

NEW ZEALAND DATA SHEET

TRILEPTAL[®] Oxcarbazepine 60 mg/mL Oral Suspension

Qualitative and quantitative composition

1 mL of the oral suspension contains 60 mg oxcarbazepine.

For a full list of excipients, see List of excipients.

Pharmaceutical form

Oral suspension.

Off-white to slightly reddish brown oral suspension.

Clinical particulars

Therapeutic indications

Trileptal[®] is indicated for the treatment of partial seizures (which include the seizure subtypes of simple, complex and partial seizures evolving to secondarily generalised seizures) and generalised tonic-clonic seizures, in adults and in children aged 1 month and above.

Trileptal is indicated as a first-line antiepileptic medicinal product for use as monotherapy or adjunctive therapy.

Trileptal can replace other antiepileptic medicinal products when current therapy provides insufficient seizure control (see Pharmacological properties - Clinical studies).

Dosage and method of administration

Dosage

Trileptal is suitable for use either as monotherapy or in combination with other antiepileptic medicinal products. In mono- and adjunctive therapy, treatment with Trileptal is initiated with a clinically effective dose given in two divided doses (see Pharmacological properties - Clinical studies). The dose may be increased depending on the clinical response of the patient. When other antiepileptic medicinal products are replaced by Trileptal, the dose of the concomitant antiepileptic medicinal product(s) should be reduced gradually on initiation of Trileptal therapy. In adjunctive therapy, as the total antiepileptic medicinal product load of the patient is increased, the dose of concomitant antiepileptic medicinal product(s) may need to be reduced and/or the Trileptal dose increased more slowly (see Interaction with other medicinal products and other forms of interaction).

Trileptal can be taken with or without food.

The prescription for Trileptal oral suspension should be given in millilitres (see Table 1 which gives the milligram dose in millilitres).

Table 1

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

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.

Trileptal oral suspension and Trileptal film-coated tablets may be interchanged at equal doses.

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

Adults and elderly patients

Monotherapy

Trileptal should be initiated with a dose of 600 mg/day (8-10 mg/kg/day) given in 2 divided doses. Good therapeutic effects are seen at doses between 600 mg/day and 2,400 mg/day. If clinically indicated, the dose may be increased by a maximum of 600 mg/day increments at approximately weekly intervals from the starting dose to achieve the desired clinical response. In a controlled hospital setting, dose increases up to 2,400 mg/day have been achieved over 48 hours.

Adjunctive therapy

Trileptal should be initiated with a dose of 600 mg/day (8-10 mg/kg/day) given in 2 divided doses. Good therapeutic effects are seen at doses between 600 mg/day and 2,400 mg/day. If clinically indicated, the dose may be increased by a maximum of 600 mg/day increments at approximately weekly intervals from the starting dose to achieve the desired clinical response.

Daily doses above 2,400 mg/day have not been studied systematically in clinical trials.

There is only limited experience with doses up to 4,200 mg/day.

Children

In mono- and adjunctive therapy, Trileptal should be initiated with a dose of 8-10 mg/kg/day given in 2 divided doses. 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. If clinically indicated, the dose may be increased by a maximum of 10 mg/kg/day increments 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 Pharmacokinetic properties).

Under adjunctive therapy and monotherapy, when normalized by body weight, apparent clearance (L/hr/kg) 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 Pharmacokinetic properties).

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

Patients with 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 dosing severely impaired patients (see Pharmacokinetic properties).

Patients with 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 Pharmacokinetic properties).

Contraindications

Known hypersensitivity to oxcarbazepine or to any of the excipients.

Special warnings and precautions for use

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.

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25-30 % of these patients may experience hypersensitivity reactions with Trileptal (see Adverse effects).

Hypersensitivity reactions, including multi-organ hypersensitivity reactions, may also occur in patients without history of hypersensitivity to carbamazepine. Such reactions can affect the skin, liver, blood

and lymphatic system or other organs, either individually or together in the context of a systemic reaction (see Adverse effects). In general, if signs and symptoms suggestive of hypersensitivity reactions occur, Trileptal should be withdrawn immediately.

Dermatological effects

Serious dermatological reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) and erythema multiforme, have been reported very rarely in association with Trileptal use. 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.

