

AUSTRALIAN PRODUCT INFORMATION – TRILEPTAL[®]

(OXCARBAZEPINE) FILM-COATED TABLET AND ORAL SUSPENSION

1 NAME OF THE MEDICINE

oxcarbazepine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of Trileptal contains 150 mg, 300 mg or 600 mg oxcarbazepine. Each mL of oral suspension contains 60 mg oxcarbazepine.

Excipients with known effect (oral suspension only): hydroxybenzoates, saccharin, sorbates, sugar alcohols.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Tablets

Trileptal 150 mg: Pale grey green, ovoid, slightly biconvex, film coated tablet with a score on both sides, imprinted T/D on one side, C/G on the other.

Trileptal 300 mg: yellow, ovoid, slightly biconvex, film coated tablet with a score on both sides, imprinted TE/TE on one side, CG/CG on the other .

Trileptal 600 mg: Light pink, ovoid, slightly biconvex, film coated tablet with a score on both sides, imprinted TF/TF on one side, CG/CG on the other.

Oral suspension

Trileptal 60 mg/mL: off-white to slightly reddish brown oral suspension supplied with an oral dosing syringe and a press-in bottle adaptor.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Trileptal is indicated for use as monotherapy or adjunctive therapy for the treatment of partial seizures and generalised tonic-clonic seizures, in adults and children.

4.2 DOSE AND METHOD OF ADMINISTRATION

Trileptal is suitable for use either as monotherapy or in combination with other antiepileptic drugs. In mono- and adjunctive therapy, treatment with Trileptal is initiated with a clinically effective dose given in two divided doses (see section 5.1 Pharmacodynamic properties, subsection Clinical trials). The dose may be increased depending on the clinical response of the patient. When other antiepileptic drugs (AEDs) are replaced by Trileptal, the dose of the concomitant AED(s) should be reduced gradually on initiation of Trileptal therapy. In adjunctive therapy, as the total antiepileptic drug load of the patient is increased, the dose of concomitant AED(s) may need to be reduced and/or the Trileptal dose increased more slowly.

Trileptal oral suspension and Trileptal film-coated tablets may be interchanged at equal doses (see section 5.2 Pharmacokinetic properties).

The prescription for Trileptal oral suspension should be given in millilitres (see conversion table, Table 1 below which gives the milligram dose in millilitres). The dose in millilitres below has been rounded off to the nearest 0.1 mL.

Table 1 **Trileptal oral suspension conversion table**

Dose in milligrams (mg)	Dose in millilitres (mL)
10 mg	0.2 mL
20 mg	0.3 mL
30 mg	0.5 mL
40 mg	0.7 mL
50 mg	0.8 mL
60 mg	1.0 mL
70 mg	1.2 mL
80 mg	1.3 mL
90 mg	1.5 mL
100 mg	1.7 mL
200 mg	3.3 mL
300 mg	5.0 mL
400 mg	6.7 mL
500 mg	8.3 mL
600 mg	10.0 mL
700 mg	11.7 mL
800 mg	13.3 mL
900 mg	15.0 mL
1,000 mg	16.7 mL

Method of administration

The tablets are scored and can be broken into two halves in order to make it easier for the patient to swallow the tablet. The oral suspension is suitable for younger children and other patients who cannot swallow tablets or where the required dose cannot be administered using tablets.

Trileptal can be taken with or without food.

Dosage Recommendations

The following dosing recommendations apply to all patients in the absence of impaired renal function (see section 5.2 Pharmacokinetic properties). Drug plasma level monitoring is not necessary to optimise Trileptal therapy.

Adults: Monotherapy and Adjunctive Therapy

Recommended initial dose

Trileptal should be initiated with a dose of 600 mg/day (8-10 mg/kg/day) given in 2 divided doses.

Maintenance dose

Good therapeutic effects are seen at doses between 600 mg/day and 2400 mg/day. If clinically indicated, the dose may be increased by a maximum of 600 mg/day at approximately weekly intervals to achieve the desired clinical response.

Maximum recommended dose

In a controlled hospital setting, dose increases up to 2400 mg/day have been achieved over 48 hours.

Daily doses above 2400 mg/day have not been studied systematically in clinical trials.

The maximum daily dose is 2400 mg/day.

Paediatric patients (below 18 years):

Recommended initial dose

In mono- and adjunctive therapy, Trileptal should be initiated with a dose of 8-10 mg/kg/day given in 2 divided doses.

Maintenance dose

In an adjunctive therapy trial in paediatric patients (aged 3 to 17 years), in which the intention was to reach a target daily dose of 46 mg/kg/day, the median daily dose was 31 mg/kg/day with a range of 6 to 51 mg/kg/day. In an adjunctive therapy trial in paediatric patients (aged 1 month to less than 4 years), in which the intention was to reach a target daily dose of 60 mg/kg/day, 56 % of patients reached a final dose of at least 55 mg/kg/day.

Maximum recommended dose

If clinically indicated, the dose may be increased by a maximum of 10 mg/kg/day at approximately weekly intervals from the starting dose, to a maximum daily dose of

60 mg/kg/day, to achieve the desired clinical response (see section 5.2 Pharmacokinetic properties).

Effect of weight adjusted MHD clearance on paediatric dosage

Under adjunctive therapy and monotherapy, when normalized by body weight, apparent clearance (L/hr/kg) of MHD (the active metabolite of oxcarbazepine) decreased with age such that children 1 month to less than 4 years of age may require twice the oxcarbazepine dose per body weight compared to adults; and children 4 to 12 years of age may require a 50 % higher oxcarbazepine dose per body weight compared to adults (see section 5.1 Pharmacodynamic properties).

Effect of concomitant enzyme-inducing antiepileptic drugs on paediatric dosage

For children 1 month to less than 4 years of age, the influence of enzyme-inducing antiepileptic drugs on their weight-normalized apparent clearance appeared higher compared to older children. For children 1 month to less than 4 years of age, an approximately 60% higher oxcarbazepine dose per body weight may be required for adjunctive therapy on enzyme-inducing antiepileptic drugs relative to monotherapy or adjunctive therapy with non-enzyme-inducing antiepileptic drugs. For older children on enzyme-inducing antiepileptic drugs, only a slightly higher dose per body weight may be required than their counterparts on monotherapy.

Trileptal has not been studied in controlled clinical trials in children below 1 month of age.

Geriatric patients (65 years or above):

No special dose recommendations are necessary in elderly patients because therapeutic doses are individually adjusted. Dosage adjustments are recommended in elderly patients with renal impairment (creatinine clearance <30 ml/min) (see section 4.2 Dose and method of administration, subsection renal impairment).

Close monitoring of sodium levels is required in patients at risk of hyponatremia (see section 4.4 Special warnings and precautions for use).

Hepatic impairment:

No dosage adjustment is required for patients with mild to moderate hepatic impairment. Trileptal has not been studied in patients with severe hepatic impairment; therefore, caution should be exercised when administering Trileptal to patients with severe hepatic impairment (see sections 5.2 Pharmacokinetic properties and 4.4 Special warnings and precautions for use).

Renal impairment

In patients with impaired renal function (creatinine clearance less than 30 mL/min), Trileptal therapy should be initiated at half the usual starting dose (300 mg/day) and increased slowly to achieve the desired clinical response (see sections 5.2 Pharmacokinetic properties and 4.4 Special warnings and precautions for use).

Other relevant information

Tablets

Trileptal 150 mg tablets: The score line on two sides of Trileptal 150 mg film-coated tablet is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Trileptal 300 mg tablets: The score line on Trileptal 300 mg film-coated tablets is to divide the tablet into equal doses.

Trileptal 600 mg tablets: The score line on two sides of Trileptal 600 mg film-coated tablet is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4.3 CONTRAINDICATIONS

Known hypersensitivity to oxcarbazepine or eslicarbazepine or to any of the excipients of Trileptal.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use Caution in the Following Circumstances

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 Trileptal. If a patient develops these reactions after treatment with Trileptal, the drug should be discontinued and an alternative treatment started.

