NEW ZEALAND DATA SHEET

1. NAME OF THE MEDICINAL PRODUCT

TRILEPTAL® Film coated tablets
Oxcarbazepine 150 mg and 600 mg, Film-Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg or 600 mg oxcarbazepine.

For a full list of excipients, see Pharmaceutical Particulars, **List of excipients**.

3. PHARMACEUTICAL FORM

Film-coated tablets
150 mg: pale grey green, ovaloid slightly biconvex tablets, scored on both sides. Embossed with T/D on one side and C/G on the other side.
600 mg: light pink, ovaloid slightly biconvex tablets scored on both sides. Embossed with TF/TF on one side and CG/CG on the other side.

The score line on two sides of Trileptal 150 mg or 600 mg film-coated tablet 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 in adults and in children aged 1 month and above for the treatment of:

- Partial seizures (which include the seizure subtypes of simple, complex and partial seizures evolving to secondarily generalised seizures) and
- Generalised tonic-clonic seizures.

Trileptal is indicated as a first-line antiepileptic drug for use as monotherapy or adjunctive therapy.

Trileptal can replace other antiepileptic drugs when current therapy provides insufficient seizure control (see **Clinical studies**).

4.2 Posology and method of administration

Posology

Trileptal is suitable for use either as monotherapy or in combination with other antiepileptic drugs. In mono- and adjunctive therapy, treatment with Trileptal is initiated with a clinically effective dose given in two divided doses (see **Clinical studies**). The dose may be increased depending on the clinical response of the patient. When other antiepileptic drugs 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 drug load of the patient is increased, the dose of concomitant antiepileptic drug(s) may need to be reduced and/or the Trileptal dose increased more slowly (see **Interactions**).

Therapeutic drug monitoring

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

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

- changes in renal function (see Dosage in renal impairment)
- pregnancy (see Pregnancy, lactation, females and males of reproductive potential and Clinical Pharmacology)

- concomitant use of liver enzyme-inducing drugs (see section 8 Interactions)

If any of these situations apply, 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.

General target population
Adults
Monotherapy and 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
Good therapeutic effects are seen at doses between 600 mg/day and 2,400 mg/day. 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.

Maximum recommended dose
In a controlled hospital setting, dose increases up to 2,400 mg/day have been achieved over 48 hours. Daily doses above 2,400 mg/day have not been studied systematically in clinical trials.

Special populations
Paediatric patients (below 18 years)

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
The target maintenance dose of Trileptal for adjunctive therapy is 30-46 mg/kg/day and should be achieved over two weeks.
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.

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 daily dose of 60 mg/kg/day, to achieve the desired clinical response (see **Pharmacokinetic properties**).

Effect of weight adjusted MHD clearance on pediatric dosage
Under adjunctive therapy and monotherapy, when normalized by body weight, apparent clearance (L/hr/kg) of MHD (the active metabolite of oxcarbazepine) decreased with age such that children 1 month to less than 4 years of age may require twice the oxcarbazepine 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 **Clinical pharmacology**).

Effect of concomitant enzyme-inducing antiepileptic drugs on pediatric dosage
For children 1 month to less than 4 years of age, the influence of enzyme-inducing antiepileptic drugs on weight-normalized apparent clearance appeared higher compared to older children. For children 1 month to less than 4 years of age, an approximately 60 % higher oxcarbazepine dose per body weight may be required for adjunctive therapy on enzyme-inducing antiepileptic drugs relative to monotherapy or adjunctive therapy with non-enzyme-inducing antiepileptic drugs. 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.

Geriatric patients (65 years or 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 <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 Warnings and precautions).

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 **Pharmacology and Warnings and precautions**).

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 **Pharmacodynamic Properties - Pharmacokinetic properties**).

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.

Trileptal can be taken with or without food (see Clinical pharmacology).

4.3 Contraindications

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

4.4 Warnings and precautions

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 **Adverse Effects**).

