Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Trileptal 150 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg oxcarbazepine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

Trileptal 150 mg Film-coated tablets
Pale grey green, ovaloid slightly biconvex tablets, scored on both sides. Debossed with "T", score, "D" on one side and "C", score, "G" on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Trileptal is indicated for the treatment of partial seizures with or without secondarily generalised tonic-clonic seizures.

Trileptal is indicated for use as monotherapy or adjunctive therapy in adults and in children of 6 years of age and above.

4.2 Posology and method of administration

Posology
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 are replaced by Trileptal, the dose of the concomitant antiepileptic medicinal product(s) should be reduced gradually on initiation of Trileptal therapy. In adjunctive therapy, as the total antiepileptic medicinal product load of the patient is increased, the dose of concomitant antiepileptic medicinal product(s) may need to be reduced and/or the Trileptal dose increased more slowly (see section 4.5).

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

Plasma level monitoring of oxcarbazepine or MHD is not routinely warranted. However, may be useful in situations where an alteration in MHD clearance is to be expected (see section 4.4). In such situations, the dose of Trileptal may be adjusted (based on plasma levels measured 2-4 hours post dose) to maintain peak MHD plasma levels < 35 mg/L.

Adults

Monotherapy

Recommended initial dose
Trileptal should be initiated with a dose of 600 mg/day (8-10 mg/kg/day) given in 2 divided doses.

Maintenance dose
If clinically indicated, the dose may be increased by a maximum of 600 mg/day at approximately weekly intervals from the starting dose to achieve the desired clinical response. Therapeutic effects are seen at doses between 600 mg/day and 2,400 mg/day.

Controlled monotherapy trials in patients not currently being treated with antiepileptic medicinal products showed 1,200 mg/day to be an effective dose; however, a dose of 2,400 mg/day has been shown to be effective in more refractory patients converted from other antiepileptic medicinal products to Trileptal monotherapy.

Maximum recommended dose
In a controlled hospital setting, dose increases up to 2,400 mg/day have been achieved over 48 hours.

Adjunctive therapy

Recommended initial dose
Trileptal should be initiated with a dose of 600 mg/day (8-10 mg/kg/day) given in 2 divided doses.

Maintenance dose
If clinically indicated, the dose may be increased by a maximum of 600 mg/day at approximately weekly intervals from the starting dose to achieve the desired clinical response. Therapeutic responses are seen at doses between 600 mg/day and 2,400 mg/day.

Maximum recommended dose
Daily doses from 600 to 2,400 mg/day have been shown to be effective in a controlled adjunctive therapy trial, although most patients were not able to tolerate the 2,400 mg/day dose without reduction of concomitant antiepileptic medicinal products, mainly because of CNS-related adverse events. Daily doses above 2,400 mg/day have not been studied systematically in clinical trials.

Elderly (65 years old and above)
No special dose recommendations are necessary in elderly patients because therapeutic doses are individually adjusted. Dosage adjustments are recommended in elderly patients with renal impairment (creatinine clearance less than 30 ml/min) (see information below on dosage in renal impairment).

Close monitoring of sodium levels is required in patients at risk of hyponatremia (see section 4.4).

Patients with hepatic impairment
No dosage adjustment is required for patients with mild to moderate hepatic impairment. Trileptal has not been studied in patients with severe hepatic impairment, therefore, caution should be exercised when dosing severely impaired patients (see section 5.2).

Patients with renal impairment
In patients with impaired renal function (creatinine clearance less than 30 ml/min) Trileptal therapy should be initiated at half the usual starting dose (300 mg/day) and increased, in at least weekly intervals, to achieve the desired clinical response(see section 5.2).

Dose escalation in renally impaired patients may require more careful observation.

Paediatric population

Recommended initial dose
In mono- and adjunctive therapy, Trileptal should be initiated with a dose of 8-10 mg/kg/day given in 2 divided doses.

Maintenance dose
In adjunctive therapy trials, a maintenance dose of 30-46 mg/kg/day, achieved over two weeks, is shown to be effective and well tolerated in children. Therapeutic effects were seen at a median maintenance dose of approximately 30 mg/kg/day.

Maximum recommended dose
If clinically indicated, the dose may be increased by a maximum of 10 mg/kg/day at approximately weekly intervals from the starting dose, to a maximum dose of 46 mg/kg/day, to achieve the desired clinical response (see section 5.2).