Multi-organ hypersensitivity

Multi-organ hypersensitivity reactions have occurred in close temporal association (median time to detection 13 days; range 4-60) to the initiation of Trileptal therapy in adult and paediatric patients. Although there have been a limited number of reports, many of these cases resulted in hospitalisation 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 lymphadenopathy, hepatitis, liver function test abnormalities, haematological abnormalities (e.g., eosinophilia, thrombocytopenia, neutropenia, pruritus, nephritis, oliguria, hepato-renal syndrome, arthralgia and asthenia). Because the disorder is variable in its expression, other organ system symptoms and signs, not noted here, may occur. If this reaction is suspected, Trileptal 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 indicates this to be a possibility (see section 4.4 Special warnings and precautions for use subsection Cross-sensitivity to carbamazepine).

Cross-sensitivity to carbamazepine

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25-30% of these patients might experience hypersensitivity reactions with Trileptal (see section 4.8 Adverse effects (Undesirable effects)). Hypersensitivity reactions may also occur in patients without history of hypersensitivity to carbamazepine. In general, if signs and symptoms suggestive of hypersensitivity reactions occur (see section 4.8 Adverse effects (Undesirable effects)), Trileptal should be withdrawn immediately.

Life-threatening Dermatological Reactions

Serious dermatological reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (Lyell's syndrome) and erythema multiforme, have been reported very rarely in association with the use of Trileptal. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and very rarely be fatal. Trileptal associated cases occurred in both children and adults. The median time to onset was 19 days. Several isolated cases of recurrence of the serious skin reaction when rechallenged with Trileptal were reported. Should a patient develop a skin reaction with Trileptal, consideration should be given to discontinuing Trileptal and prescribing another anti-epileptic medication.

Pharmacogenomics

There is growing evidence that different Human Leukocyte Antigen (HLA) alleles play a strong role in association with adverse cutaneous reactions in predisposed patients.

Association with HLA-B*1502

Retrospective studies in patients of Han Chinese and Thai origin found a strong correlation between SJS/TEN skin reactions associated with carbamazepine and the presence in these patients of the Human Leukocyte Antigen (HLA)-B*1502 allele. As the chemical structure of oxcarbazepine is similar to that of carbamazepine, there is a possibility that patients carrying the HLA-B*1502 allele also have an increased risk of SJS/TEN skin reactions with oxcarbazepine.

The frequency of HLA-B*1502 allele ranges from 2 to 12 % in Han Chinese populations, is about 8% in Thai populations, and above 15% in Philippine, Hong Kong and Malaysian populations, and around 10 % in Taiwan. Allele frequencies up to about 2 % and 6 % have been reported in Korea and India respectively. 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 allele frequencies listed here represent the percentage of paired chromosomes in the specified population that carry the allele of interest, meaning that the percentage of patients who carry a copy of the allele on at least one of their two chromosomes (i.e. "carrier frequency") is nearly twice as high as the allele frequency. Therefore, the percentage of patients who may be at risk is nearly twice the allele frequency.

Testing for the presence of the HLA-B*1502 allele should be considered in patients with ancestry in genetically at-risk populations, prior to initiating treatment with Trileptal (see below "Information for healthcare professionals"). The use of Trileptal should be avoided in tested patients who are found to be positive for HLA-B*1502 unless the benefits clearly outweigh the risks. HLA-B*1502 may be a risk factor for the development of SJS/TEN in Chinese patients taking other anti-epileptic drugs (AED) associated with SJS/TEN. Consideration should therefore be given to avoid use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable. Screening is not generally recommended in patients from populations in which the prevalence of the HLA-B*1502 is low or in current Trileptal users, as the risk of SJS/TEN is largely confined to the first

few months of therapy, regardless of HLA-B*1502 status. If testing for the presence of the HLA-B*1502 allele should be performed, high resolution “HLA-B*1502 genotyping” is recommended. The test is positive if either or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected. See “Information for Healthcare professionals” in this section.

Association with HLA-A*3101

As the chemical structure of oxcarbazepine is similar to that of carbamazepine, there is a possibility that patients carrying the HLA-A*3101 allele also have an increased risk of SJS/TEN skin reactions with oxcarbazepine.

Human Leukocyte Antigen (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 HLA-A*3101 allele varies widely between ethnic populations and its frequency is about 2 to 5 % in European populations and is 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 %. Frequency 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 % and 15 % in other native ethnicities in these same regions.

The allele frequencies listed here represent the percentage of paired chromosomes in the specified population that carry the allele of interest, meaning that the percentage of patients who carry a copy of the allele on at least one of their two chromosomes (i.e. the “carrier frequency”) is nearly twice as high as the allele frequency. Therefore, the percentage of patients who may be at risk is nearly twice the allele frequency.

There is some data that suggest HLA-A*3101 is associated with an increased risk of carbamazepine-induced cutaneous adverse drug reactions including SJS, TEN, Drug rash with eosinophilia (DRESS), or less severe Acute Generalised Exanthematous Pustulosis (AGEP) and maculopapular rash.

There are insufficient data to support a recommendation for testing the presence of the HLA-A*3101 allele in patients prior to initiating treatment with oxcarbazepine. Genetic screening is generally not recommended for any current Trileptal users, as the risk of SJS/TEN, AGEP, DRESS and maculopapular rash is largely confined to the first few months of therapy, regardless of the HLA-A*3101 status.

Limitation of genetic screening

Genetic screening must never substitute for appropriate clinical vigilance and patient management. Many Asian patients positive for HLA-B*1502 and treated with Trileptal will not develop SJS/TEN and patients negative for HLA-B*1502 of any ethnicity can still develop SJS/TEN. Similarly, many patients positive for HLA-A*3101 and treated with Trileptal 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 AED dose, compliance, concomitant medications, co-morbidities, and the level of dermatological monitoring have not been studied.

Information for Healthcare professionals

If testing for the presence of HLA-B*1502 allele is performed, high resolution “HLA-B*1502 genotyping” is recommended. The test is positive if either one or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected. Similarly, if testing for the presence of the HLA-A*3101 allele is performed, high resolution “HLA-A*3101 genotyping” is recommended. The test is positive if either one or two HLA-A*3101 alleles are detected and negative if no the HLA-A*3101 are detected.

Risk of seizure aggravation

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

Hyponatraemia

Serum sodium levels below 125 mmol/L, usually asymptomatic and not requiring adjustment of therapy, have been observed in up to 2.7% of Trileptal treated patients. Experience from clinical trials shows that serum sodium levels returned towards normal when the Trileptal dosage was reduced, discontinued or the patient was treated conservatively (e.g. restricted fluid intake).

In patients with pre-existing renal conditions associated with low sodium levels, inappropriate ADH secretion like syndrome or in patients treated concomitantly with sodium-lowering drugs (e.g. diuretics, desmopressin; and drugs associated with inappropriate ADH secretion) as well as NSAIDs (e.g. indomethacin), 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 therapy, or according to clinical need. These risk factors may apply especially to elderly patients.

For patients on Trileptal therapy when starting on sodium-lowering drugs, the same approach for sodium checks should be followed. In general, if clinical symptoms suggestive of hyponatraemia occur on Trileptal therapy (see section 4.8 Adverse Effects (Undesirable effects)), serum sodium measurement may be considered. Other patients may have serum sodium assessed as part of their routine laboratory studies.

All patients with cardiac insufficiency and secondary heart failure should have regular weight measurements to determine occurrence of fluid retention. In case of fluid retention or worsening of the cardiac condition, serum sodium levels should be checked. If hyponatraemia is observed, water restriction is an important counter-measure. As oxcarbazepine may, very rarely, lead to impairment of cardiac conduction, patients with pre-existing conduction disturbances (e.g. AV-block, arrhythmia) should be monitored carefully.

