NOVARTIS

Trileptal®

Composition

Active substance
Oxcarbazepine

Excipients
Film-coated tablets
Tableting excipients

Oral suspension
Saccharin, flavouring agents, vanillin; preservatives E 200, E 216 and E 218; excipients to 1 ml

Pharmaceutical form and quantity of active substance per unit

Film-coated tablets (scored on both sides) containing 150, 300 or 600 mg oxcarbazepine.
Oral suspension containing 60 mg oxcarbazepine per ml (1 ml or 10 ml oral dosing syringe supplied in pack).

Indications / Potential uses

Trileptal is used in the treatment of partial seizures (with or without secondary generalized tonic-clonic seizures) and generalized tonic-clonic seizures.
Trileptal is used in adults and in children aged 1 month and older.

Dosage and Administration

Administration
Trileptal is suitable for use either alone or in combination with other antiepileptic drugs. In both monotherapy and combination therapy, treatment with Trileptal should be initiated at a clinically effective dose, given as two divided doses per day. The dose may be increased depending on the patient's clinical response. In the event of combination therapy, it may be necessary to reduce the dose of the other antiepileptic and/or to increase the dose of Trileptal more slowly (see **Interactions**), due to the increase in the patient's total antiepileptic dose.
Trileptal may be taken with or without food.
The tablets are scored and can be broken in half to facilitate administration for the patient.
The oral suspension is available for younger children who are unable to swallow the tablets or in whom the prescribed dose cannot be attained using the tablets.
The bottle containing the oral suspension must be shaken well before use. The prescribed amount of solution should then be withdrawn from the bottle immediately. The amount should be rounded up to the nearest 0.5 ml if the 10 ml dosing syringe is being used (supplied with the 250 ml bottle for adults and older children) and to the nearest 0.1 ml if the 1 ml dosing syringe is being used (supplied with the 100 ml bottle for younger children).
The oral suspension may be swallowed directly from the dosing syringe or stirred into a small glass of water immediately before ingestion. After each use, the bottle must be closed and the outside of the dosing syringe wiped clean with a clean, dry tissue.
Trileptal film-coated tablets and oral suspension may be interchanged at equal doses.
The prescription for Trileptal oral suspension should be given in millilitres (see conversion table below, which gives the milligram dose in millilitres):

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 following dosage recommendations apply to all patients who do not have impaired renal function. Serum level monitoring is not necessary for optimization of Trileptal therapy (see **Pharmacokinetics**).

Adults
Monotherapy
Treatment with Trileptal may be initiated at a daily dose of 600 mg (8–10 mg/kg/day), given in two divided doses. The daily dose may be increased at one-week intervals, in increments not exceeding 600 mg, in order to achieve the desired effect. The maintenance dose ranges from 600 to 2400 mg/day, with most patients responding to a dose of 900 mg/day.
Controlled studies with monotherapy in patients not previously treated with antiepileptics have shown the efficacy of a daily dose of 1200 mg. In hard-to-treat patients who have been switched from other antiepileptics to monotherapy with Trileptal, a daily dose of 2400 mg has proven effective.

Combination therapy
Treatment with Trileptal may be initiated at a daily dose of 600 mg (8–10 mg/kg/day), given in two divided doses. The daily dose may be increased at one-week intervals, in increments not exceeding 600 mg, in order to achieve the desired effect. The maintenance dose ranges from 600 to 2400 mg/day.
A controlled study with combination therapy has shown daily doses of 600 to 2400 mg to be effective. However, most patients did not tolerate a daily dose of 2400 mg without a reduction in the dose of the other concurrently administered antiepileptics, primarily due to adverse effects involving the central nervous system.
Daily doses above 2400 mg were not systematically investigated.