Trileptal is recommended for use in children of 6 years of age and above. Safety and efficacy have been evaluated in controlled clinical trials involving approximately 230 children aged less than 6 years (down to 1 month). Trileptal is not recommended in children aged less than 6 years since safety and efficacy have not been adequately demonstrated.

All the above dosing recommendations (adults, elderly and children) are based on the doses studied in clinical trials for all age groups. However, lower initiation doses may be considered where appropriate.

Method of administration
The tablets are scored and can be broken into two halves in order to make it easier for the patient to swallow the tablet. However, the tablet cannot be divided into equal doses. For children, who cannot swallow tablets or where the required dose cannot be administered using tablets, a Trileptal oral suspension is available.

Trileptal can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance, to eslicarbazepine or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity
Class I (immediate) hypersensitivity reactions including rash, pruritus, urticaria, angioedema and reports of anaphylaxis have been received in the post-marketing period. Cases of anaphylaxis and angioedema involving the larynx, glottis, lips and eyelids have been reported in patients after taking the first or subsequent doses of Trileptal. If a patient develops these reactions after treatment with Trileptal, the 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 (e.g. severe skin reactions) with Trileptal (see section 4.8).
Hypersensitivity reactions, including multi-organ hypersensitivity reactions, may also occur in patients without a history of hypersensitivity to carbamazepine. Such reactions can affect the skin, liver, blood and lymphatic system or other organs, either individually or together in the context of a systemic reaction (see section 4.8). In general, if signs and symptoms suggestive of hypersensitivity reactions occur, Trileptal should be withdrawn immediately.

Dermatological effects
Serious dermatological reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) and erythema multiforme, have been reported very rarely in association with the use of Trileptal. 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. Patients who develop a skin reaction with Trileptal should be promptly evaluated and Trileptal withdrawn immediately unless the rash is clearly not drug related. In case of treatment withdrawal, consideration should be given to replacing Trileptal with other antiepileptic drug therapy to avoid withdrawal seizures. Trileptal should not be restarted in patients who discontinued treatment due to a hypersensitivity reaction (see section 4.3).

HLA-B*1502 allele – in Han Chinese, Thai and other Asian populations
HLA-B*1502 in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing the severe cutaneous reactions known as Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN) when treated with carbamazepine. The chemical structure of oxcarbazepine is similar to that of carbamazepine, and it is possible that patients who are positive for HLA-B*1502 may also be at risk for SJS/ TEN after treatment with oxcarbazepine. There are some data that suggest that such an association exists for oxcarbazepine. The prevalence of HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations. Whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine ora chemically-related active substance. If patients of these origins are tested positive for HLA-B*1502 allele, the use of oxcarbazepine may be considered if the benefits are thought to exceed risks.
Because of the prevalence of this allele in other Asian populations (e.g. above 15% in the Philippines and Malaysia), testing genetically at risk populations for the presence of HLA-B*1502 may be considered.
The prevalence of the HLA-B*1502 allele is negligible in e.g. European descent, African, Hispanic populations sampled, and in Japanese and Koreans (< 1%).

Allele frequencies refer to the percentage of chromosomes in the population that carry a given allele. Since a person carries two copies of each chromosome, but even one copy of the HLA-B*1502 allele may be enough to increase the risk of SJS, the percentage of patients who may be at risk is nearly twice the allele frequency.

HLA-A*3101 allele – European descent and Japanese populations

There are some data that suggest HLA-A*3101 is associated with an increased risk of carbamazepine induced cutaneous adverse reactions including SJS, TEN, Drug rash with eosinophilia (DRESS), or less severe acute generalized exanthematous pustulosis (AGEP) and maculopapular rash in people of European descent and the Japanese.
The frequency of the HLA-A*3101 allele varies widely between ethnic populations. HLA-A*3101 allele has a prevalence of 2 to 5% in European populations and about 10% in Japanese population.
The presence of HLA-A*3101 allele may increase the risk for carbamazepine induced cutaneous reactions (mostly less severe) from 5.0% in general population to 26.0% among subjects of European ancestry, whereas its absence may reduce the risk from 5.0% to 3.8%.

