SCHEDULING STATUS:
S3

PROPRIETARY NAME AND DOSAGE FORM
TRILEPTAL® 150 Film-coated tablets
TRILEPTAL® 300 Film-coated tablets
TRILEPTAL® 600 Film-coated tablets
TRILEPTAL® Oral Suspension

COMPOSITION
Film-coated tablets:
150 mg, 300 mg and 600 mg Oxcarbazepine.
Excipients:
Tablet core: silica, colloidal anhydrous; microcrystalline cellulose; hypromellose; crospovidone; magnesium stearate;
Tablet coating: for the 150 mg tablet: hypromellose, macrogol 4000, yellow iron oxide (E 172), red iron oxide (E 172), black iron oxide (E 172), talc, titanium dioxide (E 171); 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).

Oral suspension:
60 mg/ml Oxcarbazepine.
Excipients: purified water, sorbitol, propylene glycol, dispersible cellulose, ascorbic acid (E 300), yellow-plum-lemon aroma, methylparahydroxybenzoate (E 218), macrogol stearate 400, ethanol, sorbic acid (E 200), saccharin sodium, propyl parahydroxybenzoate (E 216).

Preservatives: Propyl parahydroxybenzoate 0,3 % m/v
Methyl parahydroxybenzoate 0,5 % m/v
Sorbic acid 1,2 % m/v
Anti-oxidant: Ascorbic acid 10 mg/ml

PHARMACOLOGICAL CLASSIFICATION
A 2.5 Anticonvulsants, including anti-epileptics

PHARMACOLOGICAL ACTION
Pharmacodynamic effects:
Oxcarbazepine and its active 10-monohydroxy metabolite (monohydroxy derivative), are anticonvulsants.
The pharmacological activity of oxcarbazepine is primarily exerted through the metabolite (monohydroxy derivative - MHD) of oxcarbazepine (see "Pharmacokinetics"-Biotransformation). The mechanism of action of oxcarbazepine and MHD is thought to be mainly based on blockade of voltage-sensitive sodium channels, thus resulting in stabilisation of 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 of the drugs. No significant interactions with brain neurotransmitters or modulator receptor sites were found.

Pharmacokinetics:

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 is 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 liters.
40 % 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 drug 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 children, adults, or the elderly.

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

INDICATIONS
TRILEPTAL is indicated for the treatment of partial seizures with or without secondary generalised seizures and generalised tonic-clonic seizures, in adults and in children aged 1 month and above.

TRILEPTAL may be used as monotherapy or adjunctive therapy in adults and in children of 1 month of age and above.

CONTRA-INDICATIONS
Known hypersensitivity to TRILEPTAL or to any of the excipients.

WARNINGS
Hypersensitivity:
Class I (immediate) hypersensitivity reactions including rash, pruritus, urticaria, angioedema and reports of anaphylaxis have been received in the post-marketing period. Cases of anaphylaxis and angioedema involving the larynx, glottis, lips and eyelids have been reported in patients after taking the first or subsequent doses of TRILEPTAL. If a patient

develops these reactions after treatment with TRILEPTAL, the drug should be discontinued and an alternative treatment started.
Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25-30 % of these patients may experience hypersensitivity reactions with TRILEPTAL (see "Side-effects").
Hypersensitivity reactions, including multi-organ hypersensitivity reactions, may also occur in patients without a history of hypersensitivity to carbamazapine. 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 "Side-effects"). 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 very rarely in association with TRILEPTAL use. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and very rarely be fatal. TRILEPTAL associated cases occurred in both children and adults. The median time to onset was 19 days. Several isolated cases of recurrence of the serious skin reaction when rechallenged with TRILEPTAL were reported. Should a patient develop a skin reaction with TRILEPTAL, consideration should be given to discontinuing TRILEPTAL and prescribing another anti-epileptic medication
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 of 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 oral suspension contains ethanol, less than 100 mg per dose. It contains parabenes which may cause allergic reactions (possibly delayed). It contains sorbitol and, therefore, should not be administered to patients with rare hereditary problems of fructose intolerance.