Children aged 1 month and over
In monotherapy and combination therapy, treatment should be initiated at a dose of 8–10 mg/kg/day, given in two divided doses. 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 daily dose of 60 mg/kg, in order to achieve the desired effect (see **Pharmacokinetics**).
In both combination therapy and monotherapy, clearance (litres/hour/kg) – based on bodyweight – decreases with age such that children aged from 1 month to < 4 years may require twice as high a dose of oxcarbazepine per bodyweight as adults; children aged from 4 to 12 years may require a dose of oxcarbazepine per bodyweight that is 50% higher than that in adults (see **Pharmacokinetics**).
In children aged from 1 month to < 4 years, the influence of enzyme-inducing antiepileptics on weight-normalized clearance appears higher than in older children. Children aged from 1 month to < 4 years receiving combination therapy with enzyme-inducing antiepileptics may require a dose (by bodyweight) of oxcarbazepine about 60% higher than the dose needed with either monotherapy or combination therapy with non-enzyme-inducing antiepileptics.
Older children (≥ 4 years) receiving enzyme-inducing antiepileptics may require only a slightly higher dose than their counterparts on monotherapy.
Trileptal is intended for use in children aged one month and older. There have been no controlled clinical studies in children aged less than one month.
The dosage recommendations given above are based on doses used in all age groups (adults, elderly patients and children) during clinical trials. However, lower starting doses may also be used where appropriate.

Elderly patients
Dose adjustment is recommended in elderly patients with impaired renal function (see ***Patients with impaired renal function***). For patients at risk for hyponatraemia, (see **Warnings and Precautions**).

Patients with impaired hepatic function
No dose adjustment is required in patients with mild to moderate hepatic impairment. Trileptal has not been studied in patients with severe hepatic impairment. Caution is therefore required when giving Trileptal to patients with severe hepatic impairment (see **Pharmacokinetics**).

Patients with impaired renal function
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 not less than one week until the desired clinical response is achieved (see **Pharmacokinetics**). Patients with renal impairment must be closely monitored when doses are increased.

Contraindications

Known hypersensitivity to oxcarbazepine or any of the excipients.