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 or in patients treated concomitantly with sodium-lowering medicinal products (e.g. diuretics, medicinal products 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 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 medicinal products, the same approach for sodium checks should be followed. In general, if clinical symptoms suggestive of hyponatraemia occur on Trileptal therapy (see Adverse 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 should be checked. If hyponatraemia is observed, water restriction is an important counter-measurement. As oxcarbazepine may, very rarely, lead to impairment of cardiac conduction, patients with pre-existing conduction disturbances (e.g. AV-block, arrhythmia) should be followed carefully.

Hepatic function

Very rare cases of hepatitis have been reported, which in most of the cases resolved favourably. In case of suspected hepatitis, discontinuation of Trileptal should be considered.

Haematological effects

Very rare reports of agranulocytosis, aplastic anemia and pancytopenia have been seen in patients treated with Trileptal during post-marketing experience (see Adverse 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 ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomized placebo controlled trials of antiepileptic drugs has shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known.

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.

Hormonal contraceptives

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 Interaction with other medicinal products and other forms of interaction). Additional non-hormonal forms of contraception are recommended when using Trileptal.

Alcohol

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

Withdrawal

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

Others

Trileptal oral suspension contains ethanol, less than 100 mg per dose. It contains parabens which may cause allergic reactions (possibly delayed). It contains sorbitol and, therefore, should not be administered to patients with rare hereditary problems of fructose intolerance.

Interaction with other medicinal products and other forms of interaction

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 medicinal products. The results demonstrate that oxcarbazepine and its pharmacologically active metabolite (the monohydroxy derivative, MHD) inhibit the CYP2C19. Therefore, interactions could arise when co-administering high doses of Trileptal with medicinal products that are metabolised by CYP2C19 (e.g. phenobarbital, phenytoin, see below). In some patients treated with Trileptal and medicinal products metabolized via CYP2C19 a reduction of the co-administered medicinal products 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*, the cytochromes CYP3A4 and CYP3A5 responsible for the metabolism of dihydropyridine calcium antagonists, oral contraceptives, and antiepileptic medicinal products (e.g. carbamazepine) resulting in a lower plasma concentration of these medicinal products (see below). Such level of 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 medicinal products 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 medicinal products 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 medicinal products

Potential interactions between Trileptal and other antiepileptic medicinal products were assessed in clinical studies. The effect of these interactions on mean AUCs and C_{min} are summarised in the following table.

Summary of antiepileptic medicinal product interactions with Trileptal

Antiepileptic medicinal product	Influence of Trileptal on antiepileptic medicinal product	Influence of antiepileptic medicinal product on MHD
Co-administered	Concentration	Concentration
Carbamazepine	0 - 22 % decrease	40 % decrease
Clobazam	Not studied	No influence
Felbamate	Not studied	No influence
Phenobarbital	14 - 15 % increase	30 - 31 % decrease
Phenytoin	0 - 40 % increase	29 - 35 % decrease
Valproic acid	No influence	0 - 18 % decrease

In vivo, the plasma levels of phenytoin increased by up to 40 %, when Trileptal was given at doses above 1,200 mg/day. Therefore, when using doses of Trileptal greater than 1,200 mg/day during adjunctive therapy, a decrease in the dose of phenytoin may be required (see Dosage and method of administration). The increase of phenobarbital level, however, is small (15 %) when given with Trileptal.

Strong inducers of cytochrome P450 enzymes (i.e. carbamazepine, phenytoin and phenobarbital) have been shown to decrease the plasma levels of MHD (29-40 %). No auto induction has been observed with Trileptal.

Hormonal contraceptives

Trileptal was shown to have an influence on the two components, ethinyloestradiol (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. Therefore, concurrent use of Trileptal with hormonal contraceptives may render these contraceptives ineffective (see Special warnings and precautions for use).

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.

Other medicinal product 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.

Pregnancy and lactation

Pregnancy

Data on a limited number of pregnancies indicate that oxcarbazepine may cause serious birth defects (e.g. cleft palate) when administered during pregnancy. In animal studies, increased embryo mortality, delayed growth and malformations were observed at maternally toxic dose levels (see Preclinical safety data).

Taking these data into consideration:

If women receiving Trileptal become pregnant, or plan to become pregnant, or if the need to initiate treatment with Trileptal arises during pregnancy, the medicinal product'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.

Minimum effective doses should be given.

In women of childbearing age, Trileptal should be administered as monotherapy, whenever possible. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

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

Monitoring and prevention

Antiepileptic medicinal products 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 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.

