NOVARTIS

TRILEPTAL®

300 mg and 600 mg Oxcarbazepine per film-coated tablet

Professional Information

Document status: Final

Approval date: 18 September 2026

Property of Novartis
Confidential
May not be used, divulged, published or otherwise disclosed
without the consent of Novartis

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

TRILEPTAL® 300 Film-coated tablets

TRILEPTAL® 600 Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

300 mg or 600 mg oxcarbazepine per film-coated tablet.

3. PHARMACEUTICAL FORM

TRILEPTAL 300

Yellow, ovaloid, slightly biconvex, film-coated tablets scored on both sides. Embossed with “TE/TE” on one side and “CG/CG” on the other side.

Length: Approximately 15,2 mm

Width: Approximately 6,7 mm

Thickness: Approximately 4,9 mm

TRILEPTAL 600

Light-pink, ovaloid, slightly biconvex, film-coated tablets scored on both sides.

Embossed with “TF/TF” on one side and “CG/CG” on the other side.

Length: Approximately 18,7 mm

Width: Approximately 8,2 mm

Thickness: Approximately 6,4 mm

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TRILEPTAL is indicated for the treatment of partial seizures with or without secondary generalised seizures and generalised tonic-clonic seizures, in adults.

TRILEPTAL may be used as monotherapy or adjunctive therapy in adults.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

TRILEPTAL is suitable for use either as monotherapy or in combination with other anti-epileptic medicinal products. In mono- and adjunctive therapy, treatment with TRILEPTAL is initiated with a clinically effective dose given in two divided doses. The dose may be increased depending on the clinical response of the patient. When other antiepileptic medicinal products (AEMPs) are replaced by TRILEPTAL, the dose of the concomitant AEMP(s) should be reduced gradually on initiation of TRILEPTAL therapy. In adjunctive therapy, as the total antiepileptic medicinal products load of the patient is increased, the dose of concomitant AEMP(s) may need to be reduced and/or the TRILEPTAL dose increased more slowly (see section 4.5).

TRILEPTAL can be taken with or without food.

Method of administration:

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

The 300 mg tablets are scored and can be broken into two halves in order to make it easier for the patients to swallow the tablet.

Therapeutic drug monitoring

The therapeutic effect of oxcarbazepine is primarily exerted through the active metabolite 10-monohydroxy derivative (MHD) of oxcarbazepine (see section 5).

Plasma level monitoring of oxcarbazepine or MHD is not routinely warranted. However, plasma level monitoring of MHD may be considered during TRILEPTAL therapy in order to rule out noncompliance, or in situations where an alteration in MHD clearance is to be expected, including:

- changes in renal function (see section 4.2)
- pregnancy (see section 4.6)
- concomitant use of liver enzyme-inducing drugs (see section 4.5)

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

Adults:

Monotherapy and adjunctive therapy*:*

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 increments at approximately weekly intervals from the starting dose 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. Most adult patients are controlled on dosages of 900 - 1200 mg/day.

Daily doses from 600 to 2400 mg/day have been shown to be effective in a controlled adjunctive therapy trial, although most patients were not able to tolerate the 2400 mg/day dose without reduction of concomitant anti-epileptic drugs, mainly because of CNS-related adverse events.

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

Elderly (65 years or above):

Dosages in the elderly may need to be reduced based on decreased renal function. Close monitoring of sodium levels is required in patients at risk of hyponatraemia (see section 4.4).

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 section 5.2).

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 section 5.2).

4.3 CONTRAINDICATIONS:

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

4.4 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 medication 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 section 4.8).

Hypersensitivity reactions, including multi-organ hypersensitivity reactions, may also occur in patients without a 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 section 4.8). If signs and symptoms suggestive of hypersensitivity reactions (e.g. severe skin 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 in association with TRILEPTAL use. Patients with serious dermatological reactions may require hospitalisation, as these conditions may be life-threatening and, very rarely, fatal. TRILEPTAL-associated cases occurred in 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.

Patients should be made aware of early toxic signs of the above-mentioned reactions, e.g. fever, rash, lesions in the mouth, bruising, purpura. They should be advised to contact their doctor immediately if such a reaction appears.