Warnings and Precautions

There have been reports of class I hypersensitivity reactions, such as rash, pruritus, urticaria, angioedema and even anaphylactic shock. Cases of anaphylactic angioedema involved the larynx, tongue, lips and eyelids; the reactions occurred after the first or subsequent doses of Trileptal. If a patient shows such reactions, treatment should be discontinued and the patient should be switched to another product. Patients who have had hypersensitivity reactions to carbamazepine should be informed that hypersensitivity reactions (e.g. severe skin reactions) may also occur during treatment with Trileptal at a cross-reaction rate of 25–30% (see **Adverse effects**).
Hypersensitivity reactions, including multi-organ hypersensitivity reactions, may also occur in patients without a history of hypersensitivity to carbamazepine. Such reactions may affect the skin, liver, blood, lymphatic system or other organs, either individually or in the context of a systemic reaction (see **Adverse effects**). As a matter of principle, Trileptal should be withdrawn immediately at the first sign of a hypersensitivity reaction.
There have been very rare reports of severe skin reactions – including Stevens-Johnson syndrome, toxic epidermal necrolysis (drug-induced Lyell's syndrome) and erythema multiforme – in association with the use of Trileptal. Patients with such reactions may require hospitalization, as these conditions may be life-threatening and, in very rare cases, fatal. Trileptal-associated cases have occurred in both adults and children. The median time to onset was 19 days. There have been several isolated reports of recurrence of a severe skin reaction following reintroduction of Trileptal.
If a patient develops a skin reaction while using Trileptal, consideration should be given to discontinuing Trileptal and prescribing another antiepileptic medication.
Multi-organ hypersensitivity reactions have occurred very soon after initiation of treatment with Trileptal in adults and children (usually within the first three weeks, but possibly later as well). Although few reports have been issued, some patients have been hospitalized and, in isolated cases, the condition of such patients has been considered life-threatening. The symptoms of this disorder have varied. Patients have typically presented with fever and rash, with concurrent involvement of other organ systems, but these have not been the only symptoms. Others have included lymphadenopathy, hepatitis, abnormal liver function tests, haematological anomalies (e.g. eosinophilia, thrombocytopenia, neutropenia), pruritus, nephritis, oliguria, hepatorenal syndrome, arthralgia and asthenia. Since the manifestations of the disorder are variable, there may also be symptoms, not mentioned here, affecting other organ systems. If multi-organ hypersensitivity is suspected, Trileptal should be withdrawn and alternative treatment initiated.
There have been no reports of cross reactions with other medicinal products associated with multi-organ hypersensitivity. However, experience with such products indicates that such cross reactions are possible.
In up to 2.7% of patients treated with Trileptal, serum sodium levels fell below 125 mmol/litre. As a rule, this was asymptomatic and did not require any change in treatment. If clinical intervention is considered, experience from clinical trials shows that the serum sodium level normalizes to the baseline value as soon as the dose of Trileptal is reduced, Trileptal is withdrawn, or the patient is given conservative treatment (e.g. restricted fluid intake). In patients with pre-existing renal disease who require high fluid intake, patients with pre-existing low sodium levels and patients being treated concurrently either with drugs that lower sodium levels (e.g. diuretics, desmopressin) or with NSAIDs (e.g. indometacin), serum sodium levels should be determined before initiating therapy. Thereafter, serum sodium levels should be determined after about two weeks to begin with, then either at monthly intervals, or in accordance with clinical requirements, during the first three months of treatment. The above risk factors apply in particular to elderly patients. The same approach for monitoring of serum sodium levels should be followed if treatment with a sodium-lowering drug is started in a patient receiving Trileptal. Determination of serum sodium should generally be considered if clinical signs of hyponatraemia occur during treatment with Trileptal. Otherwise, serum sodium may be assessed as part of routine monitoring of laboratory parameters.
Patients with heart failure should have their weight monitored on a regular basis in order to determine if there has been any fluid retention. In the event of fluid retention or deterioration in cardiac function, serum sodium should be checked. Fluid restriction is an important method of treatment if hyponatraemia is determined.
There have been very rare cases of impaired cardiac conduction during treatment with oxcarbazepine and patients with pre-existing disorders of cardiac conduction (e.g. atrioventricular block, arrhythmias) should therefore be closely monitored.
Very rare cases of hepatitis have been reported, which in most cases resolved favourably. If hepatic impairment is suspected, liver function should be checked and discontinuation of Trileptal considered.
As with other antiepileptics, abrupt discontinuation of Trileptal should be avoided. The dosage should be reduced gradually to minimize the risk of precipitating seizures (i.e. seizure exacerbation or status epilepticus). If Trileptal does have to be discontinued abruptly, e.g. owing to severe adverse reactions, the switch to an alternative antiepileptic drug should be effected under cover of a suitable drug (e.g. diazepam i.v., rectal; phenytoin i.v.) and under close supervision.
Oxcarbazepine has less enzyme-inducing potential than carbamazepine. Under certain conditions, the dosage of the concurrently administered antiepileptic may have to be lowered (see detailed information in the section on antiepileptics under **Interactions**).
During post-marketing experience, there have been very rare reports of agranulocytosis, aplastic anaemia and pancytopenia in patients treated with Trileptal (see **Adverse effects**). Due to the very low incidence of these conditions, and to additional factors that may also be involved (e.g. underlying disease, concomitant medication), causality cannot be established. Discontinuation of the drug should be considered if there is any evidence of significant bone marrow depression.
Female patients of child-bearing age should be told that concurrent use of Trileptal and hormonal contraceptives leads to loss of contraceptive efficacy (see **Interactions**). Additional non-hormonal contraceptives should be recommended to female patients treated with Trileptal.
Patients receiving Trileptal should avoid alcohol due to the risk of an additive sedative effect.
Trileptal oral suspension contains ethanol (less than 100 mg in the maximum ingested dose of 2400 mg). It also contains parabenes, which may cause allergic reactions (possibly delayed). The suspension also contains sorbitol and should therefore not be given to patients with rare hereditary problems of fructose intolerance.