Postpartum MHD plasma levels may also be considered for monitoring especially in the event that medication was increased during pregnancy.

In the newborn child

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.

Oxcarbazepine and its active metabolite (MHD) cross the placenta. Neonatal and maternal plasma MHD concentrations were similar in one case.

Lactation

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.

Effects on ability to drive and use machines

The use of Trileptal has been associated with adverse reactions, such as dizziness or somnolence (see Adverse effects). Therefore, patients should be advised that their physical and/ or mental abilities required for operating machinery or driving a car might be impaired.

Adverse effects

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 adverse 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 post-marketing experience were taken into account.

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: *very common*: $\geq 1/10$; *common*: $\geq 1/100 - <1/10$; *uncommon*: $\geq 1/1,000 - <1/100$; *rare*: $\geq 1/10,000 - <1/1,000$; *very rare*: $<1/10,000$, including isolated reports.

Blood and lymphatic system disorders

Uncommon	Leucopenia.
Very rare	Bone marrow depression, agranulocytosis, aplastic anaemia, pancytopenia, neutropenia, thrombocytopenia.

Immune system disorders

Very rare	Hypersensitivity (including multi-organ hypersensitivity) characterised by features such as rash, fever. Other organs or systems may be affected such as blood and lymphatic system (e.g. eosinophilia, thrombocytopenia, leukopenia, lymphadenopathy, splenomegaly), liver (e.g. abnormal liver function tests, hepatitis), muscles and joints (e.g. joint swelling, myalgia, arthralgia), nervous system (e.g. hepatic encephalopathy), kidney (e.g. proteinuria, nephritis interstitial, renal failure), lungs (e.g. dyspnea, pulmonary oedema, asthma, bronchospasms, interstitial lung disease), angioedema, anaphylactic reactions.
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Metabolism and nutrition disorders

Common	Hyponatraemia.
Very rare	Hyponatraemia associated with signs and symptoms such as seizures, confusion, depressed level of consciousness, encephalopathy (see also Nervous system disorders for further adverse effects), vision disorders (e.g. blurred vision), vomiting, nausea, folic acid deficiency, hypothyroidism.

Psychiatric disorders

Common	Confusional state, depression, apathy, agitation (e.g. nervousness), affect lability.
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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	Arrhythmia, atrioventricular block.

Vascular disorders

Very rare	Hypertension.
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Gastrointestinal disorders

Very common	Nausea, vomiting.
Common	Diarrhoea, constipation, abdominal pain.
Very rare	Pancreatitis and/or lipase and/or amylase increase.

Hepatobiliary disorders

Very rare	Hepatitis.
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Skin and subcutaneous tissue disorders

Common	Rash, alopecia, acne.
Uncommon	Urticaria.
Very rare	Angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), erythema multiforme.

Musculoskeletal, connective tissue and bone disorders

Very rare	Systemic lupus erythematosus.
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General disorders and administration site conditions

Very common	Fatigue.
Common	Asthenia.

Investigations

Uncommon	Hepatic enzymes increased, blood alkaline phosphatase increased.
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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 Special warnings and precautions for use).

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.

Overdose

Signs and symptoms

Isolated cases of overdose have been reported. The maximum dose taken was approximately 24,000 mg. All patients recovered with symptomatic treatment. Symptoms of overdose include somnolence, dizziness, nausea, vomiting, hyperkinesia, hyponatraemia, ataxia and nystagmus.

Treatment

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

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC code: N03A F02

Pharmacodynamic effects

The pharmacological activity of Trileptal (oxcarbazepine) is primarily exerted through the metabolite (MHD) of oxcarbazepine (see Pharmacokinetic properties - Biotransformation). 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. 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 aluminum 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 studies

A total of 10 double blind, well controlled trials, 2 in adjunctive therapy and 8 in 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 antiepileptic medicinal products which included carbamazepine, gabapentin, lamotrigine, phenytoin, and valproate confirm efficacy when these antiepileptic medicinal products 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/day to 2,400 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.