Cases of hyponatraemia associated with lethargy, nausea, dizziness, vomiting, headache, confusional state or other neurological manifestations and a decrease in serum (blood) osmolality, have been reported with oxcarbazepine in postmarketing adverse reactions reports

and in the published literature (see section 4.8 Adverse Effects (Undesirable effects)). Changes in water handling were assessed and correlated with plasma ADH concentrations in a study of 10 healthy volunteers and 11 epileptic patients without any other predisposing factors who were dosed with oxcarbazepine (up to a daily maximum of 2400mg) for 3 weeks (Sachdeo et al 2002*). After water loading, serum sodium and free water clearance were diminished in both groups without a concomitant increase in serum ADH levels. These findings suggest that oxcarbazepine-induced hyponatraemia may not be attributable to the syndrome of inappropriate secretion of antidiuretic hormone. Postulated mechanisms include a direct effect of oxcarbazepine on the renal collecting tubules or an enhancement of their responsiveness to circulating antidiuretic hormone.

*Sachdeo RC et al. Effects of oxcarbazepine on sodium concentration and water handling. *Annals of Neurology* 2002; 51(5): 613-620

Hypothyroidism

Hypothyroidism is a very rare adverse drug reaction of oxcarbazepine. Considering the importance of thyroid hormones in children's development after birth, it is advisable to perform a thyroid function test before the start of Trileptal therapy in the paediatric age group, especially in children aged two years or below. Thyroid function monitoring is recommended in the paediatric age group while on Trileptal therapy.

Withdrawal effects

As with all antiepileptic drugs, Trileptal should be withdrawn gradually to minimise the potential of increased seizure frequency.

Haematological effects

Very rare reports of agranulocytosis, aplastic anaemia and pancytopenia have been seen in patients treated with Trileptal during post-marketing experience (see section 4.8 Adverse Effects (Undesirable effects)). However, due to the very low incidence of these conditions and confounding factors (e.g. underlying disease, concomitant medication), causality cannot be established. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Suicidal Behaviour and Ideation

Antiepileptic drugs, including oxcarbazepine, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomised to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomised to placebo. Based on the subgroup analysis, the adjusted relative risks (estimated odds ratios) of suicidal behaviour or ideation was 1.91 (95% CI: 0.15, 56.33) for oxcarbazepine compared to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients,

representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analysed. Table 2 below shows absolute and relative risk by indication for all evaluated AEDs.

Table 2 Absolute and relative risk of suicidal thoughts or behaviour

Indication	Placebo Patients with Events Per 1,000 Patients	Drug Patients with Events Per 1,000 Patients	Relative Risk : Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1,000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing Trileptal or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Therefore patients 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. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence

or worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to healthcare providers.

Trileptal Oral Suspension

Trileptal oral suspension contains parabens (methyl hydroxybenzoate and propyl hydroxybenzoate) which may cause allergic reactions, some of which may possibly be delayed. It also contains sorbitol and, therefore, should not be administered to patients with rare hereditary problems of fructose intolerance.

Use in hepatic impairment

Very rare cases of hepatitis have been reported, which in most of the cases resolved favourably. When a hepatic event is suspected, liver function should be evaluated and discontinuation of Trileptal should be considered. Caution should be exercised when treating patients with severe hepatic impairment (see sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties).

Use in renal impairment

In patients with impaired renal function (creatinine clearance less than 30 mL/min), caution should be exercised during Trileptal treatment especially with regard to the starting dose and up titration of the dose (see section 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties).

Use in the elderly

Refer to sections 4.2 Dose and method of administration, 4.4 Special warnings and precautions for use (subheading Hyponatraemia), 5.1 Pharmacodynamic properties (subheading Clinical Trials, under Table 6), 5.2 Pharmacokinetic properties (subheading Elderly patients and Gender).

Paediatric use

Refer to sections 4.2 Dose and method of administration, 4.4 Special warnings and precautions for use (subheading Multi-organ hypersensitivity and Hypothyroidism) and 5.1 Pharmacodynamic properties (subheading Clinical Trials).

Effects on laboratory tests

Refer to sections 4.4 Special warnings and precautions for use (subheading Hyponatraemia).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Enzyme inhibition:

Oxcarbazepine was evaluated in human liver microsomes to determine its capacity to inhibit the major cytochrome P450 enzymes responsible for the metabolism of other drugs. The results demonstrate that oxcarbazepine and its pharmacologically active metabolite (the monohydroxy derivative, MHD) inhibit CYP2C19. Therefore, clinically relevant interactions could arise when co-administering high doses of Trileptal with drugs that are metabolised by CYP2C19 (phenobarbitone, phenytoin, citalopram, diazepam, hexobarbitone, imipramine, omeprazole,

proguanil, propranolol, lansoprazole, pantoprazole, amitriptyline, clomipramine, cyclophosphamide and progesterone). In some patients treated with Trileptal and drugs metabolized significantly via CYP2C19, a 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. Although inhibition of CYP 3A4/5 by oxcarbazepine and MHD did occur at high concentrations in vitro, it is not likely to be of clinical significance.

Enzyme induction:

Oxcarbazepine and MHD induce, in vitro and in vivo, the 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 drugs (see below). A decrease in plasma concentrations may also be observed in other drugs mainly metabolized by CYP3A4 and CYP3A5, for example immunosuppressants (e.g. cyclosporin).

In vitro, oxcarbazepine and MHD are weak inducers of UDP-glucuronyl transferase 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 Trileptal 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.

Antiepileptic drugs and enzyme inducing drugs:

Potential interactions between Trileptal and other antiepileptic drugs (AEDs) were assessed in clinical studies. The effect of these interactions on mean AUCs and C_{min} are summarised in table 3.

Table 3 Summary of antiepileptic drug interactions with Trileptal

AED Co-administered	Influence of Trileptal on AED Concentration	Influence of AED on MHD Concentration
Carbamazepine	0 - 22% decrease	40% decrease
Clobazam	Not studied	No influence
Felbamate	Not studied	No influence
Phenobarbitone	14 - 15% increase	30 - 31% decrease
Phenytoin	0 - 40% increase	29 - 35% decrease

Valproic acid	No influence	0 - 18% decrease
Lamotrigine	Possible decrease	No influence

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

Strong inducers of cytochrome P450 enzymes and/or UGT (e.g. carbamazepine, phenytoin and phenobarbitone) have been shown to decrease the serum levels of MHD (29-40%).

In a single case study, rifampicin, a strong inducer of certain cytochrome P450 enzymes and UGT, was shown to reduce serum MHD by 49%.

No autoinduction has been observed with Trileptal.

Hormonal contraceptives:

Trileptal was shown to have an influence on the two components, ethinylestradiol (EE) and levonorgestrel (LNG), of an oral contraceptive. The mean AUC values of EE and LNG were decreased by 48-52% and 32-52%, respectively. Studies with other oral or implant contraceptives have not been conducted. Female patients of childbearing age should be warned that the concurrent use of Trileptal with hormonal contraceptives may render this type of contraceptive ineffective (see sections 4.4 special warnings and precautions for use and 4.6 Fertility, pregnancy and lactation). Additional non-hormonal forms of contraception are recommended when using Trileptal.

Calcium antagonists:

After repeated co-administration of Trileptal, the AUC values of felodipine were lowered by 28%. However, the plasma levels remained in the recommended therapeutic range.

On the other hand, verapamil produced a decrease of 20% of the plasma levels of MHD. This decrease in plasma levels of MHD is not considered to be of clinical relevance.

Alcohol:

Caution should be exercised if alcohol is taken in combination with Trileptal therapy, due to a possible additive sedative effect.

Other drug interactions:

Cimetidine, erythromycin and dextropropoxyphene had no effect on the pharmacokinetics of MHD, whereas viloxazine produced minor changes in the MHD plasma levels (about 10% higher after repeated co-administration). Results with warfarin show no evidence of interaction with either single or repeated doses of Trileptal. Interaction studies with Trileptal and St John's wort

(Hypericum perforatum) have not been performed. Therefore, caution should be exercised when using St John's wort and Trileptal.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no human data on fertility.

In rats, fertility of both sexes was unaffected by oxcarbazepine or MHD at oral doses up to 150 and 450 mg/kg/day, respectively. However, disruption of oestrous cyclicity and reduced numbers of corpora lutea, implantations and live embryos were observed in female animals at the highest dose of MHD.

Women of child-bearing potential and contraception

Women of child bearing potential should be advised to use highly effective contraception (preferably non-hormonal; e.g. intrauterine implants) while on treatment with Trileptal. Trileptal may result in a failure of the therapeutic effect of oral contraceptive drugs containing ethinylestradiol (EE) and levonorgestrel (LNG) (see section 4.5 Interactions with other medicines and other forms of interactions).