Interactions

Enzyme inhibition
Oxcarbazepine and its pharmacologically active metabolite (the monohydroxy derivative, MHD) inhibit CYP2C19. Interactions are thus possible if high doses of Trileptal are administered together with drugs metabolized by CYP2C19 (e.g. phenytoin). Plasma levels of phenytoin increased by up to 40% when Trileptal was given at doses exceeding 1200 mg/day (see table below summarizing results with other antiepileptics). In such cases, it may be necessary to reduce the concomitantly administered dose of phenytoin (see **Dosage and Administration**).

Enzyme induction
In vitro and *in vivo*, oxcarbazepine and MHD are weak inducers of cytochrome CYP3A4 and CYP3A5, which are primarily responsible for the metabolism of, for example, dihydropyridine calcium channel blockers (e.g. felodipine), immunosuppressants (e.g. ciclosporin, tacrolimus), oral contraceptives (see below) and some other antiepileptics (e.g. carbamazepine). This results in lower serum levels of these drugs (see table below summarizing results with other antiepileptics).
In vitro, oxcarbazepine and MHD are weak inducers of UDP-glucuronyl transferase (non-specific UGT enzyme study). They therefore seem unlikely to have a clinically relevant effect *in vivo* on drugs that are mainly eliminated by conjugation via UDP glucuronyl transferases.
Even in view of the weak induction potential of oxcarbazepine and MHD, dose reduction of the concurrently administered drug may be necessary on discontinuation of Trileptal; this should be decided on the basis of clinical monitoring and determination of plasma levels.

Hormonal contraceptives
Trileptal has been shown to affect ethinyloestradiol and levonorgestrel, the two components of a hormonal contraceptive. Mean AUC for ethinyloestradiol and levonorgestrel was lowered by 48–52% and 32–52%, respectively. Concurrent use with Trileptal may therefore render hormonal contraceptives ineffective (see **Warnings and Precautions**). An alternative reliable method of contraception should be used.

Interactions with other antiepileptics
Possible interactions between Trileptal and other antiepileptics were investigated in clinical trials.
It was possible to show that strong inducers of cytochrome P450 (e.g. carbamazepine, phenytoin and phenobarbital) lower plasma concentrations of MHD (29–40%).
In the event of concomitant administration of one or more antiepileptics with oxcarbazepine, careful dose adjustment and/or monitoring of plasma levels should be considered on an individual basis.

Effects on mean AUC and C_{min} are summarized in the following table:

Summary of interactions between antiepileptics and Trileptal		
Antiepileptic agent Concurrent administration of:	Effect of Trileptal on the antiepileptic: C_{min}:	Effect of the antiepileptic on MHD (**) AUC
Carbamazepine	0–22% reduction (30% increase in carbamazepine-epoxide)	40% reduction
Clobazam	Not investigated	No effect
Felbamate	Not investigated	No effect
Lamotrigine	No effect (*)	No effect
Phenobarbital	14–15% increase	30–31% reduction
Phenytoin	0–40% increase	29–35% reduction
Valproic acid	No effect	0–18% reduction

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

No autoinduction has been observed with Trileptal.

Other drug interactions
Cimetidine, erythromycin, viloxazine, warfarin and dextropropoxyphene had no effect on the pharmacokinetics of MHD.
Patients treated with tricyclic antidepressants were included in the clinical trials; no clinically relevant interactions were observed.
Combining lithium with oxcarbazepine may lead to increased neurotoxicity.

Pregnancy and Lactation

Pregnancy

General risk associated with epilepsy and antiepileptic drugs
The rate of malformations in the offspring of women with epilepsy has been shown to be two to three times higher than the rate of about 3% found in the general population. In treated women, an increase in malformations was primarily found in those given combination therapy. It was not possible to determine to what extent the specific treatment and/or the disease was responsible for this.
In addition, effective antiepileptic therapy should not be interrupted, as aggravation of the disease is detrimental to both the mother and the fetus.