Hypersensitivity reactions, including multi-organ hypersensitivity reactions, may also occur in patients without 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 **Adverse Effects**). 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. Should a patient develop a skin reaction with Trileptal, consideration should be given to discontinuing Trileptal and prescribing another anti-epileptic drug.

Pharmacogenomics
There is growing evidence that different Human Leukocyte Antigen (HLA) alleles play a role in association with adverse cutaneous reactions in predisposed patients.

Association with HLA-B*1502

Retrospective studies in patients of Han Chinese and Thai origin found a strong correlation between SJS/TEN skin reactions associated with carbamazepine and the presence in these patients of the Human Leukocyte Antigen (HLA)-B*1502 allele. As the chemical structure of oxcarbazepine is similar to that of carbamazepine, there is a possibility that patients carrying the HLA-B*1502 allele also have an increased risk of SJS/TEN skin reactions with oxcarbazepine.

The frequency of HLA-B*1502 allele ranges from 2 to 12% in Han Chinese populations and is about 8% in Thai populations, and above 15% in the Philippines and some Malaysian populations. Allele frequencies up to about 2% and 6% have been reported in Korea and India, respectively. The frequency of the HLA-B*1502 allele is negligible in persons from European descent, several African populations, indigenous peoples of the Americas, Hispanic populations sampled and in Japanese (< 1%).

The allele frequencies listed here represent the percentage of chromosomes in the specified population that carry the allele of interest, meaning that the percentage of patients who carry a copy of the allele on at least one of their two chromosomes (i.e. the “carrier frequency”) is nearly twice as high as the allele frequency. Therefore, the percentage of patients who may be at risk is nearly twice the allele frequency.

Testing for the presence of the HLA-B*1502 allele should be considered in patients with ancestry in genetically at-risk populations, prior to initiating treatment with Trileptal. The use of Trileptal should be avoided in tested patients who are found to be positive for HLA-B*1502 unless the benefits clearly outweigh the risks. HLA-B*1502 may be a risk factor for the development of SJS/TEN in Chinese patients taking other anti-epileptic drugs (AED) associated with SJS/TEN. Consideration should therefore be given to avoid use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable. Screening is not generally recommended in patients from populations in which the prevalence of HLA-B*1502 is low or in current Trileptal users, as the risk of SJS/TEN is largely confined to the first few months of therapy, regardless of HLA B*1502 status.

Association with HLA-A*3101

Human Leukocyte Antigen (HLA)-A*3101 may be a risk factor for the development of cutaneous adverse drug reactions such as SJS, TEN, DRESS, AGEP and maculopapular rash.

The frequency of the HLA-A*3101 allele varies widely between ethnic populations and its frequency is about 2 to 5% in European populations and is about 10% in the Japanese population. 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 10% to 15% in other native ethnicities in these same regions.

The allele frequencies listed here represent the percentage of chromosomes in the specified population that carry the allele of interest, meaning that the percentage of patients who carry a copy of the allele on at least one of their two chromosomes (i.e., the “carrier frequency”) is nearly twice as high as the allele frequency. Therefore, the percentage of patients who may be at risk is nearly twice the allele frequency.

There is some data that suggest HLA-A*3101 is associated with an increased risk of carbamazepine-induced cutaneous adverse drug reactions including SJS, TEN, Drug rash with eosinophilia (DRESS), or less severe acute generalized exanthematous pustulosis (AGEP) and maculopapular rash.

There are insufficient data to support a recommendation for testing the presence of HLA A*3101 allele in patients, prior to initiating treatment with oxcarbazepine. Genetic screening is generally not recommended for any current Trileptal users, as the risk of SJS/TEN, AGEP, DRESS and maculopapular rash is largely confined to the first few months of therapy, regardless of HLA-A*3101 status.

Limitation of genetic screening

Genetic screening results must never substitute for 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. Similarly

many patients positive for HLA-A*3101 and treated with Trileptal will not develop SJS, TEN, DRESS, AGEP or maculopapular rash and patients negative for HLA-A*3101 of any ethnicity can still develop these severe cutaneous adverse reactions. The role of other possible factors in the development of, and morbidity from, these severe cutaneous adverse reactions, such as AED dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

Information for the 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, drugs 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 **Adverse 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 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. AV-block, arrhythmia) should be monitored carefully.

