opisthotonos, stiff muscles, dilated pupils, tearing, depressed righting reflex, and increased respiration; ↑ alkaline phosphatase; ↓ erythrocytic parameters; and ↑ absolute and relative liver weights. 300→200 mg/kg: ↓ locomotor activity/lethargy, recumbency/prostration, nystagmus, thinness, jerky head movements/bobbing head, instability, ptosis, relaxed nictitating membrane, exophthalmus, anorexia, and dehydration; transient, initial body weight loss, depressed body weight gain and total food consumption; and ↓ reticulocyte counts. No evident treatment-related gross or microscopic organ/ tissue changes. Majority of compound-related changes reversible by end of recovery period.
Rats	i.v.	0, 5, 12.5 or 25 in 5% glucose solution	5M/5F	14 days	5 mg/kg: No significant findings. ≥ 12.5 mg/kg: Irregular respiration almost daily in all animals shortly after dosing.

Species	Route	Dose mg/kg/d	N/dose	Duration	Findings
Dogs	i.v.	3 or 10 in 5% glucose solution	3M/3F	14 d	≥ 3 mg/kg: Transient clinical signs of minimal to slight emesis, diarrhea and salivation. 10 mg/kg: Histopathological findings of minimal to slight atrophy of thymus (M), likely stress-induced, secondary to the clinical signs. No mortalities and no effects on body weight or food consumption, or on ophthalmology, neurology, cardiography or clinical pathology parameters. Minimal to slight treatment-related clinical signs correlate with CNS-stimulation and not considered to be of toxicological relevance.
Rats	Oral gavage	0, 50, 200, 600 or 2000 in 0.5% CMC-Na	10-12M/ 10-12F	13 weeks	≥ 50 mg/kg: ↑ water consumption (M,F); echinocytosis, polyuria and proteinuria (M,F); ↑ albumin (M); ↑ bile acids, total protein, globulin and calcium (F); ↓ eosinophil count (M); and ↑ mean absolute and relative liver weights (M,F). ≥ 200 mg/kg: Dry/wet perineal staining and salivation (F); ↑ total cholesterol (M,F); ↑ bile acids, total protein, calcium and inorganic phosphorus (M); ↑ total bilirubin and albumin (F); and hepatocellular hypertrophy (M,F).

Species	Route	Dose mg/kg/d	N/dose	Duration	Findings
					≥ 600 mg/kg: Ataxia, dehydration and hypoactivity (M,F); gasping, salivation and wet perineal staining (M); inactivity and lacrimation (F); ↓ mean body weight and percent body weight gain (M); ↑ hemoglobin, MCH, MCV and gamma-GT (M); ↑ inorganic phosphorus (F); ↓ glucose and triglyceride concentrations (M,F); ↓ prothrombin time (M); and nephropathy (M). 2000 mg/kg: Mortality (2M and 1F); rales, recumbency, and stains on fur (M,F); inactivity, lacrimation and dry perineal staining (M); gasping (F); ↓ mean body weight and percent body weight gain (F); ↓ mean food consumption (M,F); ↑ hematocrit and total bilirubin (M); ↑ MCV and gamma-GT (F); ↓ WBC and lymphocyte counts (M,F); and ↓ eosinophil count (F).

Carcinogencity

Carcinogenicity studies with a duration of 104 weeks were performed in rats and mice with GP 47680 and rats with GP 47779. Treatment with GP 47680 resulted in dose-related slight increases in the incidence of liver cell tumors. These consisted of benign hepatomas in the mouse and hepatic preneoplastic and neoplastic changes in the rat. Carcinogenicity was presumed to result from liver enzyme-inducing and presumed promoting properties of GP 47680. In the GP 47779 study, treatment-related findings were observed primarily in the liver, testis, cervix, vagina and thyroid. In the liver, proliferative hepatocellular changes included foci of cellular alterations, increases in the incidence of hepatocellular adenomas and/or carcinomas, regenerative hyperplasia, centrilobular hypertrophy, vacuolation, hemorrhagic necrosis, and/or cystic degeneration. In the testis, a marginal increase in the incidence of benign interstitial cell tumors was seen. An increased incidence of granular cell aggregates or tumors in the cervix and vagina was also noted.