Risk related to oxcarbazepine
Data on administration in pregnant women are limited.
In animal studies, increased embryo mortality, delayed growth and malformations were observed with high, maternally toxic doses (see **Preclinical data**).
If a woman receiving Trileptal becomes – or plans to become – pregnant, or if Trileptal needs to be initiated during pregnancy, the need for Trileptal therapy must be reconsidered. This is particularly important during the first three months of pregnancy. The lowest effective dose should be given. In women of childbearing age, Trileptal should be given as monotherapy whenever possible, and at least during the first three months of pregnancy. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening. Effective antiepileptic therapy with oxcarbazepine must not be interrupted during pregnancy, as aggravation of the disease is detrimental to both the mother and the fetus.

Monitoring and prevention
Folic acid deficiency may occur during pregnancy. Antiepileptics have been reported to aggravate this condition. Folic acid deficiency can contribute to an increased incidence of fetal malformations. Folic acid supplementation is therefore recommended before and during pregnancy.
Vitamin B_{12} deficiency should be ruled out or treated.

Neonates
Antiepileptics have been reported to cause disturbances of coagulation in neonates. As a precaution, vitamin K1 should be considered as a preventive measure in the last few weeks of pregnancy. However, vitamin K1 should be administered to the neonate.
In rare cases antiepileptic therapy has been associated with neonatal hypocalcaemia, resulting from difficulties with calcium phosphate metabolism and bone mineralization.

Lactation
Oxcarbazepine and its active metabolite MHD are excreted in breast milk.
The effects on the infant exposed to Trileptal are unknown. For this reason, Trileptal should not be given to women who are breast-feeding.

Effects on ability to drive and use machines
Trileptal can cause dizziness and drowsiness (see **Adverse effects**), leading to impairment of the reactions. Particular caution is therefore required when driving or using machines.

Adverse effects
The most commonly reported adverse effects, which occur in over 10% of patients, are drowsiness, headache, dizziness, diplopia, nausea, vomiting and a feeling of weakness.
In clinical trials, adverse effects were for the most part mild to moderately severe and were transient, occurring primarily at the start of treatment.
The assessment of the adverse-effect profile for each body system is based on the adverse events ascribed to Trileptal in clinical trials. Clinically significant reports from the post-marketing phase have also been taken into account.

Estimated frequency in accordance with CIOMS III classification
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).

Blood and lymphatic system disorders
Uncommon: Leucopenia.
Very rare: Thrombocytopenia, bone marrow depression, agranulocytosis, aplastic anaemia, pancytopenia, neutropenia.

Metabolism and nutrition disorders
Common: Hyponatraemia under special clinical circumstances, and more frequently in elderly patients (see **Warnings and Precautions**). In very rare cases, clinically significant hyponatraemia (Na < 125 mmol/litre) may develop in patients being treated with Trileptal. It has usually occurred during the first 3 months, but there have been patients whose serum sodium levels did not fall below 125 mmol/litre until more than one year after the start of treatment (see **Warnings and Precautions**). There have also been reports of symptomatic hyponatraemia with seizures, disorientation, reduced perception, encephalopathy (see **Nervous system disorders**), visual disturbances (e.g. blurred vision), vomiting, nausea and folic acid deficiency.
Under special clinical circumstances, a "syndrome of inappropriate secretion of antidiuretic hormone" (SIADH) may occur during treatment with Trileptal (see **Warnings and Precautions**).

Psychiatric disorders
Common: Confusional state, depression, apathy, restlessness (e.g. nervousness), affect lability.

Nervous system disorders
Very common: Drowsiness (22.5%), headache (14.6%), light-headedness (22.6%), dizziness (22.6%).
Common: Ataxia, tremor, nystagmus, disturbances in attention, disturbances in memory.

Eye disorders
Very common: Diplopia (13.9%).
Common: Blurred vision, disturbances of vision.

Cardiac disorders
Very rare: Arrhythmia, atrioventricular block.

Vascular disorders
Hypertension.