Hypothyroidism
Hypothyroidism is a very rare adverse drug reaction of oxcarbazepine. Considering the importance of thyroid hormones in children's development after birth, it is advisable to perform a thyroid function test before the start of Trileptal therapy in the pediatric age group, especially in children aged two years or below. 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 of the cases resolved favourably. In case of suspected hepatitis, discontinuation of Trileptal should be considered. Caution should be exercised when treating patients with severe hepatic impairment (see Dosage and administration and Clinical pharmacology).

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 (see Dosage and administration and Clinical pharmacology).

Haematological effects
Very rare reports of agranulocytosis, aplastic anemia and pancytopenia have been seen in patients treated with Trileptal during post-marketing experience (see **Adverse 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 drug 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 randomized placebo controlled trials of antiepileptic drugs 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.

An analysis of reports of suicidality (suicidal behaviour or ideation) from placebo-controlled clinical studies of eleven medicines used to treat epilepsy as well as psychiatric disorders, and other conditions revealed that patients receiving anti-epileptic drugs had approximately twice the risk of suicidal behaviour or ideation (0.43%) compared to patients receiving placebo (0.22%). The increased risk of suicidal behaviour and suicidal ideation was observed as early as one week after starting the anti-epileptic medicine and continued through 24 weeks. The results were generally consistent among the eleven medicines. Patients who were treated for epilepsy, psychiatric disorders, and other conditions were all at increased risk for suicidality when compared to placebo, and there did not appear to be a specific demographic subgroup of patients to which the increased risk could be attributed. The relative risk for suicidality was higher in the patients with epilepsy compared to patients who were given one of the medicines in the class for psychiatric or other conditions.

All patients who are currently taking or starting on any anti-epileptic drug should be closely monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression. Health Care Professionals should inform patients, their families, and caregivers of the potential for an increase in the risk of suicidality. Prescribers should advise patients to seek medical advice immediately if they develop any symptoms suggestive of suicidality.

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 **Interactions**). 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 effects
As with all antiepileptic drugs, Trileptal should be withdrawn gradually to minimise the potential of increased seizure frequency.

4.5 Interaction with other medicinal products and other forms of interaction

Enzyme inhibition
Oxcarbazepine was evaluated in human liver microsomes to determine its capacity to inhibit the major cytochrome P450 enzymes responsible for the metabolism of other drugs. The results demonstrate that oxcarbazepine and its pharmacologically active metabolite (the monohydroxy derivative, MHD) inhibit CYP2C19. Therefore, interactions could arise when co-administering high doses of Trileptal with drugs that are metabolised by CYP2C19 (e.g. phenobarbital, phenytoin, see below). In some patients treated with Trileptal and drugs metabolized via CYP2C19 a reduction of the co-administered drugs might be necessary. In human liver microsomes, oxcarbazepine and MHD have little or no capacity to function as inhibitors for the following enzymes: CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP4A9 and CYP4A11.

Enzyme induction
Oxcarbazepine and MHD induce *in vitro* and *in vivo*, cytochromes CYP3A4 and CYP3A5 responsible for the metabolism of dihydropyridine calcium antagonists, oral contraceptives, and antiepileptic drugs (e.g. carbamazepine) resulting in a lower plasma concentration of these drugs (see below). Such level of decrease in plasma concentrations may also be observed in other drugs mainly metabolized by CYP3A4 and CYP3A5, for example immunosuppressants (e.g. cyclosporin).

In vitro, oxcarbazepine and MHD are weak inducers of UDP-glucuronyl transferase. Therefore, *in vivo* they are unlikely to have an effect on drugs 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 oxcarbazepine and MHD, a higher dose of concomitantly used drugs which are metabolized via CYP3A4 or via conjugation (UDPGT) may be necessary. In the case of discontinuation of Trileptal therapy, a dose reduction of the concomitant medication may be necessary.