Thyroid follicular hyperplasia/hypertrophy was observed in both sexes. Liver cell tumors which have been reported in the Carbamazepine study as “hepatomas” or in the Oxcarbazepine study as “benign neoplastic nodule” or “malignant hepatocellular carcinoma” can be considered similar with respect to the histology and biological behavior. Thus, treatment with Carbamazepine, Oxcarbazepine or GP 47779 resulted in identical type of liver lesions in rats upon long term treatment, although there was also evidence of a hepatotoxic component in the GP 47779 study. In addition, a promotion study with GP 47680 was conducted to determine, experimentally, the influence of GP 47680 on the formation of focal proliferative changes in the rat liver. Phenobarbital served as a reference compound. Following initiation with N-nitrosodiethylamine, the development of GGT-positive foci was enhanced by Phenobarbital (a known promotor of the development of foci of altered hepatocytes) and by GP 47680 in a similar manner with regard to the number and the size of the foci observed. Exposure of 2000 ppm GP 47680 was similar to the exposure of 500 ppm Phenobarbital with respect to the foci-enhancing (“promoting”) effects produced. The proliferative hepatic changes are accompanied by enzyme induction which may be linked to the thyroid follicular hyperplasia/hypertrophy seen in the study with GP 47779. They are, therefore, of little clinical relevance since the inductive effects of Oxcarbazepine are much less pronounced in patients. The proliferative testicular changes were observed previously in a long-term rat study with Carbamazepine, but not in the study with Oxcarbazepine. The rat testis is known to be uniquely sensitive to trophic stimuli of interstitial cells, so these tumors are of little clinical relevance. The etiology of the tumors in the female reproductive tract is unclear, but could be related to altered reproductive hormone metabolism, as a result of the hepatic enzyme induction; an increased incidence of acyclic cytology was noted in the rat fertility study with GP 47779, which could be an indication that treatment with GP 47779 does alter hormone homeostasis.

Mutagenicity

In a series of *in vitro* and *in vivo* mutagenicity tests, GP 47680 prepared by synthesis 1 or 2 was devoid of mutagenic potential with the exception of one study (chromosome study on Chinese hamster ovary cells) that revealed chromosomal aberrations considered a consequence of disturbance of the spindle apparatus rather than a result of interaction of

the test material with DNA. These effects were not evident in experiments lasting 18 hours (without activation) and those lasting 3 hours (with activation) and followed by a 15 or 39 day recovery period. GP 47779 was devoid of mutagenic, clastogenic or aneugenic effects.

Reproductive Studies

There were no adverse effects on male or female rat fertility at doses up to and including 150 mg/kg (oxcarbazepine) and 450 mg/kg/day (MHD).

In standard reproductive toxicity studies in rodents and rabbits, maternally toxic doses of both oxcarbazepine and MHD caused some increase in the incidence of embryo-fetal mortality and/or some delay in antenatal and/or postnatal growth of the offspring. There was an increase in rat fetal malformations in one of the eight embryo-fetal toxicity studies conducted with oxcarbazepine and MHD, at a dose (1000 mg/kg) which caused extreme maternal toxicity.

Oxcarbazepine and MHD cross the placenta. Neonatal and maternal plasma MHD concentrations were similar in one case.

The overall evidence from all animal studies indicates that oxcarbazepine has minor teratogenic potential at doses relevant to humans.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrTRILEPTAL® Tablets, 300 mg and 600 mg, oral, submission control 278353, Product Monograph, Novartis Pharmaceuticals Canada Inc. SEP 24, 2024.

2. PrTRILEPTAL® Tablets, 150 mg, 300 mg and 600 mg, oral, submission control 208369, Product Monograph, Novartis Pharmaceuticals Canada Inc. OCT 24, 2017.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APO-OXCARBAZEPINE

Oxcarbazepine Tablets

Read this carefully before you start taking **APO-OXCARBAZEPINE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-OXCARBAZEPINE**.