Gastrointestinal disorders
Very common: Nausea (14.1%), vomiting (11.1%).
Common: Diarrhoea, constipation, abdominal pain.
Very rare: Pancreatitis, and/or increase in lipase and/or amylase.

Hepatobiliary disorders
Uncommon: Elevated levels of transaminases and/or alkaline phosphatase.
Very rare: Hepatitis (see **Warnings and Precautions**).

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

General disorders
Very common: Fatigue (12%).
Common: Asthenia.

Other disorders
Very common: Feeling of weakness (12%).
Very rare: Systemic lupus erythematosus, hypersensitivity (including multi-organ hypersensitivity) characterized by rash, 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. abnormal liver function tests, hepatitis), muscles and joints (e.g. joint swelling, myalgia, arthralgia), nervous system (e.g. hepatic encephalopathy), kidney (e.g. proteinuria, interstitial nephritis, renal failure), lungs (e.g. dyspnoea, pulmonary oedema, asthma, bronchospasms, interstitial lung disease); angioedema and anaphylactic reactions (see **Warnings and Precautions**).
In clinical studies in children aged from 1 month to < 4 years, the most frequently reported adverse effect was drowsiness, which occurred in approximately 11% of patients. Adverse effects occurring with a frequency of ≥ 1% to < 10% (common) were ataxia, excitation, 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 24 000 mg. Symptomatic treatment was given and all patients recovered.

Signs and symptoms
Overdosage leads to symptoms such as drowsiness, light-headedness, nausea, vomiting, hyperkinesia, hyponatraemia, ataxia and nystagmus.

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

Properties and Actions
ATC code: N03A F02

Mechanism of action
The pharmacological activity of Trileptal (oxcarbazepine) is mediated principally by the MHD metabolite (monohydroxy derivative of oxcarbazepine). It is assumed that the mechanism of action of oxcarbazepine and MHD primarily lies in the blockade of voltage-sensitive sodium channels, which leads to stabilization of overly excitable neuronal membranes, inhibition of repetitive neuronal discharges and slowing down of the synaptic propagation of excitatory impulses. An increased inflow of potassium and the modulation of high-voltage-activated calcium channels may also contribute to the anticonvulsant effect of the drug. No significant interactions with brain neurotransmitter or modulator receptor sites have been found.

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

Clinical efficacy
Trileptal is used as an antiepileptic either alone or in combination with other drugs, and can replace other antiepileptic drugs if the latter provide 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 and the oral suspension. The active substance undergoes rapid and extensive metabolism to the pharmacologically active metabolite 10,11-dihydro-10-hydroxy-carbamazepine (monohydroxy derivative, MHD).
In healthy male volunteers, the mean C_{max} of MHD, following a single dose of 600 mg Trileptal film-coated tablets taken on an empty stomach, was 31.5 µmol/litre, and the corresponding t_{max} was 5 hours.
Following a single dose of 600 mg Trileptal oral suspension taken on an empty stomach, the mean C_{max} was 24.9 µmol/litre and the (median) t_{max} 6 hours in healthy male volunteers.
During repeated administration, the suspension and tablet formulations are bioequivalent.
Food does not affect either the extent or the rate of oxcarbazepine absorption, and Trileptal may thus be taken with or without food.

Distribution
The apparent distribution volume of MHD is 49 litres. About 40% of MHD is bound to serum proteins, in particular albumin. Within the relevant therapeutic range, binding was not dependent on serum concentration. Oxcarbazepine and MHD do not bind to alpha-1 acid glycoproteins.
Oxcarbazepine and its active metabolite (MHD) cross the placental barrier. Neonatal and maternal plasma MHD concentrations were similar in one case.
In a mass balance study in humans, unchanged oxcarbazepine accounted for only 2% of total radioactivity in the serum, while about 70% was attributable to MHD, with the rest being associated with minor metabolites that were quickly eliminated.
MHD reaches steady-state serum concentrations within 2–3 days in patients given Trileptal twice daily. The pharmacokinetics of MHD at steady state are linear, and there is a linear relationship between levels of MHD and dosage at daily doses of 300–2400 mg.