HLA-A*3101 allele – Other descents

The frequency of this allele is estimated to be less than 5% in the majority of Australian, Asian, African and North American populations with some exceptions within 5 to 12%. Frequency above 15% has been estimated in some ethnic groups in South America (Argentina and Brazil), North America (US Navajo and Sioux, and Mexico Sonora Seri) and Southern India (Tamil Nadu) and between 10% to 15% in other native ethnicities in these same regions.

Allele frequencies refer to the percentage of chromosomes in the population that carry a given allele. Since a person carries two copies of each chromosome, but even one copy of the HLA-A*3101 allele may be enough to increase the risk of SJS, the percentage of patients who may be at risk is nearly twice the allele frequency.

There are insufficient data supporting a recommendation for HLA-A*3101 screening before starting carbamazepine or chemically-related compounds treatment.
If patients of European descent or Japanese origin are known to be positive for HLA-A*3101 allele, the use of carbamazepine or chemically-related compounds may be considered if the benefits are thought to exceed risks.

Limitation of genetic screening

Genetic screening results must never substitute appropriate clinical vigilance and patient management. Many Asian patients positive for HLA-B*1502 and treated with Trileptal will not develop SJS/TEN, and patients negative for HLA-B*1502 of any ethnicity can still develop SJS/TEN. The same is true for HLA-A*3101 with respect to risk of SJS, TEN, DRESS, AGEP or maculopapular rash. The development of these severe cutaneous adverse reactions and its related morbidity due to other possible factors such as AED dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

Information for healthcare professionals

If testing for the presence of the HLA-B*1502 allele is performed, high-resolution "HLA-B*1502 genotyping" is recommended. The test is positive if either one or two HLA-B*1502 alleles are detected, and negative if no HLA-B*1502 alleles are detected. Similarly, if testing for the presence of the HLA-A*3101 allele is performed, high resolution "HLA-A*3101 genotyping" is recommended. The test is positive if either one or two HLA-A*3101 alleles are detected, and negative if no HLA-A*3101 alleles are detected.

Risk of seizure aggravation

Risk of seizure aggravation has been reported with Trileptal. The risk of seizure aggravation is seen especially in children but may also occur in adults. In case of seizure aggravation, Trileptal should be discontinued.

Hyponatraemia

Serum sodium levels below 125 mmol/l, usually asymptomatic and not requiring adjustment of therapy, have been observed in up to 2.7 % of Trileptal treated patients. 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 levels (e.g. inappropriate ADH secretion like syndrome) or in patients treated concomitantly with sodium-lowering medicinal products (e.g. diuretics, desmopressin) as well as NSAIDs (e.g. indometacin), serum sodium levels should be measured prior to initiating therapy. Thereafter, serum sodium levels should be measured after approximately two weeks and then at monthly intervals for the first three months during therapy, or according to clinical need. These risk factors may apply especially to elderly patients. For patients on Trileptal therapy when starting on sodium-lowering medicinal products, the same approach for sodium checks should be followed. In general, if

clinical symptoms suggestive of hyponatraemia occur on Trileptal therapy (see section 4.8), serum sodium measurement may be considered. Other patients may have serum sodium levels 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 levels should be checked. If hyponatraemia is observed, water restriction is an important counter-measurement. As oxcarbazepine may, very rarely, lead to impairment of cardiac conduction, patients with pre-existing conduction disturbances (e.g. atrioventricular-block, arrhythmia) should be followed carefully.

Hypothyroidism
Hypothyroidism is an adverse reaction (with "uncommon" frequency, see section 4.8) of oxcarbazepine. Considering the importance of thyroid hormones in children's development after birth, thyroid function monitoring is recommended in the pediatric age group while on Trileptal therapy.

Hepatic function
Very rare cases of hepatitis have been reported, which in most cases resolved favourably. When a hepatic event is suspected, liver function should be evaluated and discontinuation of Trileptal should be considered. Caution should be exercised when treating patients with severe hepatic impairment (see section 4.2 and 5.2).

Renal function
In patients with impaired renal function (creatinine clearance less than 30 mL/min), caution should be exercised during Trileptal treatment especially with regard to the starting dose and up titration of the dose. Plasma level monitoring of MHD may be considered (see section 4.2 and 5.2).

Hematological effects
Rare reports of agranulocytosis, aplastic anemia and pancytopenia have been seen in patients treated with Trileptal during post-marketing experience (see section 4.8).
Discontinuation of the medicinal product should be considered if any evidence of significant bone marrow depression develops.

