Trileptal®

Composition

Active substance: Oxcarbazepine

Excipients:

Film-coated tablets: Tableting excipients

Oral suspension: Saccharin, flavouring agents, vanillin, preservatives: E200, E216, E218, excipients to 1 ml

Pharmaceutical form and quantity of active substance per unit

Film-coated tablets (scored on both sides) containing 150 mg, 300 mg or 600 mg oxcarbazepine.

Oral suspension containing 60 mg/ml oxcarbazepine (incl. 1 ml or 10 ml oral dosing syringe).

Indications/Potential uses

Trileptal is used in the treatment of partial seizures (with or without secondary generalised tonic-clonic seizures) and generalised tonic-clonic seizures.

Trileptal is used in adults and in children aged 1 month and above.

Dosage/Administration

Administration

Trileptal is suitable for use either as monotherapy or as combination therapy with other antiepileptic drugs (AEDs). In both monotherapy and combination therapy treatment with Trileptal should be initiated at a clinically effective dose given in two divided doses per day. The dose may be increased depending on the patient's clinical response. In combination therapy it may be necessary to reduce the dose of the concomitant AED and/or to increase the Trileptal dose more slowly (see "Interactions") due to the increase in the patient's total AED dose.

Trileptal can be taken with or without food.

The tablets are scored and can be broken into two halves to facilitate administration for the patient.

The oral suspension is suitable for younger children and other patients who cannot swallow film-coated tablets or for whom the required dose cannot be achieved by dividing the film-coated tablets.

Before using Trileptal oral suspension, the bottle must be shaken well. The prescribed amount must then be immediately withdrawn from the bottle. To withdraw the prescribed amount of oral suspension from the bottle, the oral dosing syringe supplied should be used. The amount should be rounded to the nearest 0.1 ml when using the 1 ml oral dosing syringe (supplied with the 100 ml bottle for younger children) and to the nearest 0.5 ml when using the 10 ml oral dosing syringe (supplied with the 250 ml bottle for older children and adults).

The oral suspension may be swallowed directly from the oral dosing syringe or stirred into a small glass of water just before administration. After each use the bottle must be closed and the outside of the syringe cleaned with a dry, clean paper tissue.

Trileptal film-coated tablets and oral suspension are bioequivalent and interchangeable at equal doses (see “Pharmacokinetics”).

The prescription for Trileptal oral suspension should be given in millilitres (see conversion table below, which gives the corresponding quantity in millilitres for each milligram dose):

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
1000 mg	16.7 ml

Dosage

The therapeutic effect of oxcarbazepine is primarily mediated by the active metabolite 10-monohydroxy derivative (MHD) of oxcarbazepine (see "Properties/Actions", "Pharmacodynamics").

Routine monitoring of oxcarbazepine or MHD plasma concentrations is not required. However, MHD plasma concentration monitoring should be considered during Trileptal therapy to rule out a lack of treatment compliance or in situations where a change in MHD clearance is to be expected, including:

- changes in renal function (see "Patients with renal impairment" below)
- pregnancy (see "Pregnancy/Breast-feeding" and "Properties/Actions")
- concomitant use of liver enzyme-inducing drugs (see "Interactions").

The Trileptal dose may be adjusted in the situations mentioned above (based on the plasma concentration measured 2-4 hours after dosing) to maintain the peak MHD plasma concentration at <35 mg/l. The weight-adjusted MHD clearance (l/h/kg) is considerably higher in children than in adults (see "Special dosage instructions").

Adults: Monotherapy and combination therapy

The following dosage instructions apply to adult patients who do not have renal impairment.

Recommended initial dose

Treatment with Trileptal may be initiated at a daily dose of 600 mg (8-10 mg/kg/day) given in 2 divided doses. The daily dose may be increased at one-week intervals in increments not exceeding 600 mg to achieve the desired effect.

Maintenance dose

The maintenance dose ranges from 600 to 2400 mg/day with most patients responding to a dose of 900 mg/day.

Maximum recommended dose

Controlled monotherapy studies in patients not previously treated with antiepileptic drugs have demonstrated the efficacy of a daily dose of 1200 mg. In difficult-to-treat patients who had been switched from other antiepileptic drugs to monotherapy with Trileptal a daily dose of 2400 mg proved effective. In combination therapy most patients did not tolerate a maximum daily dose of 2400 mg Trileptal without reducing the dose of the co-administered antiepileptic drugs, mainly due to adverse CNS effects.

Daily doses above 2400 mg have not been studied systematically.

Special dosage instructions

Children and adolescents

Trileptal is intended for use in children aged 1 month and above. There have been no controlled clinical trials in children aged below 1 month.

Recommended initial dose

In monotherapy and combination therapy treatment should be initiated at a dose of 8-10 mg/kg/day given in two divided doses.

Maintenance dose

The target Trileptal maintenance dose in combination therapy is 30-46 mg/kg/day and should be achieved within two weeks.