Alcohol:

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

Withdrawal:

TRILEPTAL should be withdrawn gradually to minimise the potential for increased seizure frequency. If TRILEPTAL has to be discontinued abruptly, e.g. owing to severe adverse reactions, the change-over to another anti-epileptic preparation should be effected under cover of suitable medication (e.g. diazepam I.V; rectal; phenytoin I.V.) and under close supervision.

TRILEPTAL should be given only under medical supervision.

Risk of seizure aggravation:

Risk of seizure aggravation has been reported with TRILEPTAL. The risk of seizure aggravation may 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. If clinical intervention is considered, 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 section 4.8), 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 the 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 countermeasure. As TRILEPTAL may lead to impairment of cardiac conduction, patients with pre-existing conduction disturbances (e.g. AV block, dysrhythmia) should be followed carefully.

If during treatment, low or decreased white blood cell or platelet counts are observed, the complete blood count and the patient should be monitored closely. TRILEPTAL should be discontinued if any evidence of significant bone marrow depression appears.

Hypothyroidism:

Hypothyroidism is a very rare adverse drug reaction of oxcarbazepine.

Hepatic function:

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. Caution should be exercised when treating patients with severe hepatic impairment (see section 4.2).

Haematological effects:

Agranulocytosis, aplastic anaemia and pancytopaenia have been reported in patients treated with TRILEPTAL during post-marketing experience (see section 4.8). 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 medicine 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 (see section 4.4). A meta-analysis of randomised placebo-controlled trials of antiepileptic medicines, including TRILEPTAL, 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 section 4.5). Additional non-hormonal forms of contraception are recommended when using TRILEPTAL.

Patients with renal dysfunction and elderly patients should be carefully monitored as they are at higher risk of adverse reactions (see section 5.2).

TRILEPTAL has a low enzyme-inducing potential. If, in patients on adjunctive therapy, carbamazepine or other antiepileptics with enzyme-inducing properties are withdrawn and replaced by TRILEPTAL, serum concentrations of the concurrent antiepileptic medicine should be monitored to avoid possible toxicity; it may be necessary to reduce the dosage of the antiepileptic co-medication (see section 4.5).

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

In vitro and *in vivo* studies demonstrate that TRILEPTAL has a low potential for interactions with other medicines.

Enzyme inhibition:

TRILEPTAL 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 TRILEPTAL and its pharmacologically active metabolite (the monohydroxy derivative, MHD) have little or no capacity to function as inhibitors for most of the human cytochrome P450 enzymes evaluated (CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP4A9 and CYP4A11) with the exception of CYP2C19. Therefore, interactions could arise when co-administering high doses of

TRILEPTAL with medicinal products that are metabolised by CYP2C19 (e.g. phenobarbitone, phenytoin). In some patients treated with TRILEPTAL and medicinal products metabolised via CYP2C19 a reduction of the co-administered medicinal product might be necessary.

Enzyme induction:

In vitro, the UDP-glucuronyl transferase level was increased, indicating induction of this enzyme. An increase of 22 % with MHD and 47 % with TRILEPTAL were observed. TRILEPTAL 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 TRILEPTAL and MHD, a higher dose of concomitantly used medicinal products which are metabolised via CYP3A4 or via conjugation (UDPGT) may be necessary. In case of discontinuation of TRILEPTAL therapy, a dose reduction of the concomitant medication may be necessary.

Induction studies conducted with human hepatocytes confirmed TRILEPTAL and MHD as weak inducers of isoenzymes of the 2B and 3A4 CYP sub-family. The induction potential of TRILEPTAL/MHD on other CYP isoenzymes is not known.

TRILEPTAL and MHD induce *in vitro* and *in vivo,* a subgroup of the cytochrome P450 3A family (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 medicines mainly metabolised by CYP3A4 and CYP3A5, for example immunosuppressants (e.g. ciclosporin).