Suicidal behaviour
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomized placebo controlled trials of antiepileptic medicines has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for oxcarbazepine.
Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Hormonal contraceptives
Female patients of childbearing age should be warned that the concurrent use of Trileptal with hormonal contraceptives may render this type of contraceptive ineffective (see section 4.5). Additional non-hormonal forms of contraception are recommended when using Trileptal.

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

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

Monitoring of plasma levels
Although correlations between dosage and plasma levels of oxcarbazepine, and between plasma levels and clinical efficacy or tolerability are rather tenuous, monitoring of the plasma levels may be useful in the following situations in order to rule out noncompliance or in situations where an alteration in MHD clearance is to be expected, including:

- changes in renal function (see renal impairment in section 4.2).
- pregnancy (see section 4.6 and 5).
- concomitant use of liver enzyme-inducing medicines (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Enzyme induction
Oxcarbazepine and its pharmacologically active metabolite (the monohydroxy derivative, MHD)are weak inducers *in vitro* and *in vivo* of the cytochrome P450 enzymes CYP3A4 and CYP3A5 responsible for the metabolism of a very large number of medicines, for example, immunosuppressants (e.g. ciclosporin, tacrolimus), oral contraceptives (see below), and some other antiepileptic medicinal products (e.g. carbamazepine) resulting in a lower plasma concentration of these medicinal products (see table below summarizing results with other antiepileptic medicinal products).

In vitro, oxcarbazepine and MHD are weak inducers of UDP-glucuronyl transferases (effects on specific enzymes in this family are not known). Therefore, *in vivo* oxcarbazepine and MHD may have a small inducing effect on the metabolism of medicinal products which are mainly eliminated by conjugation through the UDP-glucuronyl transferases. When initiating treatment with Trileptal or changing the dose, it may take 2 to 3 weeks to reach the new level of induction.

In case of discontinuation of Trileptal therapy, a dose reduction of the concomitant medications may be necessary and should be decided upon by clinical and/or plasma level monitoring. The induction is likely to gradually decrease over 2 to 3 weeks after discontinuation.

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. Therefore, concurrent use of Trileptal with hormonal contraceptives may render these contraceptives ineffective (see section 4.4). Another reliable contraceptive method should be used.

Enzyme inhibition
Oxcarbazepine and MHD inhibit CYP2C19. Therefore, interactions could arise when co-administering high doses of Trileptal with medicinal products that are mainly metabolised by CYP2C19 (e.g. phenytoin). Phenytoin plasma levels increased by up to 40 % when Trileptal was given at doses above 1,200 mg/day (see table below summarizing results with other anticonvulsants). In this case, a reduction of co-administered phenytoin may be required (see section 4.2).

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

Summary of antiepileptic medicinal product interactions with Trileptal

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

Strong inducers of cytochrome P450 enzymes and/or UGT (i.e. rifampicin carbamazepine, phenytoin and phenobarbitone) have been shown to decrease the plasma/serum levels of MHD (29-49 %) in adults; in children 4 to 12 years of age, MHD clearance increased by approximately 35% when given one of the three enzyme-inducing antiepileptic medicinal products compared to monotherapy. Concomitant therapy of Trileptal and lamotrigine has been associated with an increased risk of adverse events (nausea, somnolence, dizziness and headache). When one or several antiepileptic medicinal products are concurrently administered with Trileptal, a careful dose adjustment and/or plasma level monitoring may be considered on a case by case basis, notably in paediatric patients treated concomitantly with lamotrigine.
No autoinduction has been observed with Trileptal.

Other medicinal product interactions

Cimetidine, erythromycin, viloxazine, warfarin and dextropropoxyphene had no effect on the pharmacokinetics of MHD.
The interaction between oxcarbazepine and MAOIs is theoretically possible based on a structural relationship of oxcarbazepine to tricyclic antidepressants.
Patients on tricyclic antidepressant therapy were included in clinical trials and no clinically relevant interactions have been observed.
The combination of lithium and oxcarbazepine might cause enhanced neurotoxicity.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential and contraceptive measures

Trileptal may result in a failure of the therapeutic effect of oral contraceptive medicines containing ethinylestradiol (EE) and levonorgestrel (LNG) (see section 4.4 and 4.5). Women of child bearing potential should be advised to use highly effective contraception (preferably non-hormonal; e.g. intrauterine implants) while on treatment with Trileptal.