In a combination therapy study in children and adolescents aged 3 to 17 years in which the intention was to reach a daily target dose of 46 mg/kg/day the median daily dose was 31 mg/kg/day (range: 6 to 51 mg/kg/day). In a combination therapy study in children aged 1 month to under 4 years in which the intention was to achieve a daily target 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 daily dose may be increased at one-week intervals in increments not exceeding 10 mg/kg/day, up to a maximum dose of 60 mg/kg/day, to achieve the desired effect.

Effect of weight-adjusted MHD clearance on paediatric dosage

In both combination therapy and monotherapy MHD (active metabolite of oxcarbazepine) clearance based on body weight (l/h/kg) is considerably higher in children (particularly those aged from 1 month to under 4 years) than in adults (see "Pharmacokinetics"). Therefore, children aged from 1 month to <4 years may require double the oxcarbazepine dose per kg body weight and children aged from 4 to 12 years may require a 50% higher oxcarbazepine dose per kg body weight.

Effect of co-administered enzyme-inducing antiepileptic drugs on paediatric dosage

In children aged from 1 month to under 4 years the influence of enzyme-inducing antiepileptic drugs on weight-normalised clearance appears to be greater than in older children. Children aged from 1 month to under 4 years receiving combination therapy with enzyme-inducing antiepileptic drugs may require a 60% higher oxcarbazepine dose per body weight compared to monotherapy or combination therapy with non-enzyme-inducing antiepileptic drugs. Older children (≥4 years) treated with enzyme-inducing antiepileptic drugs may require only a slightly higher dose per body weight than those receiving monotherapy.

The dosage recommendations given above (adults, elderly patients and children) are based on doses used in clinical studies in all age groups. However, lower starting doses may also be used where indicated.

Elderly patients (aged 65 and over)

It is not necessary to adjust the dose based on age alone as the therapeutic oxcarbazepine dose is determined individually (see "Pharmacokinetics"). However, dose adjustment is recommended in elderly patients with renal impairment (creatinine clearance <30 ml/min) (see "Patients with renal impairment"). Close monitoring of sodium levels is required in patients at risk of hyponatraemia (see "Warnings and precautions").

Patients with hepatic impairment

No dose adjustment is required in patients with mild to moderate hepatic impairment. Trileptal has not been studied in patients with severe hepatic impairment. Therefore, caution is advised when administering Trileptal to such patients (see "Warnings and precautions" and "Pharmacokinetics").

Patients with renal impairment

In patients with renal impairment (creatinine clearance <30 ml/minute) Trileptal therapy should be initiated at half the usual starting dose (300 mg/day) and increased at intervals of no less than one week until the desired clinical response is achieved (see "Warnings and precautions" and "Pharmacokinetics"). Patients with renal impairment must be closely monitored when increasing the dose.

Contraindications

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

Warnings and precautions

Hypersensitivity reactions

Hypersensitivity reactions, including class I reactions and other hypersensitivity reactions, have been reported under treatment with oxcarbazepine. If such symptoms develop, Trileptal should be discontinued and the patient switched to treatment with another antiepileptic drug.

Class I reactions: Symptoms ranging from rash, pruritus, urticaria, dyspnoea, bronchospasm and angioedema to anaphylactic shock have been reported. The cases of anaphylactic angioedema involved the larynx, tongue, lips and eyelids; such reactions were observed both after the first dose and after subsequent doses of Trileptal.

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that the cross-reaction rate for hypersensitivity reactions (e.g. serious skin reactions) with Trileptal treatment is 25-30%. For this reason patients should be specifically asked about previous treatment with carbamazepine before starting Trileptal therapy. Patients with a history of hypersensitivity reactions to carbamazepine should generally only be treated with Trileptal if the potential benefit justifies the potential risk. If signs or symptoms of hypersensitivity develop, Trileptal should be discontinued immediately.

Other hypersensitivity reactions, including multi-organ hypersensitivity reactions: Such reactions have been observed both in adults and children in close temporal association (mostly within the first 3 weeks, possibly also later) with the commencement of treatment. Symptoms varied greatly. Patients normally exhibited not only fever and a rash, but also involvement of other organ systems. In this context there have been reports of asthenia, pruritus, arthralgia, joint swelling, lymphadenopathy, splenomegaly, haematological abnormalities (e.g. eosinophilia, thrombocytopenia, neutropenia), pulmonary oedema, interstitial lung changes, abnormal liver function tests, hepatitis, proteinuria, oliguria, interstitial nephritis, renal failure and hepatorenal syndrome. Symptoms in other organ systems may also occur. Some cases led to hospitalisation, with isolated cases being regarded as life-threatening.

Such hypersensitivity reactions were also observed in patients without a history of hypersensitivity to carbamazepine.

Serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis (drug-induced Lyell's syndrome) and erythema multiforme have been reported in very rare cases in association with Trileptal use. Patients with serious skin reactions may require hospitalisation as these conditions are life-threatening. Trileptal-associated cases have occurred in both children and adults. The median time to onset was 19 days.