Antiepileptic medicinal products:

Potential interactions between TRILEPTAL and other antiepileptic medicinal products (AEMPs) 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 products interactions with TRILEPTAL

AEMP	**Influence of TRILEPTAL on AEMP**	**Influence of AEMP on MHD**
Co-administered	Concentration	Concentration
Carbamazepine	0 - 22 % decrease (30 % increase of carbamazepine-epoxide)	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

In vivo, the 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.

The increase of phenobarbitone level, however, is small (15 %) when given with TRILEPTAL.

Strong inducers of cytochrome P450 enzymes and/or UGT (i.e. rifampicin, carbamazepine, phenytoin and phenobarbitone) have been shown to decrease the plasma levels of MHD (29 – 49 %).

No auto-induction 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. Therefore, concurrent use of TRILEPTAL with hormonal contraceptives may render these contraceptives less effective (see section 4.4).

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 products interactions:

Cimetidine and erythromycin 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.

The interaction between oxcarbazepine and MAOIs is theoretically possible based on a structural relationship of oxcarbazepine to tricyclic antidepressants.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy:

Data on a limited number of pregnancies indicate that TRILEPTAL 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. Data on epileptic pregnant women receiving oxcarbazepine and unborn child exposed to oxcarbazepine during pregnancy remain inconclusive. However, risk of potential teratogenicity and neurodevelopmental disorders cannot be excluded.

Taking these data into consideration:

- If women receiving TRILEPTAL become pregnant, plan to become pregnant, or if the need to initiate treatment with TRILEPTAL arises during pregnancy, the medicinal products' potential benefits must be carefully weighed against the potential risk of foetal malformations (e.g. cleft palate). 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. The potential for congenital abnormalities in the offspring of women treated with combination therapies is greater than those receiving monotherapy.
- Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.
- During pregnancy, 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 such as TRILEPTAL 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 K_1 should be administered as a preventive measure in the last few weeks of pregnancy and to the newborn.

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

Lactation:

Breastfeeding while taking TRILEPTAL is not recommended. TRILEPTAL and its active metabolite (MHD) are excreted in breast milk. Limited data indicate that the breastfed infants' MHD plasma concentrations correspond up to 5 % of the maternal MHD plasma concentration. Although exposure appears to be low, risk to the infant cannot be excluded.

Infertility:

There are no human data on fertility.

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

4.7 Effects on the ability to drive and use machines

Adverse reactions such as dizziness, somnolence, ataxia, diplopia, blurred vision, visual disturbances, hyponatraemia and depressed level of consciousness were reported with TRILEPTAL (for the complete list of undesirable effects, see section 4.8), especially at the start of treatment or in connection with dose adjustments (more frequently during the up-titration phase). Patients should therefore exercise due caution when driving a vehicle or operating machinery.

4.8 UNDESIRABLE 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 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 post-marketing experience were taken into account.

Adverse reactions are ranked under headings of frequency, with the most frequent first, using the following convention:

very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon

(≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), including isolated reports.

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 rash and fever. Other organs or systems may be affected, such as the blood and lymphatic system (e.g. eosinophilia, thrombocytopenia, leucopenia, lymphadenopathy, splenomegaly); liver (e.g. hepatitis, abnormal liver function tests); muscle and joints (e.g. joint swelling, myalgia, arthralgia); nervous system (e.g. hepatic encephalopathy); kidney (e.g. renal failure, nephritis interstitial, proteinurea; lungs (e.g. pulmonary oedema, asthma, bronchospasms, interstitial lung disease, dyspnoea); and 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 also **Nervous system disorders** for further undesirable effects), vision disorders (e.g. blurred vision), vomiting, and nausea, folic acid deficiency and hypothyroidism.
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, dysrhythmia.
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.
∗ **according to CIOMS III frequency classification**	

Adverse reactions occurring at an incidence of ≥ 1 % - < 10 % (common) were: ataxia, irritability, vomiting, lethargy, fatigue, nystagmus, tremor, decreased appetite, and blood uric acid increased.

Post-Marketing reported Side-Effects

The following adverse drug reactions have been derived from post-marketing experience with TRILEPTAL via spontaneous case reports and literature cases. It is not possible to reliably estimate their frequency. 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 lethargy, nausea, dizziness, decrease in serum (blood) osmolality, vomiting, headache, confusional state or other neurological signs and symptoms

Immune system disorders:

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).