Use in pregnancy – Pregnancy Category D

Oxcarbazepine and its active metabolite (MHD) cross the human placenta.

Animal data

Standard reproductive toxicity studies in rodents and rabbits revealed effects such as increases in the incidence of embryo-fetal mortality and/or some delay in antenatal and/or postnatal growth of the offspring at maternally toxic dose levels.

When pregnant rats were given oxcarbazepine orally during the period of organogenesis, increased incidences of foetal malformations (craniofacial, cardiovascular and skeletal) and variations were observed at 300 and 1000 mg/kg/day. These doses also caused maternal toxicity, but there is no evidence to suggest that teratogenicity was secondary to the maternal effects. Increased resorptions and decreased foetal body weights were seen at 1000 mg/kg/day.

No evidence of teratogenic activity was seen when MHD was administered to pregnant rats and rabbits at oral doses up to 500 and 200 mg/kg/day respectively. Increased resorptions were seen at the highest dose in both species. Decreased foetal weight and delayed ossification were seen in the rat study at 250 and 500 mg/kg/day.

Oral administration of oxcarbazepine (75 and 150 mg/kg/day) to rats during late gestation caused whole litter loss in the perinatal period (accompanied by maternal deaths at 150 mg/kg/day). A similar study with MHD showed a slight delay in parturition at 250 mg/kg/day, but birth weight and survival of the offspring were not affected.

The overall evidence from animal studies is insufficient to rule out a teratogenic effect of oxcarbazepine in humans.

Risk summary

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. The congenital malformations seen with oxcarbazepine therapy were ventricular septal defect, atrioventricular septal defect, cleft palate with cleft lip, Down's syndrome, dysplastic hip (both unilateral and bilateral), tuberous sclerosis and congenital malformation of the ear. Based on data in a North American pregnancy registry, the risk of major congenital malformations, defined as a structural abnormality with surgical, medical, or cosmetic importance, diagnosed during pregnancy or within 12 weeks of birth was 2.2% (95% CI 0.6 to 5.5%) among mothers exposed to oxcarbazepine monotherapy in the first trimester. When compared with pregnant women not exposed to any antiepileptic drugs the relative risk (RR) of congenital abnormality in pregnant women on oxcarbazepine is (RR) 1.6, 95% CI 0.46 to 5.7. Based on data from the EURAP Registry (European and International Registry of Antiepileptic Drugs and Pregnancy), the prevalence of major congenital malformations assessed after 1 year of birth was 3.0% (95% CI: 1.4 to 5.4).

There are no adequate and well controlled clinical studies to judge the safety of the use of oxcarbazepine during pregnancy. However, oxcarbazepine is closely related structurally to carbamazepine, which is considered to be teratogenic in humans. Given this fact, and the findings of teratogenic activity in animals, it is likely that oxcarbazepine is a human teratogen. Please refer to the carbamazepine Product Information section "Use in Pregnancy" for details of birth defects associated with this agent. If a woman receiving Trileptal becomes pregnant, or if the need to initiate treatment with Trileptal arises during pregnancy, the drug's potential benefits must be carefully weighed against the potential risk of foetal malformations. This is particularly important during the first three months of pregnancy.

The risk of having an abnormal child as a result of antiepileptic medication is far outweighed by the dangers to the mother and foetus of uncontrolled epilepsy.

Clinical considerations

It is recommended that:

Women on antiepileptic drugs receive pre-pregnancy counselling with regard to the risk of foetal abnormalities;

Antiepileptic drugs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication;

Folic acid supplementation (5 mg) should be commenced four weeks prior to and continue for twelve weeks after conception;

Specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.

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 Trileptal 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 sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties). Postpartum MHD plasma levels may also be considered for monitoring especially in the event that medication was increased during pregnancy.

Bleeding disorders in the newborn caused by antiepileptic agents have been reported. As a precaution, vitamin K1 should be administered as a preventive measure in the last few weeks of pregnancy and to the newborn.

Use in lactation

Risk summary

Oxcarbazepine and its active metabolite (MHD) are excreted in human breast milk. A milk-to-plasma concentration ratio of 0.5 was found for both. The effects on the infant exposed to Trileptal by this route are unknown. Therefore, Trileptal should not be used during breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Adverse reactions such as dizziness, somnolence, ataxia, diplopia, blurred vision, visual disturbances, hyponatraemia and depressed level of consciousness have been observed with the use of Trileptal (for the complete list of ADRs see section 4.8 Adverse effects (Undesirable effects)), 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 operating machinery or driving a vehicle.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The most commonly reported adverse reactions are somnolence, headache, dizziness, diplopia, nausea, vomiting and fatigue occurring in more than 10% of patients.

In clinical trials, adverse events (AEs) were generally mild to moderate in severity, of transient nature and occurred predominantly at the start of treatment.

The analysis of the undesirable effect profile by body system is based on AEs from clinical trials assessed as related to Trileptal. In addition, clinically meaningful reports on adverse experiences from named patient programs and postmarketing experience were taken into account.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 4) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common: $\geq 1/10$; common: $\geq 1/100$ to $< 1/10$; uncommon: $\geq 1/1000$ to $< 1/100$; rare: $\geq 1/10000$ to $< 1/1000$; very rare: $< 1/10000$

Table 4 Adverse drug reactions

Blood and lymphatic system disorders	
Uncommon	Leucopenia.
Very rare	Bone marrow depression, aplastic anaemia, agranulocytosis, pancytopenia, thrombocytopenia, neutropenia.
Immune system disorders	
Very rare	Anaphylactic reactions, hypersensitivity (including multi-organ hypersensitivity) characterised by features such as abnormal liver function tests, rash, fever. Other organs or systems may be affected such as blood and lymphatic system (e.g. lymphadenopathy, eosinophilia, leucopenia, splenomegaly), liver (e.g. hepatitis, abnormal liver function tests), muscles and joints (e.g. joint swelling, myalgia, arthralgia), nervous system (e.g. hepatic encephalopathy), kidney (e.g. renal failure, nephritis interstitial, proteinuria), lungs (e.g. pulmonary oedema, asthma, bronchospasms, interstitial lung disease, dyspnoea), angioedema.
Endocrine disorders	
Common	Weight increased
Very rare	Hypothyroidism
Metabolism and nutrition disorders	
Common	Hyponatraemia.
Very rare	Hyponatraemia associated with signs and symptoms such as seizures, encephalopathy, depressed level of consciousness, confusion, (see “Nervous system disorders” for further adverse effects), vision disorders (e.g. blurred vision), hypothyroidism, vomiting, nausea, folic acid deficiency.
Psychiatric disorders	
Common	Agitation (e.g. nervousness), affect lability, confusional state, depression, apathy.
Nervous system disorders	
Very common	Somnolence, headache, dizziness.
Common	Ataxia, tremor, nystagmus, disturbance in attention, amnesia.
Eye disorders	
Very common	Diplopia.

Common	Vision blurred, visual disturbance
Ear and labyrinth disorders	
Common	Vertigo.
Cardiac disorders	
Very rare	Atrioventricular block, arrhythmia.
Vascular disorders	
Very rare	Hypertension.
Gastrointestinal disorders	
Very common	Vomiting, nausea.
Common	Diarrhoea, abdominal pain, constipation.
Very rare	Pancreatitis and/or lipase and/or amylase increase.
Hepato-biliary disorders	
Very rare	Hepatitis.
Skin and subcutaneous tissue disorders	
Common	Rash, alopecia, acne.
Uncommon	Urticaria.
Very rare	Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), angioedema, erythema multiforme.
Musculoskeletal, connective tissue and bone disorders	
Very rare	Systemic lupus erythematosus.
General disorders and administration site conditions	
Very common	Fatigue.
Common	Asthenia.
Investigations	
Uncommon	Hepatic enzymes increased, blood alkaline phosphatase increased.
Very rare	Amylase increase, lipase increase.