Should a patient develop a skin reaction with Trileptal, consideration should be given to discontinuing Trileptal and switching to another antiepileptic therapy. Several isolated cases of recurrence of a serious skin reaction upon resuming Trileptal treatment have been reported.

There is growing evidence that different HLA alleles play a role in connection with adverse immune and skin reactions in predisposed patients.

*Association with the HLA-B*1502 allele*

Retrospective studies in patients of Han Chinese or Thai descent demonstrated a strong correlation between SJS/TEN skin reactions associated with the use of carbamazepine and the presence of the human leukocyte antigen (HLA)-B*1502 allele. As the chemical structure of oxcarbazepine is similar to that of carbamazepine, patients carrying the HLA-B*1502 allele are also presumed to have an increased risk of SJS/TEN skin reactions with oxcarbazepine. Some data describe such an association for oxcarbazepine as well.

The prevalence of carriers of this allele is around 20% in the Philippines, 13.5% in Vietnam, 2-12% in the Han Chinese population, at least 8% in Thailand and 2-6% in Korea and India. In contrast, the prevalence of the HLA-B*1502 allele is negligible (<1%) in the Caucasian, African, Japanese, indigenous American and Hispanic populations.

The values given here relate to the prevalence of homozygous allele carriers. The proportion of heterozygotes (and thus of people with a potentially increased risk of skin reactions) is nearly twice as high.

Patients at increased risk because of their descent should be tested before initiating treatment with Trileptal to determine if they are carriers of the HLA-B*1502 allele. Trileptal should not be used in patients who test positive unless the benefits clearly outweigh the risks. When making a decision regarding therapy, it must be borne in mind that HLA-B*1502 is also a risk factor for other antiepileptic drugs. Screening for HLA-B*1502 is not required in population groups with a low prevalence. Similarly, screening is not appropriate in patients who have already used Trileptal for a prolonged period as SJS/TEN usually occurs only in the first few months of therapy.

*Association with the HLA-A*3101 allele*

The human leukocyte antigen (HLA)-A*3101 may be a risk factor for the development of adverse skin reactions such as SJS/TEN, drug rash with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP) and maculopapular rash. In particular, there are data that suggest that the HLA-A*3101 allele is associated with an increased risk of

carbamazepine-induced skin reactions (SJS/TEN, DRESS, AGEP) and maculopapular rash.

The prevalence of this allele varies widely in different ethnic populations. The prevalence in the European population is around 2-5% and around 10% in the Japanese population. The prevalence of this allele is estimated to be less than 5% in the majority of the Australian, Asian, African and North American populations.

The values given here relate to the prevalence of homozygous allele carriers. The proportion of heterozygotes (and thus of people with a potentially increased risk of skin reactions) is nearly twice as high.

Screening for HLA-A*3101 is not recommended in population groups with a low prevalence. Similarly, screening is not appropriate in patients who have already used Trileptal for a prolonged period as SJS/TEN, DRESS, AGEP and maculopapular rash usually occur only in the first few months of therapy.

Patients of European or Japanese descent who carry the HLA-A*3101 allele may be treated with Trileptal provided that the benefits outweigh the risks.

Genetic screening results are not a substitute for appropriate monitoring of the patient, particularly as the risk of severe skin reactions may also be influenced by other factors (such as comorbidities).

Risk of seizure aggravation

A risk of seizure aggravation has been reported with Trileptal. The risk of seizure aggravation is primarily exists in children, but it may also exist in adults. In case of seizure aggravation Trileptal should be discontinued.

Hyponatraemia

In up to 2.7% of patients treated with Trileptal serum sodium levels fell below 125 mmol/l, which was usually asymptomatic and did not require adjustment of therapy. If clinical intervention is being considered, experience from clinical studies shows that serum sodium levels return to baseline once the Trileptal dose is reduced, Trileptal is discontinued or the patient is treated conservatively (e.g. by restricted fluid intake).

Serum sodium levels should be measured prior to initiating therapy in patients with pre-existing renal conditions requiring a high fluid intake, patients with pre-existing low sodium levels (e.g. syndrome of inappropriate ADH secretion) and

patients treated concomitantly with sodium-lowering medicinal products (e.g. diuretics, desmopressin) or with NSAIDs (e.g. indomethacin). Thereafter, serum sodium levels should initially be measured after approximately two weeks and then at monthly intervals for the first three months of treatment or according to clinical need. The aforementioned risk factors are particularly present in elderly patients. For patients on Trileptal therapy in whom treatment with sodium-lowering medicinal products is being initiated the same approach should be followed to determine serum sodium levels. In general, if clinical symptoms suggestive of hyponatraemia occur during Trileptal treatment, serum sodium measurement should be considered. In all other patients it is sufficient to assess serum sodium levels as part of routine laboratory tests.