Skin and subcutaneous tissue disorders:

Acute Generalised Exanthematous Pustulosis (AGEP).

Injury, poisoning and procedural complications

Fall.

Nervous system disorders

Speech disorders (including dysarthria); more frequent during up-titration of the 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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any

suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose:

Symptoms of overdose include somnolence, dizziness, nausea, vomiting, hyperkinesia, hyponatraemia, ataxia and nystagmus. There is no specific antidote. Treatment is symptomatic and supportive. Removal of the medicine by administering activated charcoal should be considered.

5. PHARMACOLOGICAL PROPERTIES

PHARMACOLOGICAL ACTION

5.1 Pharmacodynamic properties:

A 2.5 Anticonvulsants, including anti-epileptics

Pharmacotherapeutic group: Antiepileptics, ATC code: N03A F 02

Oxcarbazepine and its active, 10-monohydroxy metabolite (monohydroxy derivative), are anticonvulsants. The pharmacological activity of oxcarbazepine is primarily exerted through its metabolite (monohydroxy derivative - MHD) and is thought to be mainly based on blockade of voltage-sensitive sodium channels, thus resulting in stabilisation of hyper-excited 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.

5.2 Pharmacokinetic properties:

Absorption:

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

After single dose administration of 600 mg oxcarbazepine to healthy male volunteers under fasted conditions, the mean C_{max} value of MHD was 34 μmol/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 oxcarbazepine 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.

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, oxcarbazepine can be taken with or without food.

Distribution:

The apparent volume of distribution of MHD is 49 litres.

Forty percent of the active metabolite, the monohydroxy derivative, 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.

Biotransformation:

Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to MHD, which is primarily responsible for the pharmacological effect of oxcarbazepine. 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 the active metabolite (MHD) averaged 9,3 ± 1,8 h. Upon repeated oral dosing of oxcarbazepine, the pharmacokinetics of the unchanged medicine and its active metabolite do not change, indicating absence of auto-induction and accumulation characteristics.

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. Oxcarbazepine 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 oxcarbazepine is administered as a single 300 mg dose in renal impaired patients (creatinine clearance < 30 mL/min), the elimination half-life of MHD is prolonged, with a corresponding 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.

Elderly:

Following administration of single (300 mg) and multiple doses (600 mg/day) of oxcarbazepine in elderly volunteers (60 - 82 years of age), the maximum plasma concentrations and AUC values of MHD were 30 % - 60 % higher than in younger volunteers (18 - 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 adults or the elderly.

Pregnancy:

Due to physiological changes during pregnancy, MHD plasma levels may gradually decrease throughout pregnancy (see section 4.6).

6. LIST OF PHARMACEUTICAL PARTICULARS

6.1 EXCIPIENTS

Tablet core: silica, colloidal anhydrous; microcrystalline cellulose; hypromellose; crospovidone; magnesium stearate

Tablet coating: for the 300 mg tablet: hypromellose, macrogol 8000, yellow iron oxide (E 172), talc, titanium dioxide (E 171); and for the 600 mg tablet: hypromellose, macrogol 4000, red iron oxide (E 172), black iron oxide (E 172), talc, titanium dioxide (E 171).

6.3 SHELF-LIFE

24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Blister packs:

Store at or below 30 °C and protect from moisture.

Plastic containers:

Store at or below 30 °C and protect from moisture. Keep well closed.

6.5 NATURE AND CONTENTS OF THE CONTAINER

TRILEPTAL 300 and 600 film-coated tablets are supplied in blister packs of 50 or plastic containers of 60.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd

Magwa Crescent West,

Waterfall City, Jukskei View

Johannesburg, 2090

+27113476600

8. REGISTRATION NUMBER:

TRILEPTAL 300: X/2.5/205

TRILEPTAL 600: X/2.5/206

9. DATE OF FIRST AUTHORISATION

9 March 1994 (300 mg)

5 March 1994 (600 mg)

10. DATE OF REVISION OF THE TEXT

18 September 2026

2023-PSBGLC-1361-s