Suicidal ideation and behaviour:

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications (see "Special precautions").

INTERACTIONS
In vitro and *in vivo* studies demonstrate that TRILEPTAL has a low potential for drug interactions.

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 metabolized 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 metabolized 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 metabolized 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.

<u>Summary of antiepileptic medicinal products interactions with TRILEPTAL</u>

AEMP	Influence of TRILEPTAL on AEMP	Influence of AEMP on MHD
Co-administerd	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 (i.e. carbamazepine, phenytoin and phenobarbitone) have been shown to decrease the plasma levels of MHD (29-40 %).
No auto-induction has been observed with TRILEPTAL.

Hormonal contraceptives:
TRILEPTAL was shown to have an influence on the two components, 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 "Special precautions").

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, erythromycin and dextropropoxyphene had no effect on the pharmacokinetics of MHD, whereas viloxazine produced minor changes in the MHD plasma levels (about 10 % higher after repeated co-administration). Results with warfarin show no evidence of interaction with either single or repeated doses of TRILEPTAL.
The use of TRILEPTAL is contra-indicated in combination with monoamine-oxidase inhibitors (MAOIs). Before administering TRILEPTAL, MAOIs should be discontinued for a minimum of 2 weeks, or longer if the clinical situation permits.

PREGNANCY AND LACTATION
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.
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.
- Patients should be counseled 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-monohydroxyderivative (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.

Use during lactation:
TRILEPTAL and its active metabolite are excreted in breast milk. A milk-to-plasma concentration ratio of 0,5 were found for both. The effects on the infant exposed to TRILEPTAL by this route are unknown. Therefore, breast-feeding while taking TRILEPTAL is not recommended.

DOSAGE AND DIRECTIONS FOR USE
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' INTERACTIONS')
TRILEPTAL can be taken with or without food.
The prescription for TRILEPTAL oral suspension should be given in milliliters (see conversion table below which gives the milligram dose in milliliters).

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

900 mg	15.0 mL
1,000 mg	16.7 mL

Method of administration:
The following dosing recommendations apply to all patients, in the absence of impaired renal function (see 'PHARMACOKINETICS'). Drug plasma level monitoring is not necessary to optimize TRILEPTAL therapy.
The tablets are scored and can be broken in two halves in order to make it easier for the patients to swallow the tablet..
For younger children, who cannot be administered using tablets, a TRILEPTAL oral suspension is available.
Before using TRILEPTAL oral suspension, the bottle should be shaken well and the dose prepared immediately afterwards. The prescribed amount of oral suspension should be withdrawn from the bottle using the oral syringe supplied. The amount should be rounded to the nearest 0.5 ml when using the 10 ml syringe (supplied with the bottle containing 250 ml for older children and adults) and to the nearest 0.1 ml when using the 1 ml syringe (supplied with the bottle containing 100 ml, for younger children).

TRILEPTAL oral suspension may be swallowed directly from the syringe or can be mixed in a small glass of water just prior to administration. After each use, close the bottle and wipe the outside of the syringe with a clean, dry tissue.
TRILEPTAL oral suspension and TRILEPTAL film-coated tablets may be interchanged at equal doses.

Adults and elderly patients:
Monotherapy:
TRILEPTAL should be initiated with a dose of 600 mg/day (8-10 mg/kg/day) given in 2 divided doses. Good therapeutic effects are seen at doses between 600 mg/day and 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. 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.

Adjunctive therapy:
TRILEPTAL should be initiated with a dose of 600 mg/day (8-10 mg/kg/day) given in 2 divided doses. Good therapeutic effects are seen at doses between 600 mg/day and 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.
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 trial.
Dosages in the elderly may need to be reduced based on decreased renal function.