Very rarely, clinically relevant hyponatraemia (Na <125 mmol/l) can develop during Trileptal therapy. This generally occurred during the first 3 months of treatment, although there were patients who first developed a serum sodium level <125 mmol/l one year following initiation of therapy. Cases were also observed involving seizures, disorientation, depressed level of consciousness, encephalopathy, visual disturbances (e.g. blurred vision), vomiting, nausea and folic acid deficiency.

In isolated cases syndrome of inappropriate ADH secretion (SIADH) may occur under Trileptal therapy.

Pre-existing cardiac disease

Patients with heart failure should have regular weight measurements to determine the occurrence of fluid retention. In case of fluid retention or worsening of cardiac function serum sodium levels should be measured. If hyponatraemia is determined, fluid restriction is an important treatment measure.

As oxcarbazepine may in very rare cases lead to impairment of cardiac conduction, patients with pre-existing conduction disturbances (e.g. AV block, arrhythmias) should be carefully monitored.

Hypothyroidism

Hypothyroidism is a very rare adverse effect of oxcarbazepine. In view of the importance of thyroid hormones for childhood development after birth it is advisable to carry out a thyroid function test before initiating Trileptal therapy in the paediatric age group, particularly in children aged 2 years and under. In the

paediatric age group it is also recommended to monitor thyroid function during Trileptal therapy. In patients with hypothyroidism monitoring of thyroid function is recommended to determine the dose for hormone replacement therapy.

Suicidality

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic drugs in several indications. A meta-analysis of randomised, placebo-controlled studies with antiepileptic drugs also showed a slightly increased risk of suicidal ideation and behaviour. The mechanism triggering this adverse effect is not known and the available data do not rule out the possibility of an increased risk when taking Trileptal.

Therefore, patients should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and their carers) should be advised to seek medical advice if signs of suicidal ideation or behaviour emerge.

Other risks and precautions

Very rare cases of agranulocytosis, aplastic anaemia or pancytopenia have been reported in the post-marketing setting in patients treated with Trileptal. Due to the very low incidence of these conditions and additional factors that may also play a role (e.g. underlying disease, concomitant medication) causality cannot be established. Discontinuation of the medicinal product should be considered if any signs of relevant bone marrow depression occur.

Hepatic function

Very rare cases of hepatitis have been reported, which in most cases resolved spontaneously. In case of suspected hepatic impairment hepatic function should be assessed and discontinuation of Trileptal treatment should be considered. Caution is advised when treating patients with severe hepatic impairment (see "Dosage/Administration" and "Properties/Actions").

Renal function

In patients with renal impairment (creatinine clearance below 30 ml/min) caution is advised during Trileptal treatment, especially concerning the starting dose and up-titration of the dose (see "Dosage/Administration" and "Pharmacokinetics").

There have been reports of reduced bone mineral density through to overt osteoporosis with the occurrence of fractures during long-term use of Trileptal. The precise mechanism by which oxcarbazepine affects bone metabolism is not yet known.

Withdrawal effects

As with other antiepileptic drugs, sudden withdrawal of Trileptal must be avoided. The dosage should be reduced gradually to minimise the risk of triggering seizures, i.e. aggravation of seizures or status epilepticus. If abrupt withdrawal of Trileptal is unavoidable – due to severe adverse effects, for example – a suitable drug (e.g. i.v. or rectal diazepam; i.v. phenytoin) should be administered during the changeover period to another antiepileptic drug and the patient monitored closely.

Oxcarbazepine has a weaker enzyme-inducing effect than carbamazepine. The dose of other co-administered antiepileptic drugs may need to be lowered (see "Interactions").

Special precautions during pregnancy

Antiepileptic drugs may aggravate folic acid deficiency. Since folic acid deficiency during pregnancy is associated with an increased rate of fetal malformations, 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 during pregnancy. It is recommended that efficacy be carefully monitored in women treated with Trileptal during pregnancy. To ensure that adequate seizure prophylaxis is maintained throughout the entire pregnancy, MHD plasma concentrations should be measured where necessary. Post-partum MHD plasma concentration monitoring may be indicated if the Trileptal dosage had to be increased during pregnancy.

Fertility

There are no data available on fertility in humans. Animal studies did not demonstrate impaired fertility, but did show a negative effect on female reproduction parameters, meaning a risk of impairment of female fertility cannot be ruled out (see "Preclinical data").

Interactions

Hormonal contraceptives: Patients of childbearing age should be advised that the concomitant use of Trileptal with hormonal contraceptives may render the contraception ineffective (see "Interactions"). Additional, non-hormonal contraceptive measures should be recommended to patients treated with Trileptal.

Vitamin B_{12} deficiency should either be ruled out or treated.

Alcohol: Patients treated with Trileptal should avoid alcohol due to a possible additive sedative effect.

Trileptal suspension contains ethanol (less than 100 mg/maximum dose of 2400 mg). It also contains parabens, which may trigger allergic reactions (possibly delayed). As the suspension contains sorbitol, it should not be administered to patients that suffer from the rare, hereditary problem of fructose intolerance.