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general:
In the treated population, an increase in malformations has been noted with polytherapy, particularly in polytherapy including valproate.
Moreover, effective anti-epileptic therapy must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Risk related to oxcarbazepine:
There is moderate amount of data on pregnant women (300-1000 pregnancy outcomes). However, the data on oxcarbazepine associated with congenital malformation is limited. There is no increase in the total rate of malformations with Trileptal as compared with the rate observed in the general population (2-3%). Nevertheless, with this amount of data, a moderate teratogenic risk cannot be completely excluded. Study results related to the risk of neurodevelopmental disorders in children exposed to oxcarbazepine during pregnancy are conflicting and a risk cannot be excluded.
Data from an observational population-based registry study from the Nordic countries suggests an increased risk for children being born small for gestational age (SGA; defined as birth weight below the 10^{th} percentile for their sex and gestational age) following prenatal exposure to oxcarbazepine. The risk of SGA in children of women with epilepsy receiving oxcarbazepine was 15.2% compared with 10.9% in children of women with epilepsy not receiving an anti-seizure medication.

Taking these data into consideration:

- If women receiving Trileptal become pregnant or plan to become pregnant, the use of this product should be carefully re-evaluated. Minimum effective doses should be given, and monotherapy whenever possible should be preferred at least during the first three months of pregnancy.
- During pregnancy, an effective antiepileptic oxcarbazepine treatment must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Monitoring and prevention:
Some antiepileptic medicinal products may contribute to folic acid deficiency, a possible contributory cause of foetal abnormality. Folic acid supplementation is recommended before and during pregnancy. As the efficacy of this supplementation is not proved, a specific antenatal diagnosis should be offered even for women with a supplementary treatment of folic acid.
Data from a limited number of women indicate that plasma levels of the active metabolite of oxcarbazepine, the 10-monohydroxy derivative (MHD), may gradually decrease throughout pregnancy. It is recommended that clinical response should be monitored carefully in women receiving Trileptal treatment during pregnancy to ensure that adequate seizure control is maintained. Determination of changes in MHD plasma concentrations should be considered. If dosages have been increased during pregnancy, postpartum MHD plasma levels may also be considered for monitoring.

In the newborn child:
Bleeding disorders in the newborn have been reported with hepatic inductor antiepileptic medicines. As a precaution, vitamin K_1 should be administered as a preventive measure in the last few weeks of pregnancy and to the newborn.

Breastfeeding

Oxcarbazepine and its active metabolite (MHD) are excreted in human breast milk. Limited data indicate that the breastfed infants' MHD plasma concentrations are 0.2-0.8 µg/ml, corresponding to up to 5 % of the maternal MHD plasma concentration. Although exposure appears to be low, a risk to the infant cannot be excluded. Therefore, a decision whether to breastfeed

while using Trileptal should take into consideration both the benefit of breastfeeding and the potential risk of side effects in the infant. If breastfed, the infant should be monitored for adverse effects such as drowsiness and poor weight gain.

Fertility
There is no data on fertility in humans.
In rats, oxcarbazepine had no effects on fertility. Effects on reproductive parameters in female rats were observed for MHD at doses comparable to those in humans (see section 5.3).

4.7 Effects on ability to drive and use machines

Trileptal has moderate influence on the ability to drive and use machines. Adverse reactions such as dizziness, somnolence, ataxia, diplopia, blurred vision, visual disturbances, hyponatremia and depressed level of consciousness were reported with Trileptal (for complete list of ADRs see section 4.8), especially at the start of treatment or in connection with dose adjustments (more frequently during the up titration phase). Patients should therefore exercise due caution when driving a vehicle or operating machinery.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions are somnolence, headache, dizziness, diplopia, nausea, vomiting and fatigue occurring in more than 10% of patients.

The safety profile is based on adverse events from clinical trials assessed as related to Trileptal. In addition, clinically meaningful reports on adverse experiences from named patient programs and postmarketing experience were taken into account.