Metabolism
Cytosolic enzymes in the liver rapidly convert oxcarbazepine to MHD, which is primarily responsible for the pharmacological effect of Trileptal. MHD is further metabolized by conjugation with glucuronic acid. Small amounts (4% of the dose) are oxidized to the pharmacologically inactive metabolite 10,11-dihydroxy derivative (DHD).

Elimination
Oxcarbazepine is primarily excreted via the kidney, principally in the form of metabolites. More than 95% of the dose is present in the urine, with less than 1% as unchanged oxcarbazepine. Less than 4% of the administered dose is excreted in the faeces. About 80% of the dose is excreted in the urine either as MHD glucuronide (49%) or as unchanged MHD (27%); inactive DHD represents about 3% of the dose and the conjugate of oxcarbazepine about 13%.
Oxcarbazepine is rapidly eliminated from the serum with a half-life between 1.3 and 2.3 hours. In contrast, the mean serum half-life of MHD is 9.3 ± 1.8 hours.

Pharmacokinetics in special patient populations

Elderly patients
Following administration of single (300 mg) and multiple (600 mg/day) doses of Trileptal, maximum serum concentrations and AUC values of MHD were 30–60% higher in older (60–82 years) than in younger (18–32 years) volunteers.
Comparisons of creatinine clearance in younger and older volunteers indicate that the difference was caused by age-related reduction of creatinine clearance. No special dose recommendations are necessary in patients with normal renal function since therapeutic doses are individually titrated (see section on dosage in elderly patients).

Children
Weight-adjusted MHD clearance decreases as age and weight increase, and gradually approaches that of adults. Mean weight-adjusted clearance in children aged from 1 month to < 4 years is 93% higher than in adults. Therefore, MHD exposure in these children is expected to be about half that of adults when treated with a similar weight-adjusted dose. Mean weight-adjusted clearance in children aged from 4 to 12 years is 43% higher than in adults. MHD exposure in these children is therefore expected to be about two-thirds that of adults when treated with a similar weight-adjusted dose.
As weight increases, for patients aged 13 years and above, weight-adjusted MHD clearance is expected to reach that of adults.

Sex
No sex-specific differences were observed in children, adults or elderly patients.

Patients with impaired hepatic function
The pharmacokinetics and metabolism of oxcarbazepine and MHD were investigated following administration of single oral doses of 900 mg in healthy volunteers and patients with impaired liver function. A slight to moderate impairment of liver function had no effect on the pharmacokinetics of oxcarbazepine or MHD. Trileptal has not been studied in patients with severe hepatic impairment.

Patients with impaired renal function
There is a linear correlation between creatinine clearance and renal clearance of MHD. Following oral administration of single 300 mg doses of Trileptal in patients with renal impairment (creatinine clearance < 30 ml/minute), the elimination half-life of MHD is extended by 60–90% (16–19 hours), with a corresponding doubling of AUC.

Preclinical data
Preclinical data indicate no special hazard for humans based on repeated dose toxicity, safety pharmacology and genotoxicity studies with oxcarbazepine and the pharmacologically active metabolite, the monohydroxy derivative (MHD).
Evidence of nephrotoxicity was noted in repeated dose toxicity rat studies but not in dog or mouse 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 a delayed hypersensitivity reaction.

Reproductive toxicity
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. In one of the eight embryotoxicity studies conducted with either oxcarbazepine or the pharmacologically active metabolite (MHD), there was an increase in rat fetal malformations at a dose which also showed maternal toxicity (see **Pregnancy and Lactation**).

Carcinogenicity
In 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 entirely 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 to the anticipated clinical exposure. The mechanism for the development of these tumours has not been elucidated. Thus, the clinical relevance of these findings is not known.

Other information

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

Special precautions for storage
See folding box

Pack sizes
Country specific pack sizes

Manufacturer
See folding box.

Information last revised
October 2007

Approval date (text)
19 October 2007

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists
1330394 R02 09 A/H