Interactions

The following table provides an overview of the interactions of oxcarbazepine with other antiepileptic drugs. See the text below the table for details.

Summary of antiepileptic drug interactions with Trileptal

Antiepileptic drug **Co-administered:**	**Influence of Trileptal on antiepileptic drug** **C_{min}:**	**Influence of antiepileptic drug on MHD (**)** **AUC:**
Carbamazepine	0-22% decrease (30% increase in carbamazepine epoxide)	40% decrease
Clobazam	Not studied	No influence
Felbamate	Not studied	No influence
Lamotrigine	No influence (*)	No influence
Phenobarbital	14-15% increase	30-31% decrease
Phenytoin	0-40% increase	29-35% decrease
Valproic acid	No influence	0-18% decrease

(*: No effect on C_{min}, AUC or C_{max})
(**: MHD: Monohydroxy derivative (pharmacologically active metabolite of oxcarbazepine))

Influence of other medicinal products on oxcarbazepine pharmacokinetics

Strong inducers of cytochrome P450 such as rifampicin, carbamazepine, phenytoin or phenobarbital decrease plasma/serum levels of MHD by 29-40%.

Therefore, monitoring of plasma levels and/or dose adjustment should be considered if one or more of these medicinal products are co-administered with oxcarbazepine.

Cimetidine, erythromycin, viloxazine, warfarin and dextropropoxyphene had no effect on the pharmacokinetics of MHD.

Influence of oxcarbazepine on the pharmacokinetics of other medicinal products

Enzyme inhibition

Oxcarbazepine and its pharmacologically active metabolite (the monohydroxy derivative, MHD) inhibit CYP2C19. Therefore, interactions can arise when co-administering high doses of Trileptal with medicinal products that are metabolised by CYP2C19 (e.g. phenytoin). Plasma levels of phenytoin increased by up to 40% when Trileptal was administered at doses above 1200 mg/day (see table above). In this case a dose reduction of co-administered phenytoin may be required (see "Dosage/Administration").

Enzyme induction

In vitro and *in vivo*, oxcarbazepine and MHD are weak inducers of cytochromes CYP3A4 and CYP3A5, which are primarily responsible for the metabolism of, for example, dihydropyridine calcium antagonists (e.g. felodipine), immunosuppressants (e.g. ciclosporin, tacrolimus), oral contraceptives (see below) and several other antiepileptic drugs (e.g. carbamazepine). This leads to lower serum concentrations of these medicinal products.

In vitro, oxcarbazepine and MHD are weak inducers of UDP-glucuronyl transferase (non-specific UGT enzyme study). Therefore, oxcarbazepine and MHD are unlikely to have a clinically relevant effect *in vivo* on medicinal products mainly eliminated by conjugation via UDP-glucuronyl transferases.

Despite the weak induction potential of oxcarbazepine and MHD a dose reduction of the co-administered medicinal products may be necessary in the case of discontinuation of Trileptal therapy; this decision should be taken based on clinical and plasma level monitoring.

No autoinduction has been observed with Trileptal.

Hormonal contraceptives: In a study with a combined contraceptive (ethinylestradiol and levonorgestrel) co-administration of oxcarbazepine

decreased the mean AUC of ethinylestradiol and levonorgestrel by 48-52% and 32-52%, respectively. Other hormonal contraceptives have not been investigated. Therefore, concomitant use of Trileptal may cause a relevant reduction in the contraceptive efficacy of hormonal contraceptives (see "Warnings and precautions") and other reliable methods of contraception should be used.

Tricyclic antidepressants

No clinically relevant interactions were observed in the clinical studies.

Pharmacodynamic interactions

The combination of lithium and oxcarbazepine may lead to increased neurotoxicity.

Pregnancy/Breast-feeding

Pregnancy

General risks associated with epilepsy and the use of antiepileptic drugs

It has been shown that the rate of malformations in the children of women with epilepsy is two to three times higher than the rate of approximately 3% in the general population. In women receiving treatment an increase in malformations was seen particularly in those receiving combination therapy; however, the extent to which the relevant treatment and/or the condition itself were responsible could not be established. Effective antiepileptic treatment should not be interrupted during pregnancy since aggravation of the illness is associated with risks to both the mother and the fetus.

Risks due to oxcarbazepine

Clinical data on the administration of oxcarbazepine to humans during pregnancy are limited. The most frequent congenital malformations occurring during oxcarbazepine therapy were ventricular septal defect, atrioventricular septal defect, cleft lip and palate, Down's syndrome, hip dysplasia (unilateral or bilateral), tuberous sclerosis and congenital malformation of the ear. Based on data from a North American pregnancy register the frequency of serious congenital malformations, defined as structural anomalies which are surgically, medically or cosmetically significant, diagnosed within 12 weeks from birth, was 2.0% (95% CI, 0.6 to 5.1%) if the mother received oxcarbazepine monotherapy in the first trimester. Compared to women who did not receive anticonvulsants

during pregnancy the relative risk (RR) of congenital anomaly in pregnant women treated with oxcarbazepine was 1.6 (95% CI 0.46 to 5.7).