Children:
In mono- and adjunctive therapy, TRILEPTAL should be initiated with a dose of 8-10 mg/kg/day given in 2 divided doses.
In an adjunctive therapy trial in paediatric patients (aged 3 to 17 years), in which the intention was to reach a target daily dose of 46 mg/kg/day, the median daily dose was 31 mg/kg/day with a range of 6 to 51 mg/kg/day. In an adjunctive therapy trial in paediatric

patients (aged 1 month to less than 4 years) in which the intention was to reach a target daily dose of 60 mg/kg/day, 56 % of patients reached a final dose of at least 55 mg/kg/day .
If clinically indicated, the dose may be increased by a maximum of 10 mg/kg/day increments at approximately weekly intervals from the starting dose, to a maximum daily dose of 60 mg/kg/day, to achieve the desired clinical response.
Under adjunctive therapy and monotherapy, when normalized by body weight, apparent clearance (L/hr/kg) decreased with age such that children 1 month to less than 4 years of age may require twice the TRILEPTAL dose per body weight compared to adults; and children 4 to 12 years of age may require a 50 % higher oxcarbazepine dose per body weight compared to adults (see section 'PHARMACOKINETICS')
For children 1 month to less than 4 years of age, the influence of enzyme-inducing antiepileptic medicinal products on their weight-normalized apparent clearance appeared higher compared to older children. For children 1 month to less than 4 years of age, about 60 % higher TRILEPTAL dose per body weight may be required for adjunctive therapy on enzyme-inducing antiepileptic medicinal products relative to monotherapy or adjunctive therapy with non-enzyme-inducing antiepileptic medicinal products. For older children on enzyme-inducing antiepileptic medicinal products, only a slightly higher dose per body weight may be required than their counterparts on monotherapy
TRILEPTAL has not been studied in controlled clinical trials in children below 1 month of age.

Patients with hepatic impairment:
No dosage adjustment is required for patients with mild to moderate hepatic impairment. TRILEPTAL has not been studied in patients with severe hepatic impairment; therefore, caution should be exercised when dosing severely impaired patients (see 'PHARMACOKINETICS').

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 'PHARMACOKINETICS').

SIDE-EFFECTS AND SPECIAL PRECAUTIONS
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 heading of
frequency, the most frequent first, using the following convention: very common: (≥ 1/10); common: (≥ 1/100, - <1/10); uncommon: (≥1/1,000, - <1/100); rare: (≥ 1/10,000, - <1/1,000); very rare: (<1/10,000), including isolated reports.

Blood and lymphatic system disorders	
Uncommon	Leucopenia.

Very rare	Bone marrow depression, agranulocytosis, aplastic anaemia, pancytopenia, neutropenia, and thrombocytopenia.
Immune system disorders	
Very rare	Hypersensitivity (including multi-organ hypersensitivity) characterised by features such as rash, fever. Other organs or systems may be affected such as blood and lymphatic system (e.g. eosinophilia, thrombocytopenia, leucopenia, lymphadenopathy, splenomegaly); liver (e.g. abnormal liver function tests, hepatitis); muscle and joints (e.g. joint swelling, myalgia, arthralgia); nervous system (e.g. hepatic encephalopathy); kidney (e.g. proteinuria, nephritis interstitial, renal failure); lungs (e.g. dyspnoea, pulmonary oedema, asthma, bronchospasms, interstitial lung disease); angioedema. Anaphylactic reactions.
Metabolism and nutrition disorders	
Common	Hyponatraemia.
Very rare	Hyponatraemia associated with signs and symptoms such as seizures, confusion, depressed level of consciousness, encephalopathy (see also Nervous system disorders for further undesirable effects), vision disorders (e.g. blurred vision), vomiting, and nausea. Folic acid deficiency. Hypothyroidism
Psychiatric disorders	
Common	Confusional state, depression, apathy, agitation (e.g. nervousness), affect lability.
Nervous system disorders	
Very common	Somnolence, headache, dizziness.
Eye disorders	
Very common	Diplopia.
Common	Vision blurred, visual disturbance.
Ear and labyrinth disorders	
Common	Vertigo.
Cardiac disorders	
Vascular disorders	Hypertension
Very rare	Arrhythmia, atrioventricular block.
Gastrointestinal disorders	
Very common	Nausea, vomiting.
Common	Diarrhoea, constipation, abdominal pain.
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	Angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), 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.
	∗ **according to CIOMS III frequency classification**

Very rarely clinically significant hyponatraemia (sodium < 125 mmol/L) can develop during TRILEPTAL use. It generally occurred during the first 3 months of treatment with TRILEPTAL, although there were patients who first developed a serum sodium < 125 mmol/L more than 1 year after initiation of therapy (see section 'SPECIAL PRECAUTIONS').