An adjunctive therapy, rater-blind, trial in children (aged 1 month to less than 4 years) with inadequately-controlled partial seizures on one to two concomitant antiepileptic medicinal products was conducted, comparing two doses of oxcarbazepine. The primary measure of effectiveness was a between group comparison of the absolute change in study specific seizure frequency per 24 hours compared to the seizure frequency at baseline. This comparison was statistically significant in favour of Trileptal 60 mg/kg/day. A monotherapy, rater-blind, trial in children (aged 1 month to 16 years) with inadequately controlled or new-onset partial seizures was conducted comparing two doses of oxcarbazepine. The primary measure of effectiveness was a between group comparison of the time to meet exit criteria which was not statistically significant. The majority of patients in both treatment groups did not experience any video EEG-confirmed seizures during the study and completed this 5-day study without exiting.

It has been shown that Trileptal has similar efficacy to other first line antiepileptic medicinal products (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 significant 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.

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). After single dose administration of 600 mg Trileptal oral suspension to healthy male volunteers under fasted conditions, the mean C_{max} value of MHD was 24.9 micromol/L, with a corresponding median t_{max} of 6 hours.

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 attributable to minor secondary metabolites which were rapidly eliminated.

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

Distribution

The apparent volume of distribution of MHD is 49 litres.

Approximately 40 % of MHD, is bound to serum proteins, predominately 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.

Biotransformation

Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to MHD, which 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 pharmacologically inactive metabolite (10,11-dihydroxy derivative, 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. 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.

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 hours.

Dose proportionality

Steady-state plasma concentrations of MHD are reached within 2 to 3 days in patients when Trileptal is given twice a day. At steady-state, the pharmacokinetics of MHD is linear and show dose proportionality across the dose range of 300 to 2,400 mg/day.

Special populations

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, in 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 93 % 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 43 % 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.

Pregnancy

Due to physiological changes during pregnancy, MHD plasma levels may gradually decrease throughout pregnancy (see Pregnancy and Lactation).

Elderly

Following administration of single (300 mg) and multiple doses (600 mg/day) of Trileptal in 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 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.

Preclinical safety data

Preclinical data indicated no special hazard for humans based on repeated dose toxicity, safety pharmacology and genotoxicity studies with oxcarbazepine and the pharmacologically active metabolite, monohydroxy derivative (MHD).

Evidence of nephrotoxicity was noted in repeated dose toxicity rat studies but not in dog or mice studies. As there are no reports of such changes in patients, the clinical relevance of this finding in rats remains unknown.

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

Animal studies revealed effects such as increases in the incidence of embryo mortality and some delay in antenatal and/or postnatal growth at maternally toxic dose levels. There was an increase in rat foetal malformations in one of the eight embryo toxicity studies, which were conducted with either oxcarbazepine or the pharmacologically active metabolite (MHD), at a dose which also showed maternal toxicity (see Pregnancy and Lactation).

In the carcinogenicity studies, liver (rats and mice), testicular and female genital tract granular cell (rats) tumours were induced in treated animals. The occurrence of liver tumours was most likely a consequence of the induction of hepatic microsomal enzymes; an inductive effect which, although it cannot be excluded, is weak or absent in patients treated with Trileptal. Testicular tumours may have been induced by elevated luteinizing hormone concentrations. Due to the absence of such an increase in humans, these tumours are considered to be of no clinical relevance. A dose-related increase in the incidence of granular cell tumours of the female genital tract (cervix and vagina) was noted in the rat carcinogenicity study with MHD. These effects occurred at exposure levels comparable with the anticipated clinical exposure. The mechanism for the development of these tumours has not been elucidated. Thus, the clinical relevance of these tumours is unknown.

Pharmaceutical particulars

List of excipients

Propyl parahydroxybenzoate (E 216); saccharin sodium; sorbic acid (E 200); macrogol stearate 400; methyl parahydroxybenzoate (E 218); yellow-plum-lemon flavour; ascorbic acid (E 300); dispersible cellulose; propylene glycol; sorbitol 70 % (non-crystallising); water purified.

Ethanol is a component of the flavour.

Incompatibilities

None known.

Shelf life

Three years.

Use within 7 weeks after first opening the bottle.

Special precautions for storage

Store in the original package.

Trileptal must be kept out of the reach and sight of children.

Nature and content of container

Brown (amber) glass bottles with a child resistant cap, packed in a cardboard box together with a polypropylene oral syringe and press-in bottle adaptor.

Pack sizes:

100 mL with 1 mL oral syringe.

250 mL with 10 mL oral syringe.

Instructions for use and handling, and disposal

No special requirements.

Medicine classification

Prescription Medicine

Name and address

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Date of preparation

10 October 2011