Animal studies demonstrated an increased incidence of embryo mortality, delayed growth and isolated cases of malformations at high, maternally toxic doses (see "Preclinical data").

Taking these data into consideration:

If women receiving Trileptal therapy become pregnant, plan to become pregnant or if Trileptal treatment must be initiated during pregnancy, the necessity of Trileptal treatment should be re-evaluated. This is particularly important during the first 3 months of pregnancy. The lowest effective dose should be given. In women of childbearing age and at least in the first 3 months of pregnancy Trileptal should be administered as monotherapy whenever possible. Patients should be counselled regarding the possibility of an increased risk of malformations and antenatal screening options.

Neonates

Bleeding disorders have been reported in neonates following intrauterine exposure to antiepileptic drugs. Neonates should therefore be given vitamin K1. The administration of vitamin K1 to the mother during the last few weeks of pregnancy may also be considered as a precautionary measure.

Rare cases of hypocalcaemia have been observed in neonates whose mothers were treated with antiepileptic drugs during pregnancy. These cases were due to disorders of calcium phosphate metabolism and bone mineralisation.

Women of childbearing potential and contraceptive measures

Women of childbearing potential should be advised to use highly effective contraceptive methods during Trileptal treatment (preferably non-hormonal, e.g intrauterine implants). Trileptal may lead to failure of the therapeutic effect of contraceptives containing oral ethinylestradiol (EE) and levonorgestrel (LNG) (see "Warnings and precautions" and "Interactions").

Breast-feeding

Oxcarbazepine and its active metabolite (MHD) pass into breast milk.

The effects of Trileptal on breast-fed infants are unknown. Women should therefore not breastfeed during treatment with Trileptal.

Effects on ability to drive and use machines

Adverse effects such as dizziness, somnolence, ataxia, diplopia, blurred vision, visual disturbances, hyponatraemia and reduced consciousness have been reported with Trileptal (see "Adverse effects"), especially at the start of therapy or in connection with dose adjustment (more frequently during the up-titration phase). Patients should therefore exercise due caution when driving or operating machinery.

Adverse effects

Summary of the safety profile

The most frequently reported adverse effects, occurring in over 10% of patients, are somnolence, headache, dizziness, diplopia, nausea, vomiting and fatigue.

The analysis of the adverse effect profile by system organ class is based on adverse effects attributed to Trileptal in clinical studies. In addition, clinically relevant reports on adverse effects received from named-patient programmes and in the post-marketing phase have been taken into account.

Estimated frequencies: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), frequency not known (primarily based on spontaneous post-marketing reports; precise frequency cannot be estimated).

Blood and lymphatic system disorders

Uncommon: Leukopenia.

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

Immune system disorders

Very rare: Anaphylactic reactions, hypersensitivity reactions (see "Warnings and precautions").

Frequency not known: DRESS syndrome (drug rash with eosinophilia and systemic symptoms) (see "Warnings and precautions").

Endocrine disorders

Common: Increased weight.

Very rare: Hypothyroidism.

Metabolism and nutrition disorders

Common: Hyponatraemia, more frequently in elderly patients (see "Warnings and precautions").

Very rare: Clinically relevant hyponatraemia (Na <125 mmol/l) (see "Warnings and precautions"), hypothyroidism.

Frequency not known: Condition similar to syndrome of inappropriate ADH secretion with signs and symptoms of lethargy, nausea, dizziness, decreased serum osmolality, vomiting, headache, confusion or other neurological signs and symptoms.

Psychiatric disorders

Common: Agitation (e.g. nervousness), affect lability, confusional state, depression, apathy.

Nervous system disorders

Very common: Light-headedness (22.6%), dizziness (22.6%), somnolence (22.5%), headache (14.6%).

Common: Tremor, ataxia, nystagmus, disturbance in attention, amnesia.

Frequency not known: Speech disorders (including dysarthria); more common during the up-titration of the Trileptal dose.

Eye disorders

Very common: Diplopia (13.9%).

Common: Blurred vision, visual disturbances.

Cardiac disorders

Very rare: Atrioventricular block, arrhythmia.

Vascular disorders:

Very rare: Hypertension.

Gastrointestinal disorders

Very common: Nausea (14.1%), vomiting (11.1%).

Common: Diarrhoea, abdominal pain, constipation.

Very rare: Pancreatitis and/or increased lipase and/or amylase.

Hepatobiliary disorders

Uncommon: Increased transaminases and/or alkaline phosphatase.

Very rare: Hepatitis (see "Warnings and precautions").

Skin and subcutaneous tissue disorders

Common: Rash, alopecia, acne.

Uncommon: Urticaria.

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis (drug-induced Lyell's syndrome), angiooedema, erythema multiforme (see "Warnings and precautions"), systemic lupus erythematosus.

Frequency not known: Drug-induced skin rash with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP) (see "Warnings and precautions").