Adverse reactions (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category, using the following convention (CIOMS III) is also provided for each adverse reaction: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 1 Adverse reactions

Blood and lymphatic system disorders	
Uncommon	leucopenia.
Rare	bone marrow depression, aplastic anemia, agranulocytosis, pancytopenia, neutropenia.
Very rare	thrombocytopenia.
Immune system disorders	
Rare	anaphylactic reactions
Very rare	hypersensitivity[#]
Endocrine disorders Common	Weight increased
Uncommon	hypothyroidism
Metabolism and nutrition disorders	
Common	hyponatraemia[†]
Rare	Inappropriate ADH secretion like syndrome with signs and symptoms of lethargy, nausea, dizziness, decrease in serum (blood) osmolality, vomiting, headache, confusional state or other neurological signs and symptoms.
Psychiatric disorders	
Common	agitation (e.g. nervousness), affect lability, confusional state, depression, apathy .
Nervous system disorders	
Very common	somnolence, headache, dizziness.
Common	ataxia, tremor, nystagmus, disturbance in attention, amnesia, Speech disorders (including dysarthria); more frequent during up titration of Trileptal dose.

Eye disorders	
Very common	diplopia.
Common	vision blurred, visual disturbance.
Ear and labyrinth disorders	
Common	vertigo.
Cardiac disorders	
Very rare	atrioventricular block , arrhythmia.
Vascular disorders	
Uncommon	hypertension
Gastrointestinal disorders	
Very common	Vomiting, nausea.
Common	diarrhoea, , abdominal pain, constipation.
Very rare	pancreatitis and/or lipase and/or amylase increase.
Hepato-biliary disorders	
Very rare	hepatitis.
Skin and subcutaneous tissue disorders	
Common	rash, alopecia, acne.
Uncommon	urticaria.
Rare	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Acute Generalized Exanthematous Pustulosis (AGEP)
Very rare	Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), angioedema, erythema multiforme (see section 4.4).
Musculoskeletal, connective tissue and bone disorders	
Rare	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 Trileptal affects bone metabolism has not been identified.
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.
Rare	decrease in T4 (with unclear clinical significance)
Injury, poisoning and procedural complications	
Uncommon	Fall

Description of selected adverse reactions

[#]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. hepatitis, abnormal liver function tests,), muscles and joints (e.g. joint swelling, myalgia, arthralgia), nervous system (e.g. hepatic encephalopathy), kidneys (e.g. renal failure, nephritis interstitial, proteinuria), lungs (e.g. pulmonary oedema, asthma, bronchospasms, interstitial lung disease, dyspnea), angioedema.

[†] Serum sodium levels below 125 mmol/l have been observed in up to 2.7 % of Trileptal treated patients with frequency common (see section 4.4). In most cases, the hyponatriaemia is asymptomatic and does not require adjustment of therapy.

Very rarely, the hyponatriaemia is associated with signs and symptoms such as seizures, encephalopathy, depressed level of consciousness, confusion, (see also Nervous system disorders for further undesirable effects), vision disorders (e.g. blurred vision), hypothyroidism, vomiting, and nausea. Low serum sodium levels generally occurred during the first 3 months of treatment with Trileptal, although there were patients who first developed a serum sodium level <125 mmol/l more than 1 year after initiation of therapy (see section 4.4).

Paediatric population

In general, the safety profile in children was similar to that observed in the adult population (see section 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, www.hpra.ie.

4.9 Overdose

Isolated cases of overdose have been reported. The maximum dose taken was approximately 48,000 mg.

Symptoms

Electrolyte and fluid balance conditions: hyponatraemia
Eye disorders: diplopia, miosis, blurred vision
Gastrointestinal disorders: nausea, vomiting, hyperkinesia
General disorders and administration site conditions: fatigue
Investigations: respiratory rate depression, QTc prolongation
Nervous system disorders: drowsiness and somnolence, dizziness, ataxia and nystagmus, tremor, disturbances in coordination (coordination abnormal), convulsion, headache, coma, loss of consciousness, dyskinesia
Psychiatric disorders: aggression, agitation, confusional state
Vascular disorders: hypotension
Respiratory, thoracic and mediastinal disorders: dyspnoea

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC code: N03A F 02

Mechanism of action
The pharmacological activity of oxcarbazepine is primarily exerted through the metabolite (MHD) (see section 5.2). The mechanism of action of oxcarbazepine and MHD is thought to be mainly based on the blockade of voltage-sensitive sodium channels, thus resulting in stabilisation of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminishment of propagation of synaptic impulses. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may also contribute to the anticonvulsant effects. No significant interactions with brain neurotransmitter or modulator receptor sites were found.