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

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

Immune system disorders:
Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).

Skin and subcutaneous tissue disorders:
Acute Generalised Exanthematous Pustulosis (AGEP).

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.

Special Precautions:
TRILEPTAL should be given only under medical supervision.

*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 Side-Effects), serum sodium measurement may be considered. Other patients may have serum sodium assessed as part of their routine laboratory studies.

All patients with cardiac insufficiency and secondary heart failure should have regular weight measurements to determine occurrence of fluid retention. In case of fluid retention or worsening of the cardiac condition, serum sodium should be checked. If hyponatraemia is observed, water restriction is an important counter-measurement. As TRILEPTAL, very rarely, lead to impairment of cardiac conduction, patients with pre-existing conduction disturbances (e.g. AV-block, arrhythmia) should be followed carefully.
If during treatment, low or decreased white blood cell or platelet counts are observed, the patient and the complete blood count should be monitored closely. TRILEPTAL should be discontinued if any evidence of significant bone-marrow depression appears.

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

Haematological effects:
Very rare reports of agranulocytosis, aplastic anaemia and pancytopaenia have been seen in patients treated with TRILEPTAL during post-marketing experience (see *Side-effects*). However, due to the very low incidence of these conditions and confounding factors (e.g. underlying disease concomitant medication), causality cannot be established.
Discontinuation of the 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. A meta-analysis of randomised placebo controlled trials of antiepileptic medicines 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 Interactions). 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' PHARMACOKINETICS').

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

Effects on ability to drive and use machines:
The use of TRILEPTAL has been associated with adverse reactions such as dizziness or somnolence. Therefore, patients should be advised that their physical and/or mental abilities required for operating machinery or driving a car might be impaired.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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 drug by gastric lavage and/or inactivation by administering activated charcoal should be considered.

IDENTIFICATION

TRILEPTAL 150
Pale grey green, ovaloid, slightly biconvex, film-coated tablets scored on both sides. Embossed with "T/D on one side and "C/G" on the other side.
Length: Approximately 11,2 mm
Width: Approximately 5,7 mm
Thickness: Approximately 4,1 mm

TRILEPTAL 300
Yellow, ovaloid, slightly biconvex, film-coated 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

TRILEPTAL Oral Suspension:
Off-white to slightly reddish brown oral suspension with a fruity odour.

PRESENTATION

TRILEPTAL 150, 300 and 600 film-coated tablets are supplied in blister packs or plastic containers of 60.

TRILEPTAL Oral Suspension is supplied in brown (amber) glass bottles with a child-resistant cap and is packed in a cardboard box together with polypropylene oral syringe and press-in bottle adaptor.

Pack sizes:
100 ml with a 1 ml oral syringe
250 ml with a 10 ml syringe

STORAGE INSTRUCTIONS
Tablets
Blister packs:
Store below 30 °C and protect from moisture.
Keep out of the reach and sight of children.

Plastic containers:
Store below 30 °C and protect from moisture. Keep well closed.
Keep out of the reach and sight of children.

Suspension:
Store below 30 °C
Store in the original package.
Use within 7 weeks after first opening the bottle.
Keep out of the reach and sight of children.

REGISTRATION NUMBERS
TRILEPTAL 150: 34/2.5/0442
TRILEPTAL 300 : X/2.5/205
TRILEPTAL 600 : X/2.5/206
TRILEPTAL Oral Suspension: 36/2.5/0409

NAME AND BUSINESS ADDRESS OF THE HOLDER OF CERTIFICATES OF REGISTRATON
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