Serious Warnings and Precautions

- **Blood Disorders:** APO-OXCARBAZEPINE has been reported to cause serious adverse effects such as:
  - agranulocytosis (low white blood cell levels),
  - aplastic anemia (when cells meant to develop into mature blood cells are damaged),
  - leucopenia (low white blood cell levels),
  - thrombocytopenia (low blood platelet levels), and
  - hepatitis (inflammation of the liver).

Your healthcare professional will closely monitor your health for potential signs and symptoms of these blood disorders. If bone marrow depression appears, your healthcare professional may stop your treatment with APO-OXCARBAZEPINE.

- **Skin Reactions:** APO-OXCARBAZEPINE can also cause serious and sometimes fatal skin reactions such as:
  - Stevens-Johnson Syndrome (SJS),
  - Toxic Epidermal Necrolysis (TEN),
  - Drug Reaction withEosinophilia And Systemic Symptoms (DRESS),
  - Acute Generalized Exanthematous Pustulosis (AGEP), and
  - maculopapular rash.

Some of these skin reactions are genetically linked, especially if you are of Asian descent. Your healthcare professional may perform a blood test to determine if APO-OXCARBAZEPINE is suitable for you.

- Tell your healthcare professional right away if you notice or develop a rash or any serious skin reactions. This can include red skin, blistering of the lips, eyes or mouth, and skin peeling accompanied by fever. Your healthcare professional may stop your treatment with APO-OXCARBAZEPINE.

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

What is APO-OXCARBAZEPINE used for?

APO-OXCARBAZEPINE is used alone or with other medicines to treat partial seizures in adults and children (6 to 16 years of age).

How does APO-OXCARBAZEPINE work?

APO-OXCARBAZEPINE is an anticonvulsant or antiepileptic drug used to treat epilepsy. It is thought to work by keeping the brain's "overexcitable" nerve cells under control. This may help to suppress or reduce the frequency of partial seizures.

What are the ingredients in APO-OXCARBAZEPINE?

Medicinal ingredient: Oxcarbazepine

Nonmedicinal ingredients:
Colloidal silicon dioxide, crospovidone, ferric oxide yellow, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methylcellulose, polyethylene glycol and titanium dioxide.

APO-OXCARBAZEPINE comes in the following dosage forms:

Tablets: 150 mg, 300 mg and 600 mg.

Do not use APO-OXCARBAZEPINE if:

- you are allergic to oxcarbazepine, eslicarbazepine acetate (an ingredient related to oxcarbazepine), or any of the other ingredients in APO-OXCARBAZEPINE**.**

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-OXCARBAZEPINE. Talk about any health conditions or problems you may have, including if you:

- have a history of allergic reactions to carbamazepine (such as a rash);
- have or had kidney problems;
- have or had liver problems;
- have or had heart problems;
- are of an Asian descent;
- are taking other antiepileptic medicines (used to treat epilepsy);
- are pregnant or plan to become pregnant;
- are breastfeeding or plan to breastfeed;
- are taking diuretic medicines (used to get rid of salt and water by increasing the amount of urine produced);
- have low sodium levels in your blood level;
- have a history, or family history, of bone disease.

Other warnings you should know about:

APO-OXCARBAZEPINE can cause the following:

- **Bone disorders:** Treatment with antiepileptic drugs, such as oxcarbazepine, for long periods can decrease bone mineral density. This may lead to weakened or brittle bones.

- **Hyponatremia** (low sodium levels in the blood)**:** Treatment with APO-OXCARBAZEPINE can cause hyponatremia. Your healthcare professional will monitor you/your child closely for signs and symptoms of hyponatremia. They may decide to reduce or stop your treatment with APO-OXCARBAZEPINE.

- **Hypothyroidism** (underactive/low thyroid): Treatment with APO-OXCARBAZEPINE can cause hypothyroidism. Your healthcare professional will monitor the status of your thyroid hormone levels, especially in children. They may decide to reduce or stop your treatment with APO-OXCARBAZEPINE.

- **Mental and motor impairment:** Treatment with APO-OXCARBAZEPINE can affect your mental and motor performance. This can cause difficulty with concentration, speech problems, language problems, drowsiness, fatigue, coordination abnormalities, ataxia, and walking problems. Tell your healthcare professional if you experience any of these symptoms.