Very rarely clinically significant hyponatraemia (sodium < 125 mmol/L) can develop during Trileptal use. It generally occurred during the first 3 months of treatment with Trileptal, although there were patients who first developed a serum sodium < 125 mmol/L more than 1 year after initiation of therapy (see section 4.4 Special warnings and precautions for use, subsection Hyponatraemia).

In clinical trials in children aged 1 month to less than 4 years, the most commonly reported adverse reaction was somnolence occurring in approximately 11% of patients. Adverse reactions occurring at an incidence of $\geq 1\%$ - < 10% (common) were: ataxia, irritability, vomiting, lethargy, fatigue, nystagmus, tremor, decreased appetite, and blood uric acid increased.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Trileptal via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Metabolism and nutrition disorders

Inappropriate ADH secretion like syndrome with signs and symptoms of Hyponatraemia associated with lethargy, nausea, dizziness, decrease in serum (blood) osmolality, vomiting, headache, confusional state or other neurological signs and symptoms and a decrease in serum (blood) osmolality (see section 4.4 Special warnings and precautions for use, subsection Hyponatraemia).

Skin and subcutaneous tissue disorders

Drug rash with eosinophilia and systemic symptoms (DRESS), Acute Generalized Exanthematous Pustulosis (AGEP).

Injury, poisoning and procedural complications

Fall.

Nervous system disorders

Speech disorders (including dysarthria); more frequent during up titration of Trileptal dose.

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 Trileptal. The mechanism by which oxcarbazepine affects bone metabolism has not been identified.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Isolated cases of overdose have been reported. The maximum dose taken was approximately 24,000 mg. All patients recovered with symptomatic treatment.

Signs and Symptoms

Electrolyte and fluid balance conditions: hyponatremia

Eye disorders: diplopia, miosis, blurred vision

Gastrointestinal disorders: nausea, vomiting, hyperkinesia

General disorders and administration site conditions: fatigue

Investigations: respiratory rate depression, QTc prolongation

Nervous system disorders: drowsiness and somnolence, dizziness, ataxia, nystagmus, tremor, disturbances in coordination (coordination abnormal), convulsion, headache, coma, loss of consciousness, dyskinesia

Psychiatric disorders: aggression, agitation, confusional state

Vascular disorders: hypotension

Respiratory, thoracic and mediastinal disorders: dyspnoea

Management

There is no specific antidote. Symptomatic and supportive treatment should be administered as appropriate. Inactivation of the drug by administering activated charcoal should be considered.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The pharmacological activity of Trileptal (oxcarbazepine) is primarily exerted through the active metabolite (10-monohydroxy derivative, MHD) of oxcarbazepine (see section 5.2 Pharmacokinetic properties). The mechanism of action of oxcarbazepine and MHD is thought to be mainly based on blockade of voltage-sensitive sodium channels, thus resulting in stabilisation of hyperexcited neural membranes, inhibition of repetitive neuronal firing and diminishment of propagation of synaptic impulses. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may also contribute to the anticonvulsant effects of the drugs. No significant interactions with brain neurotransmitter or modulator receptor sites were found.

Oxcarbazepine and its active metabolite (MHD) are potent and efficacious anticonvulsants in animals. They protected rodents against generalised tonic-clonic and, to a lesser degree, clonic seizures, and abolished or reduced the frequency of chronically recurring partial seizures in Rhesus monkeys with aluminium implants. No tolerance (i.e. attenuation of anticonvulsive activity) against tonic-clonic seizures was observed when mice and rats were treated daily for 5 days or 4 weeks, respectively, with oxcarbazepine or MHD.

Clinical trials

A total of 10 double blind controlled trials of Trileptal, 2 as adjunctive therapy and 8 as monotherapy, were conducted in patients with partial seizures, which included the seizure subtypes of simple, complex and partial seizures evolving to secondarily generalised seizures. All comparative trials also included patients with generalised tonic-clonic seizures. Two dose-control monotherapy substitution trials, in which patients received a variety of concomitant anti-epileptic drugs (AEDs), including carbamazepine, gabapentin, lamotrigine, phenytoin and valproate, confirm efficacy when these AEDs were substituted by Trileptal. Two trials were conducted in children (aged 3 to 17 years), one in adjunctive therapy versus placebo, the other a monotherapy comparison with phenytoin. Efficacy was demonstrated with doses ranging from 600 mg - 2400 mg/day in all the primary efficacy parameters, which included mean or percentage change in seizure frequency from baseline in the adjunctive trials, and time to meeting pre-defined exit criteria or the percentage of patients meeting exit criteria in the monotherapy trials.

It has been shown that Trileptal has similar efficacy to other first line antiepileptic drugs (i.e. valproic acid, phenytoin and carbamazepine) with a statistically significantly better tolerability profile than phenytoin, as judged by withdrawals due to adverse events, and a statistically significantly longer retention rate (i.e. proportion of patients who stayed on treatment). Similar proportions of patients with partial and generalised tonic-clonic seizures who were treated with Trileptal were seizure free over the 12-month treatment period of these trials.

In addition, an adjunctive therapy, rater blind, trial in 128 patients (1 month to < 4 years of age) with inadequately-controlled partial seizures on one to two concomitant anti-epileptic drugs (AEDs) was conducted. Patients who experienced at least 2 study specific seizures (i.e. electrographic partial seizures with a behavioural correlate) during the 72 hours baseline period were randomly assigned to either Trileptal 10 mg/kg/day or were titrated up to 60 mg/kg/day within 26 days. Patients were maintained on their randomized target dose for 9 days and seizures were recorded through continuous video-EEG monitoring during the last 72 hours of the maintenance period. The primary measure of effectiveness in this trial was a between group comparison of the change in seizure frequency per 24 hours compared to the seizure frequency at baseline. For the entire group of patients enrolled, this comparison was statistically significant in favour of Trileptal 60 mg/kg/day. Note that the two dose groups were re-assessed at different times relative to the qualifying baseline period, with the High-dose group having an additional 26 day titration period, during which seizure frequency may have declined for other reasons not directly related to the dose.

Table 5 Absolute change in partial seizure frequency (SST1) per 24 hours (ITT population)

	Oxcarbazepine Low N=57	Oxcarbazepine High N=59	P-value*
Baseline Mean (SD)	13.29 (22.34)	10.27 (17.82)	
Treatment Mean (SD)	10.50 (24.08)	2.67 (4.40)	
Absolute Change Mean (SD)	-2.79 (16.02)	-7.60 (17.38)	
Median Absolute Change	-1.37	-2.00	0.043

Partial seizure frequency is calculated as the number of SST1 seizures experienced during the continuous video-EEG monitoring in the treatment phase, divided by the length of the period in hours and multiplied by 24.

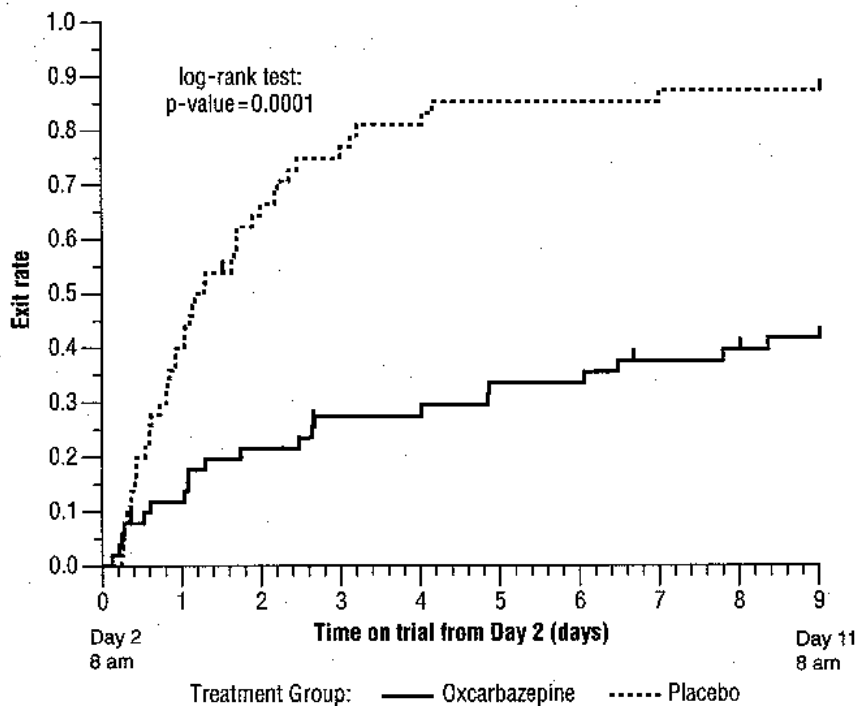
* P-value based on comparison for the median absolute change between the High-dose OXC group and the Low-dose OXC group from the Rank Analysis of Covariance model stratifying by age groups with the SST1 seizure frequency per 24 hours at baseline as covariate.