Pharmacodynamic effects
Oxcarbazepine and its active metabolite (MHD), are potent and efficacious anticonvulsants in animals. They protected rodents against generalised tonic-clonic and, to a lesser degree, clonic seizures, and abolished or reduced the frequency of chronically recurring partial seizures in Rhesus monkeys with aluminum implants. No tolerance (i.e. attenuation of anticonvulsive activity) against tonic-clonic seizures was observed when mice and rats were treated daily for 5 days or 4 weeks, respectively, with oxcarbazepine or MHD.

Clinical efficacy and safety
A prospective, open-label, multicentre, non-comparative, 24 week observational post marketing study has been conducted in India. Out of a study population of 816 patients, 256 pediatric patients (1 month to 19 years) with generalised tonic-clonic seizures (either secondary or primary) were treated with oxcarbazepine monotherapy. The initial oxcarbazepine dose for all patients > 6 years was 8-10 mg/kg/day given in 2 divided doses. For the 27 subjects aged 1 month to 6 years, the dose range for the initial dose was 4.62 – 27.27 mg/kg/day and 4.29 – 30.00 mg/kg/day maintenance dose. The primary endpoint was reduction in seizure frequency from baseline at week 24. In the age group 1 month to 6 years (n=27) the number of seizures changed from 1 [range] [1-12] to 0 [0-2], in the age group 7 years to 12 years (n=77) the frequency changed from 1 [1-22] to 0 [0-1] and in the age group 13-19 years (n=152), the frequency changed from 1 [1-32] to 0 [0-3]. No specific safety concerns in the pediatric patients were identified. Data supporting benefit/risk from the study regarding children under the age of 6 are inconclusive (see section 4.2).

Based on the data from the randomized controlled trials, the use of oxcarbazepine is not recommended in children below the age of 6 since safety and efficacy have not been adequately demonstrated (see section 4.2).

Paediatric population
Two randomised, rater-blinded, dose-controlled efficacy studies (Study 2339 and Study 2340) were conducted in paediatric patients aged 1 month to <17 years of age (n=31 patients aged 6 to <17 years; n=189 patients aged <6 years old). In addition, a number of open-label studies that enrolled children were conducted. In general, the safety profile of oxcarbazepine in younger children (<6 years old) was similar to that in older children (≥6 years old). However, in some studies in younger children (<4 years old) and older children (≥4 years old), a ≥ 5-fold difference in the proportion of patients with convulsions (7.9% vs. 1.0%, respectively) and status epilepticus (5% vs. 1%, respectively) was observed.

5.2 Pharmacokinetic properties

Absorption
Following oral administration of Trileptal, oxcarbazepine is completely absorbed and extensively metabolised to its pharmacologically active metabolite (MHD).
After single dose administration of 600 mg Trileptal to healthy male volunteers under fasted conditions, the mean C_{max} value of MHD was 34 µmol/ml, with a corresponding median t_{max} of 4.5 hours.
In a mass balance study in man, only 2 % of total radioactivity in plasma was due to unchanged oxcarbazepine, approximately 70 % was due to MHD, and the remainder attributable to minor secondary metabolites which were rapidly eliminated.
Food has no effect on the rate and extent of absorption of oxcarbazepine, therefore, Trileptal can be taken with or without food.

Distribution
The apparent volume of distribution of MHD is 49 litres.
Approximately 40 % of MHD, is bound to serum proteins, 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.
Oxcarbazepine and MHD cross the placenta. Neonatal and maternal plasma MHD concentrations were similar in one case.

Biotransformation
Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to MHD, which is primarily responsible for the pharmacological effect of Trileptal. MHD is metabolised further by conjugation with glucuronic acid. Minor amounts (4 % of the dose) are oxidised to the pharmacologically inactive metabolite (10, 11-dihydroxy derivative, DHD).

Elimination
Oxcarbazepine is cleared from the body mostly in the form of metabolites which are predominantly excreted by the kidneys. More than 95 % of the dose appears in the urine, with less than 1 % as unchanged oxcarbazepine. Faecal excretion accounts for less than 4 % of the administered dose. Approximately 80 % of the dose is excreted in the urine either as glucuronides of MHD (49 %) or as unchanged MHD (27 %), whereas the inactive DHD accounts for approximately 3 % and conjugates of oxcarbazepine account for 13 % of the dose.
Oxcarbazepine is rapidly eliminated from the plasma with apparent half-life values between 1.3 and 2.3 hours. In contrast, the apparent plasma half-life of MHD averaged 9.3 ± 1.8 h..