- **Seizure aggravation:** Treatment with APO-OXCARBAZEPINE has been associated with seizure aggravation, especially in children. If you notice you are having more seizures or changes in the pattern of your seizures, tell your healthcare professional right away. They will determine if your dose should be reduced or stopped.

- **Suicidal thoughts or behaviour:** Antiepileptic drugs, such as APO-OXCARBAZEPINE, can increase the risk of suicidal thoughts and behaviours (harming or killing themselves). If at any time you have these thoughts, contact your healthcare professional right away.

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

Pregnancy:

If you are able to get pregnant, plan to become pregnant, are pregnant, or are taking hormonal birth control, there are specific risks you should discuss with your healthcare professional.

- APO-OXCARBAZEPINE can affect hormonal birth control drugs such as “the pill”. Therefore, you should use either a different method of birth control or an additional non-hormonal method while you are taking APO-OXCARBAZEPINE. This should help to prevent an unwanted pregnancy. Tell your healthcare

professional right away, if you get irregular vaginal bleeding or spotting. If you have any questions about this, talk to your healthcare professional.

- There may be a risk to your baby if you take antiepileptic drugs during pregnancy. Tell your healthcare professional if you are pregnant or plan to become pregnant. They will discuss the benefits and potential risks with you, and help you to decide whether you should take APO-OXCARBAZEPINE.

- Taking APO-OXCARBAZEPINE during pregnancy can also affect the amount of oxcarbazepine in your blood. Your healthcare professional may recommend regular blood testing during your pregnancy to check that APO-OXCARBAZEPINE is appropriately controlling your seizures.

- Antiepileptic drugs, such as APO-OXCARBAZEPINE, can decrease your levels of folic acid. This can lead to fetal abnormality. Your healthcare professional may recommend taking folic acid supplements before and during pregnancy.

- Stopping APO-OXCARBAZEPINE abruptly can worsen your seizures. **Do not stop your treatment with APO-OXCARBAZEPINE during pregnancy without first checking with your healthcare professional.**

Breastfeeding:

- The active ingredient in APO-OXCARBAZEPINE can pass into breast milk. This could cause side effects for breast-fed babies. Talk with your health care professional about the risks and benefits of breastfeeding while taking APO-OXCARBAZEPINE.

Tests and Monitoring: Your healthcare professional may assess your health before and during your treatment with APO-OXCARBAZEPINE. This can include blood tests to identify your genetics, assess your sodium levels, assess thyroid hormone levels, and monitor the levels of the drug.

Driving and using machines: APO-OXCARBAZEPINE can cause dizziness, drowsiness, visual disturbances, blurred visions, and hyponatremia (low sodium levels in the blood), especially at the beginning of your treatment. Before you drive or do tasks that require special attention, wait until you know how you respond to APO-OXCARBAZEPINE.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APO-OXCARBAZEPINE:

- hormonal contraceptives that contain ethinylestradiol and levonorgestrel such as the birth-control pill.
- other antiepileptic medicines such as carbamazepine, phenobarbital, phenytoin, valproic acid, lamotrigine, and phenytoin.

- medicines that are used to treat bacterial infections such as rifampicin.
- medicines known as calcium antagonists that decrease blood pressure such as felodipine and verapamil.
- medicines that reduce the level of sodium in your blood such as diuretics (increases the amount of urine produced to help the kidneys get rid of salt and water).
- medicines that can affect your body's immune system such as cyclosporine.
- alcohol which may increase the sedative effects (making you more sleepy). Avoid alcohol as much as possible and ask your healthcare professional for advice.

How to take APO-OXCARBAZEPINE:

- APO-OXCARBAZEPINE should be taken twice a day at about the same time of every day.
- APO-OXCARBAZEPINE can be taken with or without food.
- Do not stop your treatment with APO-OXCARBAZEPINE without first checking with your healthcare professional. To prevent sudden worsening of your seizure, your healthcare professional will not discontinue your medicine abruptly.