A monotherapy trial was conducted in 92 paediatric patients (1 month to 16 years of age) with inadequately-controlled or new-onset partial seizures. Patients were hospitalized and randomized to either Trileptal 10 mg/kg/day or were titrated up to 40-60 mg/kg/day within three days while withdrawing the previous AED on the second day of Trileptal therapy. Seizures were recorded through continuous video-EEG monitoring from day 3 to day 5. Patients either completed the 5 day treatment or met one of the two exit criteria: 1) three study specific seizures (i.e. electrographic partial seizures with a behavioural correlate), 2) a prolonged study specific seizure. The primary measure of effectiveness was a between group comparison of the time to meet exit criteria in which the difference between the curves was not statistically significant ($p=0.904$). The majority of patients from both dose groups completed the 5-day study without exiting. The percentage of patients exiting the study was 22.2 % (10/45) for the Low-dose group and 21.4 % (9/42) for the High-dose group.

Key Placebo-Controlled Monotherapy Trials

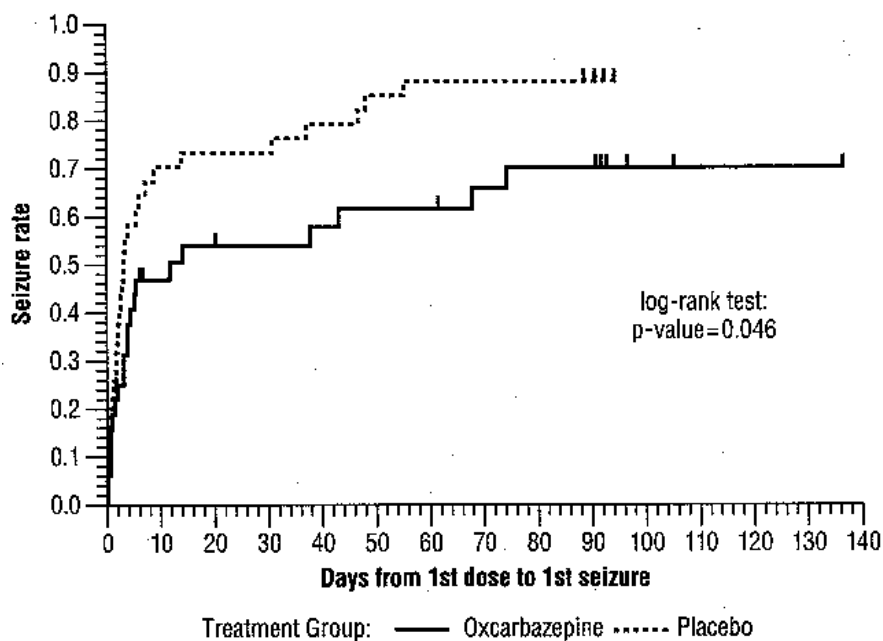
Trial 004 was a placebo-controlled trial conducted in 102 patients (11-62 years of age) with refractory partial seizures who had completed an inpatient evaluation for epilepsy surgery. Patients had been withdrawn from all anti-epileptic drugs (AEDs) and were required to have 2-10 partial seizures within 48 hours prior to randomisation. Patients were randomised to receive either placebo or Trileptal 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 generalised seizures, where such seizures were not seen in the 1-year period prior to randomisation, 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 favour of Trileptal (refer Figure 1), $p=0.0001$.

Figure 1: Kaplan-Meier estimates of exit rate by treatment group



Trial 025 was a placebo-controlled trial conducted in 67 untreated patients (8-69 years of age) with newly-diagnosed and recent-onset partial seizures. Patients were randomized to placebo or Trileptal, 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 favour of Trileptal (refer Figure 2), $p=0.046$.

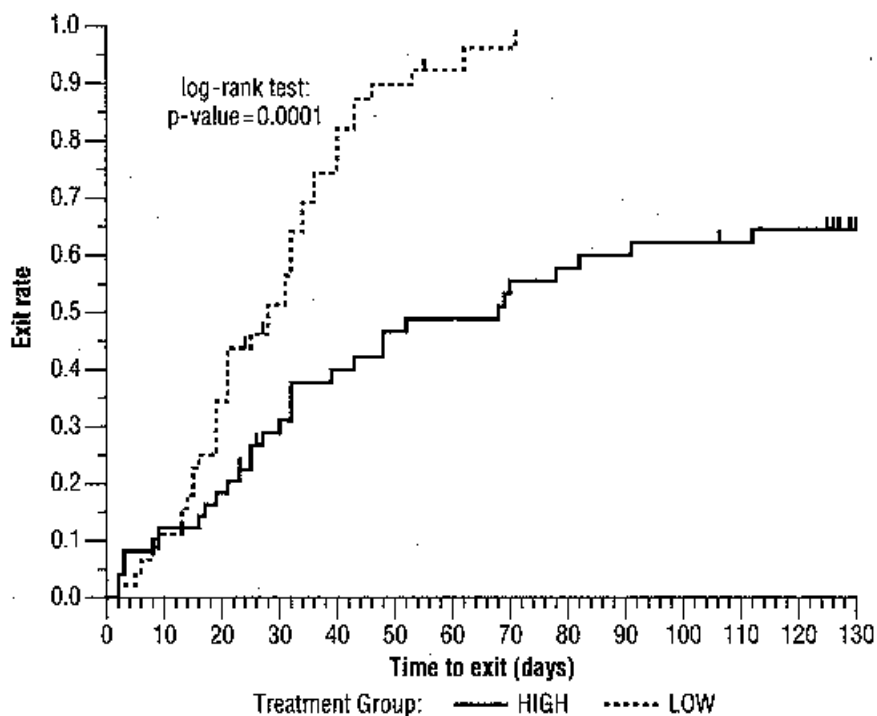
Figure 2: Kaplan-Meier estimates of first seizure event rate by treatment group



Key Dose-Controlled Monotherapy Trials

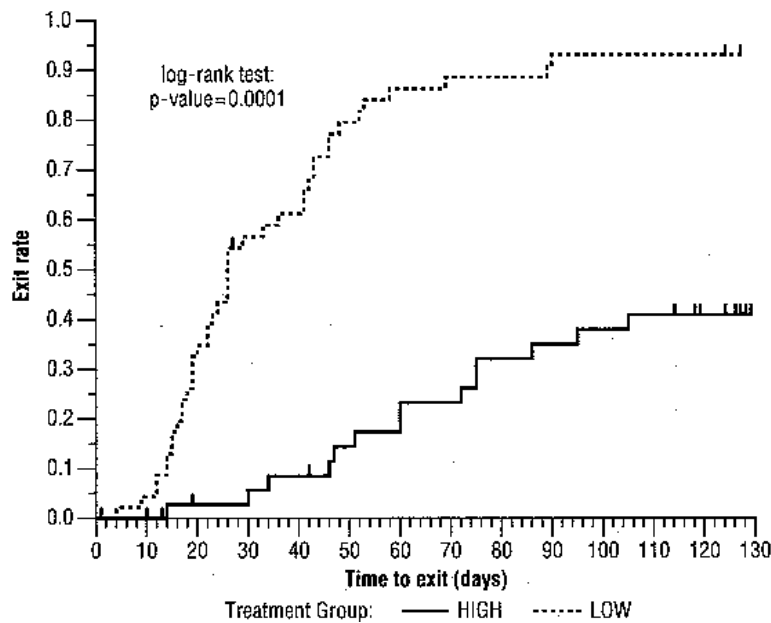
Trial 026 substituted Trileptal monotherapy at 2400 mg/day for carbamazepine (CBZ) in 143 patients (12-65 years of age) whose partial seizures were inadequately controlled on CBZ monotherapy at a stable dose of 800 to 1600 mg/day, and maintained this Trileptal dose for 56 days (baseline phase). Patients who were able to tolerate titration of Trileptal to 2400 mg/day during simultaneous CBZ withdrawal were randomly assigned to either 300 mg/day of Trileptal or 2400 mg/day Trileptal. 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 generalised seizure if none had occurred during baseline, or 4) a prolonged generalised 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 favour of the Trileptal 2400 mg/day group (refer Figure 3), $p=0.0001$.