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

Special populations

Patients with hepatic impairment
The pharmacokinetics and metabolism of oxcarbazepine and MHD were evaluated in healthy volunteers and hepatically-impaired subjects after a single 900 mg oral dose. Mild to moderate hepatic impairment did not affect the pharmacokinetics of oxcarbazepine and MHD. Trileptal has not been studied in patients with severe hepatic impairment.

Patients with renal impairment
There is a linear correlation between creatinine clearance and the renal clearance of MHD. When Trileptal is administered as a single 300 mg dose, in renally impaired patients (creatinine clearance < 30 mL/min) the elimination half-life of MHD is

prolonged by 60-90 % (16 to 19 hours) with a two fold increase in AUC compared to adults with normal renal function (10 hours).

Children
The pharmacokinetics of Trileptal were evaluated in clinical trials in pediatric patients taking Trileptal in the dose range 10-60 mg/kg/day. Weight-adjusted MHD clearance decreases as age and weight increases approaching that of adults. The mean weight-adjusted clearance in children 4 to 12 years of age is approximately 40% higher than that of adults. Therefore, MHD exposure in these children is expected to be about two-thirds that of adults when treated with a similar weight-adjusted dose. As weight increases, for patients 13 years of age and above, the weight-adjusted MHD clearance is expected to reach that of adults.

Pregnancy
Data from a limited number of women indicate that MHD plasma levels may gradually decrease throughout pregnancy (see section 4.6).

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

5.3 Preclinical safety data

Non-clinical data indicated no special hazard for humans based on safety pharmacology and genotoxicity studies with oxcarbazepine and the pharmacologically active metabolite, monohydroxy derivative (MHD).

Evidence of nephrotoxicity was noted in repeated dose toxicity rat studies but not in dog or mice studies.

Immunotoxicity

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

Mutagenicity
Oxcarbazepine increased mutation frequencies in one Ames test in vitro in the absence of metabolic activation in one of five bacterial strains. Oxcarbazepine and MHD produced increases in chromosomal aberrations and/or polyploidy in the Chinese hamster ovary assay in vitro in the absence of metabolic activation. MHD was negative in the Ames test, and no mutagenic or clastogenic activity was found with either oxcarbazepine or MHD in V79 Chinese hamster cells in vitro. Oxcarbazepine and MHD were both negative for clastogenic or aneugenic effects (micronucleus formation) in an in vivo rat bone marrow assay.

Reproductive toxicity
In rats, fertility in both sexes was unaffected by oxcarbazepine at oral doses up to 150 mg/kg/day, at which there is no safety margin. Disruption of estrous cyclicity and reduced numbers of corpora lutea, implantations and live embryos were observed in female animals for MHD at doses comparable to those in humans (see section 4.6).
Standard reproductive toxicity studies in rodents and rabbits revealed effects such as increases in the incidence of embryo-foetal mortality and/or some delay in antenatal and/or postnatal growth of the offspring at maternally toxic dose levels. There was an increase in rat foetal malformations in one of the eight embryo-foetal toxicity studies, which were conducted with either oxcarbazepine or MHD, at a doses which also caused maternal toxicity (see section 4.6).

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

effects occurred at exposure levels comparable with the anticipated clinical exposure. The mechanism for the development of these tumours has not been fully elucidated but could be related to increased estradiol levels specific to the rat. The clinical relevance of these tumours is unclear.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Tablet coating:
hypromellose
talc
titanium dioxide (E 171).
macrogol 4000
iron oxide, yellow (E 172)
iron oxide red (E 172)
iron oxide black (E 172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister containing 10 tablets. Blister material: PVC/PE/PVDC with aluminium foil backing.

Blister pack of 30, 50, 100, 200 and/or 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Novartis Ireland Limited,Termini, 3 Arkle Road,Sandyford, Dublin 18, Ireland

8 MARKETING AUTHORISATION NUMBER

PA0896/033/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 18 February 2000

Date of last renewal: 26th October 2016

10 DATE OF REVISION OF THE TEXT

November 2026