Musculoskeletal disorders

Frequency not known: Reduced bone mineral density, osteopenia, osteoporosis, fractures (in long-term use).

General disorders

Very common: Fatigue (12%).

Common: Asthenia.

Investigations

Very rare: Increased amylase, increased lipase.

Injury and post-surgical complications

Frequency not known: Fall.

Paediatric patients

In clinical studies in children aged from 1 month to under 4 years the most commonly reported adverse effect was somnolence, occurring in approximately 11% of patients. Adverse effects occurring at an incidence of ≥1% to <10% were: ataxia, irritability, vomiting, lethargy, fatigue, nystagmus, tremor, decreased appetite and increased blood uric acid.

Overdose

Isolated cases of overdose have been reported. The maximum dose taken was 48 g.

Symptoms

Symptoms of overdose include: hyponatraemia, diplopia, miosis, blurred vision, nausea, vomiting, hyperkinesia, fatigue, respiratory depression, QTc prolongation, light-headedness, somnolence, dizziness, nystagmus, ataxia, tremor, coordination disorders (abnormal coordination), convulsions, headache, coma, loss of consciousness, dyskinesia, aggression, agitation, confusional state, hypotension and dyspnoea.

Treatment

There is no specific antidote. Appropriate symptomatic and supportive treatment should be given. Decreasing resorption by means of gastric lavage and/or administration of activated charcoal should be considered. Monitoring of vital functions is recommended, with particular attention being paid to electrolyte disturbances, cardiac conduction disturbances and respiratory problems.

Properties/Actions

ATC code: N03AF02

Mechanism of action

The pharmacological activity of Trileptal (oxcarbazepine) is primarily mediated through the metabolite MHD (monohydroxy derivative of oxcarbazepine). 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 hyperexcitable neural membranes, inhibition of repetitive neuronal firing and slowed propagation of synaptic impulses. Increased potassium influx and modulation of high-voltage-activated calcium channels may also contribute to the

anticonvulsant effect. No significant interactions with brain neurotransmitter or modulator receptor sites have been found.

Pharmacodynamics

Oxcarbazepine and its active metabolite MHD are effective antiepileptic drugs in animals. They protect rodents against generalised tonic-clonic and, to a lesser degree, clonic epileptic seizures and suppress or reduce the frequency of chronically recurring partial seizures in rhesus monkeys with aluminium implants. No development of tolerance (i.e. reduction of anticonvulsant activity) in the treatment of tonic-clonic seizures was observed when mice and rats were treated daily for 5 days or 4 weeks, respectively, with oxcarbazepine or MHD.

Clinical efficacy

Trileptal is used as an antiepileptic drug either in monotherapy or in combination therapy and can replace other antiepileptic drugs if existing treatment provides inadequate control of seizures.

Pharmacokinetics

Absorption

Oxcarbazepine is rapidly absorbed from the gastrointestinal tract. At least 95% is absorbed following administration of the film-coated tablets or suspension. The active substance undergoes rapid and extensive metabolism to the pharmacologically active metabolite 10,11-dihydro-10-hydroxy-carbamazepine (monohydroxy derivative, MHD).

After single-dose administration of 600 mg Trileptal film-coated tablets to healthy male subjects under fasted conditions the mean C_{max} of MHD was 31.5 µmol/l and the corresponding t_{max} was 5 hours.

After single-dose administration of 600 mg Trileptal oral suspension to healthy male subjects under fasted conditions the mean C_{max} was 24.9 µmol/l and the median t_{max} was 6 hours.

Both dosage forms of oxcarbazepine (tablet and oral suspension) are bioequivalent since the geometric mean ratios (90% confidence interval) of MHD C_{max} and AUC after a single dose and at steady state were between 0.85 and 1.06.

Food has no effect on the extent and rate of absorption of oxcarbazepine; therefore, Trileptal can be taken with or without food (see "Dosage/Administration").

Steady-state serum concentrations of MHD are reached in patients within 2-3 days when Trileptal is given twice a day. At steady state MHD absorption kinetics are linear in the dose range between 300 and 2400 mg/day.

Distribution

The apparent volume of distribution of MHD is 49 l. 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 glycoproteins.

Oxcarbazepine and its active metabolite (MHD) cross the placental barrier. In one case similar plasma MHD concentrations were measured in a neonate and its mother.

Metabolism

Oxcarbazepine is rapidly converted by cytosolic enzymes in the liver to MHD, which is primarily responsible for the pharmacological effect of Trileptal. In a mass balance study in humans only 2% of total radioactivity in serum was due to unchanged oxcarbazepine and approximately 70% to MHD; the remainder was due to minor metabolites that were rapidly eliminated.

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 predominantly excreted via the kidneys, mostly in the form of metabolites. More than 95% of the dose appears in the urine, with less than 1% as unchanged oxcarbazepine. Less than 4% of the administered dose is excreted via the faeces. Approximately 80% of the dose is excreted in the urine either as glucuronides of MHD (49%) or as unchanged MHD (27%); inactive DHD represents around 3% of the dose and conjugates of oxcarbazepine around 13%.