Figure 3: Kaplan-Meier estimates of exit rate by treatment group



Trial 028 was a monotherapy substitution trial conducted in 87 patients (11-66 years of age) whose seizures were inadequately controlled on 1 or 2 AEDs. Patients were randomised to either Trileptal 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 favour of the Trileptal 2400 mg/day group (14/34; 41.2%) compared to the Trileptal 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 favour of the Trileptal 2400 mg/day group (refer Figure 4), $p=0.0001$.

Figure 4: Kaplan-Meier estimates of exit rate by treatment group



Key Active-Controlled Monotherapy Trials

Four double-blind, active-control trials compared the clinical utility, efficacy and safety of Trileptal with standard antiepileptic drugs: valproate (OT/F01) and phenytoin in newly diagnosed adults and adolescents (OT/F02) and adolescents and children (OT/F04) with epilepsy, and carbamazepine in newly diagnosed or untreated adult patients with epilepsy (OT/E25).

Trials OT/F01, OT/F02 and OT/F04 were of a similar design and consisted of four phases: a 14-day Screening Phase, a 56-week Double-blind Treatment Phase consisting of an 8-week Titration Period and a 48-week Maintenance Period, followed by a 12-month Open-label Follow-Up Phase and a Long-term Extension Phase. The flexible titration schedule involved a starting single dose of either 300 mg Trileptal or 300 mg valproate (VPA) or 100 mg phenytoin (PHT), which was titrated to the optimum daily dose administered in a t.i.d. regimen. The maximum doses permitted were 2400 mg/day Trileptal, 2400 mg/day VPA and 800 mg/day PHT.

The key entry criteria were: 2 or more seizures in the previous 6 months and no previous anticonvulsant therapy. All studies included patients with both partial seizures and generalised tonic-clonic seizures. The primary efficacy analysis was a logistic regression on the proportion of seizure-free patients during the 12-month Maintenance Period.

No statistically significant differences between treatment groups were observed with respect to seizure frequency and the proportion of seizure-free patients during the Maintenance Period in these trials. The proportion of seizure-free Trileptal-treated patients ranged from 56% to 61% (OT/F02, OT/F04), 54% to 60% for PHT-treated patients (OT/F02, OT/F04) and 54% for VPA-treated patients (OT/F01). The proportion of patients with generalised tonic-clonic seizures who were seizure-free ranged from 59% to 72% for Trileptal-treated patients (OT/F04, OT/F01), 54% to 68% for PHT-treated patients (OT/F04, OT/F02) and 62% for VPA-treated patients (OT/F01). The retention rate of Trileptal-treated adolescents and children was

statistically significantly longer than for the PHT group (OT/F04), while there were no statistically significant differences found between Trileptal-treated and VPA or PHT-treated adult and adolescent patients (OT/F01, OT/F02). The occurrence of premature discontinuations due to adverse events was statistically significantly higher for PHT than for Trileptal in both trials while no statistically significant differences were found with VPA-treated patients.

Trial OT/E25 was a multicentre, double-blind, parallel group study of three phases in which 128 patients were randomised and treated with Trileptal and 134 with CBZ. In the Screening Phase patients already treated were maintained on their current AEDs. In the Double-blind Treatment Phase patients were randomised to receive either Trileptal or carbamazepine (CBZ) and were tapered and discontinued from their AEDs. The Double-blind Treatment Phase consisted of 3 periods: a 2 month Titration Period, a 6 month t.i.d. Maintenance Period and an optional 4 month b.i.d. Maintenance Period. An open label extension phase followed. Patients with generalised tonic-clonic seizures or partial onset seizures were included. The patients were either newly diagnosed or inadequately treated (>2 seizures during the previous 6 months) or tolerating current AED treatment. The primary objective was to compare the safety and efficacy of Trileptal monotherapy versus CBZ monotherapy.

The primary efficacy variable was the number of seizures observed during the first 2 months before the end of the trial or dropouts if this occurred in the t.i.d. maintenance phase. Secondary variables included a global evaluation of therapeutic effect by the investigator using a 4-point scale and the proportion of patients in whom the incidence of seizures was reduced by 50% during the final 2 months of the study compared to the screening phase. The trial was designed to detect a large difference even though this population is characterised as having low seizure frequency. The number of seizures observed during the final 2 months preceding the end of the trial or trial drop out was not significantly different between the Trileptal-treated and CBZ-treated patients. Secondary analyses did not demonstrate a difference in global evaluation of therapeutic effect or scales of seizure severity. There was also no difference in the percentage of patients with a 50% reduction in seizure frequency between the OXC-treated and CBZ-treated patients (20% and 22%, respectively). The frequency and profile of adverse events were similar between the treatment groups.

Key Trileptal Adjunctive Therapy Trials

The effectiveness of Trileptal as an adjunctive therapy for partial seizures was established in two multicentre, randomised, double-blind, placebo-controlled trials, one in 692 patients (15-66 years of age) and one in 264 paediatric patients (3-17 years of age). Patients in these trials were on 1-3 concomitant AEDs. In both of the trials, patients were stabilised on optimum dosages of their concomitant AEDs during an 8-week baseline phase. Patients who experienced at least 8 (minimum of 1-4 per month) partial seizures during the baseline phase were randomly assigned to placebo or to a specific dose of Trileptal 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 (paediatrics) or 24 week (adults) maintenance period.

In the adult trial, patients received fixed doses of 600, 1200 or 2400 mg/day. In the paediatric trial, patients received maintenance doses in the range of 30-46 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 favour of Trileptal at all doses tested in both trials ($p=0.0001$ for all doses for both trials). The number of patients randomised to each dose, the median baseline seizure rate, and the median percentage seizure rate reduction for each trial are shown in Table 6. 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 section 4.8 Adverse effects (Undesirable effects)), an outcome not seen in the monotherapy studies.

Table 6: 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 (paediatrics)	Trileptal	136	12.5	34.81
	Placebo	128	13.1	9.4
2 (adults)	Trileptal 2400 mg/day	174	10.0	49.91
	Trileptal 1200 mg/day	177	9.8	40.21
	Trileptal 600 mg/day	168	9.6	26.41
	placebo	173	8.6	7.6

1 $p=0.0001$; * = # per 28 days

Subset analyses of the antiepileptic efficacy of Trileptal 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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration of Trileptal tablets, oxcarbazepine is completely absorbed and extensively metabolised to its pharmacologically active metabolite (10-monohydroxy derivative, MHD).

In a mass balance study in man, only 2% of total radioactivity in plasma was due to unchanged oxcarbazepine. Approximately 70% was due to MHD and the remainder was attributable to minor secondary metabolites which were rapidly eliminated.

After single dose administration of 600 mg Trileptal tablets to healthy male volunteers under fasted conditions, the mean C_{max} value of MHD was 34 micromol/L, with a corresponding median t_{max} of 4.5 hours.

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

Food has no effect on the rate and extent of absorption of oxcarbazepine. Therefore, Trileptal can be taken with or without food.

A study in healthy male volunteers comparing the bioavailability of Trileptal oral suspension and Trileptal tablets under fasted conditions following a single 600 mg dose and at steady state (600 mg twice daily for 4 days) shows that, at steady state, Trileptal oral suspension is bioequivalent to the 600 mg strength Trileptal tablet. The single dose and steady state results are presented in tables 7 and 8 below.