Usual dose:

Your healthcare professional will determine the right dose for you/your child depending on your unique situation. Take APO-OXCARBAZEPINE exactly as prescribed by your healthcare professional. Your healthcare professional may start with a low dose and slowly adjust the dose as needed.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-OXCARBAZEPINE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you/your child miss/misses one dose, take it as soon as you remember. However, if it is almost time for your next dose, do not take the missed dose. Instead, take the next scheduled regular dose. Do not double the dose at any time.

If you have forgotten to take several doses, contact your healthcare professional.

What are possible side effects from using APO-OXCARBAZEPINE?

These are not all the possible side effects you may have when taking APO-OXCARBAZEPINE. If you experience any side effects not listed here, tell your healthcare professional.

The most common side-effects may include:
- sleepiness
- unsteadiness

- diarrhea
- double vision
- abnormal vision
- uncontrolled eye movement
- blurred vision
- abnormal gait (unable to walk normally)
- anxiety
- nervousness
- feeling of depression
- mood swing
- memory problems
- difficulty concentrating
- apathy (feeling indifferent/loss of interest)
- agitation
- trembling
- problems with muscle coordination
- acne
- weight increase

There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures in patients on long term-treatment with APO-OXCARBAZEPINE.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Decreased white blood cells: frequent infections with fever, chills, sore throat, or mouth ulcers		√	
RARE			
Suicidal thoughts or actions: thoughts, plans and actions taken for the purpose of killing or harming yourself		√	
VERY RARE			
Allergic reactions: swelling of the lips, eyelids, face, throat, or mouth, difficulty in breathing, speaking or swallowing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives, or rash			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Hypersensitivity reactions: skin rash, hives, itching, shortness of breath, wheezing, runny nose, watery eyes, fever, swollen glands (swelling of the lymph nodes), and pain in the muscles and joints			√
Serious skin reactions (including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Rash With Eosinophilia And Systemic Symptoms (DRESS), Acute Generalized Exanthematous Pustulosis (AGEP), and maculopapular rash): blistering of the skin and/or mucous membranes of the lips, eyes, mouth, nasal passages or genitals , rash, hives, itching, dermatitis, redness, blistering, or peeling of skin			√
Systemic lupus erythematosus (an autoimmune disease that occurs when your body's immune system attacks your own tissues and organs, including your joints, skin, kidneys, blood cells, heart and lungs): fatigue, fever, joint pain, stiffness, swelling, rash on the face hat covers the cheeks and the bridge of the nose or rashes elsewhere on the body, skin lesions, shortness of breath, chest pain, dry eyes, headaches, confusion, or memory loss			√
Decrease blood cells: tiredness, shortness of breath when exercising, looking pale, headache, chills, dizziness, frequent infections leading to fever, sore throat, mouth ulcers		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Thrombocytopenia (low blood platelets): bleeding or bruising more easily and/or longer than usual if you hurt yourself, nose bleeds, reddish or purplish patches, unexplained blotches on the skin, skin that is red or warm, coldness, tingling, numbness, pale skin, muscle pain, muscle spasms, or weakness		√	
Hyponatremia (low sodium in the blood): lack of energy, confusion, muscular twitching, achy, stiff, uncoordinated muscles, coma, or significant worsening of convulsions		√	
Hepatitis (inflammation of the liver): nausea, loss of appetite, vomiting combined with itching, upper stomach (abdominal) pain, yellowing of the skin or eyes, fatigue, fever, light coloured stool, trouble thinking clearly, or yellowing of the skin		√	
Flu-like symptoms accompanied with liver disorders		√	
Hypothyroidism (underactive/low thyroid): weight gain, tiredness, hair loss, muscle weakness, feeling cold, dry skin, constipation, puffy face, heavier than normal or irregular menstrual periods, or enlarged thyroid gland		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on

how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- The tablets should be stored at room temperature 15°C - 30°C. Do not use APO-OXCARBAZEPINE after the expiry date which is printed on the label.
- Do not use any APO-OXCARBAZEPINE pack that is damaged or show signs of tampering.
- Keep APO-OXCARBAZEPINE out of the reach and sight of children.

If you want more information about APO-OXCARBAZEPINE:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

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