The half-life of oxcarbazepine is between 1.3 and 2.3 h. In contrast, the mean serum half-life of MHD is 9.3 ± 1.8 h.

Pharmacokinetics in special patient populations

Children

Weight-adjusted MHD clearance decreases as age and weight increase, gradually reaching that of adults. The mean weight-adjusted clearance in children aged 1 month to under 4 years is 93% higher than in adults. Therefore, MHD exposure in these children is estimated to be about half that of adults when treated with a similar, weight-adjusted dose. The mean weight-adjusted clearance in children aged 4 to 12 years is 43% higher than in adults. Therefore, MHD exposure in these children is estimated to be about two-thirds that of adults when treated with a similar, weight-adjusted dose.

In patients aged 13 years and above, as weight increases, the weight-adjusted MHD clearance is expected to reach that of adults.

Elderly patients

Following administration of a single dose (300 mg) and multiple doses (600 mg/day) of Trileptal in elderly (60 to 82 years of age) subjects the maximum serum concentration and AUC of MHD were 30-60% higher than in younger subjects (18 to 32 years of age).

Comparisons of creatinine clearance in young and elderly subjects indicate that the difference was due to the age-related reduction in creatinine clearance.

Gender

No gender-related differences have been observed in children, adults or elderly patients.

Patients with hepatic impairment

The pharmacokinetics and metabolism of oxcarbazepine and MHD were evaluated in healthy subjects and hepatically impaired patients 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 was administered as a single 300 mg oral dose to renally

impaired patients (creatinine clearance <30 ml/min), the elimination half-life of MHD was prolonged by 60-90% (16 to 19 h), with a corresponding two-fold increase in AUC.

Preclinical data

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

Reproductive toxicity

In rats of both sexes oxcarbazepine or MHD had no effect on fertility at doses of up to 150 and 450 mg/kg/day, respectively. However, after administering the maximum MHD dose, a disturbance of oestrus cyclicity and a reduced number of corpora lutea, implants and live embryos were observed. Subchronic treatment of rats with 100 mg/kg/day oxcarbazepine led to apoptotic and degenerative effects in the uterus and ovaries as well as impaired folliculogenesis. The risk of reduced fertility cannot be ruled out.

Standard studies on developmental toxicity in rodents and rabbits revealed findings including increased embryo-fetal mortality and/or some delay in antenatal and/or postnatal growth at maternally toxic doses. There was an increase in rat fetal malformations in one of the eight embryo-fetal toxicity studies, which were conducted with either oxcarbazepine or MHD at doses that were also maternally toxic. Overall, the data suggest that oxcarbazepine has minor teratogenic potential at doses relevant to humans. However, a teratogenic effect of oxcarbazepine cannot be fully ruled out based on the animal studies.

Mutagenicity

In an *in vitro* Ames test oxcarbazepine increased the mutation frequency without metabolic activation in one in five bacterial strains. In an *in vitro* test with Chinese hamster ovarian cells oxcarbazepine and MHD increased the number of chromosomal aberrations and polyploidy without metabolic activation. MHD was negative in the Ames test and no *in vitro* mutagenic or clastogenic activity was detected in Chinese hamster V79 cells. In an *in vivo* test in rats neither oxcarbazepine nor MHD showed a clastogenic or aneugenic effect (formation of micronuclei) on bone marrow. None of the studies are suggestive of a relevant *in vivo* genotoxic potential for oxcarbazepine or MHD.

Carcinogenicity

In carcinogenicity studies liver tumours (in rats and mice), testicular tumours and female genital tract granular cell tumours (in rats) were induced in treated animals. The occurrence of liver tumours was most likely a consequence of the induction of hepatic microsomal enzymes, which, although it cannot be completely ruled out, is weak or absent in patients treated with Trileptal. Testicular tumours may have been induced by elevated luteinising 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 to those in clinical use. The development mechanism of these tumours could not be fully elucidated; however, it may be connected to increased oestradiol levels specific to rats. Therefore, the clinical relevance of these tumours is unknown.

Immunotoxicity

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

Other information

Shelf life

Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage

Film-coated tablets: Protect from moisture and do not store above 30°C.

Oral suspension: Protect from light and do not store above 30°C. Once the bottle is opened, the suspension should not be used for more than 7 weeks.

Swissmedic number

55120, 52852.

Pack sizes

150 mg film-coated tablets: 50.

300 mg film-coated tablets: 50.

600 mg film-coated tablets: 50 [B].

100 ml *oral suspension containing 60 mg/ml (incl. 1 ml oral dosing syringe).*

250 ml [B] *oral suspension containing 60 mg/ml (incl. 10 ml oral dosing syringe).*

Marketing authorisation holder

Novartis Pharma Schweiz AG, Risch; domicile: 6343 Rotkreuz, Switzerland

Information last revised

October 2017