Table 7 Mean ± SD Pharmacokinetic Parameters

	SINGLE DOSE		STEADY STATE	
	Tablet	Suspension	Tablet	Suspension
AUC(0-t)* (µmol.h/L)	700 ± 136	656 ± 122	900 ± 137	916 ± 121
C _{max} (µmol/L)	31.5 ± 6.6	24.9 ± 6.1	89.4 ± 12.2	91.1 ± 17.9
T _{max} (h)	5.4 ± 2.7	6.3 ± 2.5	4.5 ± 1.5	4.0 ± 1.3
t _{1/2} (h)	9.3 ± 1.0	9.2 ± 1.8	-	-

* AUC was measured to infinity for single dose AUC(0-∞) and measured to 12 hours at steady state AUC(0-12).

Table 8 Mean Ratios (Suspension/Tablet) and 90% Confidence Intervals

	SINGLE DOSE		STEADY STATE	
	Mean Ratio	90% C.I.	Mean Ratio	90% C.I.
AUC#	0.93	0.90 - 0.97	1.02	0.99 - 1.06
C _{max} #	0.77	0.72 - 0.82	1.01	0.95 - 1.06

Geometric mean ratios and 90% confidence intervals of log-transformed data

Distribution

The apparent volume of distribution of MHD is 49 litres. Approximately 40% of MHD is bound to serum proteins, predominantly to albumin. Binding was 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 to MHD, mainly by cytosolic enzymes in the liver. MHD is primarily responsible for the pharmacological effect of Trileptal. MHD is metabolised further by conjugation with glucuronic acid. Minor amounts (4% of the dose) are oxidised to the metabolite (10, 11-dihydroxy derivative, DHD).

Excretion

Oxcarbazepine is rapidly eliminated from the plasma with apparent half-life values between 1.3 and 2.3 hours. In contrast, the apparent plasma half-life of MHD averaged 9.3 ± 1.8 h. 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. Faecal 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%), whereas the inactive DHD accounts for approximately 3% and conjugates of oxcarbazepine account for 13% of the dose.

Pharmacokinetics

Patients with hepatic impairment

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. Trileptal has not been studied in patients with severe hepatic impairment.

Patients with renal impairment

There is a linear correlation between creatinine clearance and the renal clearance of MHD. When Trileptal is administered as a single 300 mg dose to renally impaired patients (creatinine clearance < 30 mL/min), the elimination half-life of MHD is prolonged by up to 19 hours, with a two fold increase in AUC.

Children

Weight-adjusted MHD clearance decreases as age and weight increases approaching that of adults. The mean weight-adjusted clearance in children 1 month to less than 4 years of age is about 90 % higher than that of adults. Therefore, MHD exposure in these children is expected to be about one-half that of adults when treated with a similar weight-adjusted dose. The mean weight-adjusted clearance in children 4 to 12 years of age is about 40 % higher than that of adults. Therefore, MHD exposure in these children is expected to be about two-thirds that of adults when treated with a similar weight-adjusted dose. As weight increases, for patients 13 years of age and above, the weight-adjusted MHD clearance is expected to reach that of adults.

Elderly patients

Following administration of single (300 mg) and multiple doses (600 mg/day) of Trileptal to elderly volunteers (60 to 82 years of age), the maximum plasma concentrations and AUC values of MHD were 30% - 60% higher than in younger volunteers (18 to 32 years of age). Comparisons of creatinine clearances in young and elderly volunteers indicate that the

difference was due to age-related reductions in creatinine clearance. No special dose recommendations are necessary because therapeutic doses are individually adjusted.

Gender

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

In gene mutation assays, oxcarbazepine produced a slight increase in the mutation frequency of one bacteria strain in the absence of metabolic activation in one of three studies (negative in the presence of metabolic activation) and did not induce gene mutations in V79 Chinese hamster cells *in vitro*. MHD was negative in those studies. In assays of clastogenic activity, oxcarbazepine and MHD produced increases in chromosomal aberrations and polyploidy in Chinese hamster ovary cells *in vitro* in the absence of metabolic activation. Similar activity was not observed in the presence of metabolic activation, in an *in vivo* rat micronucleus assay, or with oxcarbazepine in V79 Chinese hamster cells *in vitro*.

Carcinogenicity

In 2-year studies, oxcarbazepine was administered in the diet to mice and rats at doses of up to 100 and 250 mg/kg/day, respectively. The pharmacologically active metabolite MHD was administered orally by gavage to rats only, at doses of up to 600 mg/kg/day. In mice, a dose-related increase in the incidence of hepatocellular adenomas was observed at oxcarbazepine doses greater than 40 mg/kg/day and above. In rats treated with oxcarbazepine, the incidence of hepatocellular carcinomas was increased in females at all doses levels (≥ 25 mg/kg/day). In rats treated with MHD, the incidence of hepatocellular adenomas and/or carcinomas was increased at doses of 250 mg/kg/day and above. There was an increase in the incidence of benign testicular interstitial cell tumours in rats treated with oxcarbazepine or MHD at 250 mg/kg/day. The incidence of granular cell tumours in the cervix and vagina was increased at all doses of MHD (≥ 75 mg/kg/day). Induction of hepatocellular tumours in mice and rats was probably secondary to hepatic enzyme induction; an inductive effect which, although it cannot be excluded, is weak or absent in patients treated with Trileptal. The clinical relevance of the other tumour types is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablets: colloidal anhydrous silica, microcrystalline cellulose, hypromellose, crospovidone, magnesium stearate, macrogol 8000 (300 mg tablet only), macrogol 4000 (150 and 600 mg tablets only), purified talc, titanium dioxide, iron oxide yellow (150 and 300 mg tablets only), iron oxide red (150 and 600 mg tablets only), iron oxide black (150 and 600 mg tablets only).

Oral suspension: purified water, sorbitol solution (70 percent) (non-crystallising), propylene glycol, dispersible cellulose, ascorbic acid, yellow-plum-lemon aroma, methyl hydroxybenzoate, PEG-8 stearate, sorbic acid, saccharin sodium and propyl hydroxybenzoate. Ethanol is a component of the flavour.

6.2 INCOMPATIBILITIES

Refer to section 4.5 Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in the original package below 30°C. Keep out of the reach of children. Use the oral suspension within 7 weeks of first opening the bottle.

Instructions for use and handling

Before taking Trileptal oral suspension, the bottle should be shaken well and the dose prepared immediately afterwards. The prescribed amount of oral suspension should be withdrawn from the bottle using the oral syringe supplied. The amount should be rounded to the nearest 0.5 mL when using the 10 mL syringe (supplied with the bottle containing 250 mL for older children and adults) and to the nearest 0.1 mL when using the 1 mL syringe (supplied with the bottle containing 100 mL for younger children). Trileptal oral suspension may be swallowed directly from the syringe or can be mixed in a small glass of water just prior to administration. After each use, the bottle should be closed and the outside of the syringe wiped with a dry, clean tissue.

6.5 NATURE AND CONTENTS OF CONTAINER

Tablets - Packs of 50 and 100 tablets.

Oral solution - 100mL with 1mL oral dosing syringe; 250mL with 10mL oral dosing syringe.

Not all pack sizes or container types may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

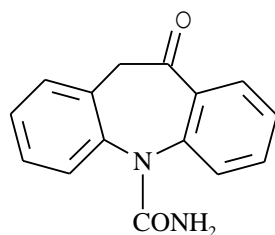
Chemical structure

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

Empirical formula: C₁₅H₁₂N₂O₂

Molecular weight: 252.3

Structural formula:



Oxcarbazepine is a white to faintly orange powder; slightly soluble in chloroform, dichloromethane, acetone and methanol; practically insoluble in ethanol, ether and water; sensitive to light in solutions. Melting point 219°C with decomposition.

CAS number

28721-07-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Novartis Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
Macquarie Park NSW 2113

9 DATE OF FIRST APPROVAL

Trileptal 150 mg tablet: 9 October 2000

Trileptal 300 mg and 600 mg tablets: 13 October 2000

Trileptal Oral Suspension: 17 December 2000

10 DATE OF REVISION

8 November 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Delete maximum recommended dose
4.2	Information on scoring
4.6	Use in Pregnancy EURAP data on major congenital malformations added.

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