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

Antiepileptic drugs and enzyme inducing drugs
Potential interactions between Trileptal and other antiepileptic drugs were assessed in clinical studies. The effect of these interactions on mean AUCs and C_{min} are summarised in Table 2.

Table 2: Summary of antiepileptic medicinal product interactions with Trileptal

Antiepileptic drug co-administered	**Influence of Trileptal on antiepileptic drug concentration**	**Influence of antiepileptic rdug on MHD concentration**
Carbamazepine	0 - 22 % decrease	40 % decrease
Clobazam	Not studied	No influence
Felbamate	Not studied	No influence
Phenobarbital	14 - 15 % increase	30 - 31 % decrease
Phenytoin	0 - 40 % increase	29 - 35 % decrease
Valproic acid	No influence	0 - 18 % decrease
Lamotrigine	No influence	No influence

In vivo, plasma levels of phenytoin increased by up to 40 %, when Trileptal was given at doses above 1,200 mg/day. Therefore, when using doses of Trileptal greater than 1,200 mg/day during adjunctive therapy, a decrease in the dose of phenytoin may be required (see Dosage and administration). The increase of phenobarbital level, however, is small (15 %) when given with Trileptal.

Strong inducers of cytochrome P450 enzymes and/or UGT (e.g. rifampicin, carbamazepine, phenytoin and phenobarbital) have been shown to decrease the plasma levels of MHD (29-49 %).
No auto induction has been observed with Trileptal.

Hormonal contraceptives
Trileptal was shown to have an influence on the two components, ethinyloestradiol (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 ineffective (see Warnings and precautions and Pregnancy, lactation, females and males of reproductive potential).

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 product 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.

4.6 Pregnancy, lactation and females and males of reproductive potential

Pregnancy
Risk summary
Offspring of epileptic mothers are known to be more prone to developmental disorders, including malformations.

Based on data in a North American pregnancy registry, the prevalence of major congenital malformations, defined as a structural abnormality with surgical, medical, or cosmetic importance, diagnosed within 12 weeks of birth was 2.2% (95% CI 0.6 to 5.5) among mothers exposed to oxcarbazepine monotherapy in the first trimester. When compared with pregnant women not exposed to any antiepileptic drugs the relative risk (RR) of major congenital abnormality in pregnant women on oxcarbazepine is (RR) 2.0%, 95% CI 0.5 to 7.4.

Based on data in EURAP registry (European and International Registry of Antiepileptic Drugs and Pregnancy) the prevalence of major congenital malformations (classified according to 2005 EUROCAT criteria) in offspring exposed prenatally to oxcarbazepine monotherapy assessed after 1 year after birth was 3.0% (95% CI, 1.4 - 5.4).

Most frequently observed congenital malformations with the use of oxcarbazepine were ventricular septal defect, atrioventricular septal defect, cleft palate with cleft lip, Down's syndrome, dysplastic hip (both unilateral and bilateral), tuberous sclerosis and congenital malformation of the ear.

Data on epileptic pregnant women receiving oxcarbazepine and unborn child exposed to oxcarbazepine during pregnancy remain inconclusive. However, risk of potential teratogenicity and neurodevelopmental disorders cannot be completely excluded.

Specialist medical advice regarding the potential risks to a foetus caused by both seizures and antiepileptic treatment should be given to all women of childbearing potential taking antiepileptic treatment, and especially to women planning pregnancy and women who are pregnant.

Clinical considerations
Taking these data into consideration:

If women receiving Trileptal become pregnant, or plan to become pregnant, or if the need to initiate treatment with Trileptal arises during pregnancy, the drug's potential benefits must be carefully weighed against the potential risk of congenital malformations and neurodevelopment disorders. This is particularly important during the first three months of pregnancy.

Minimum effective doses should be given.

In women of childbearing age, whenever possible, it is recommended that Trileptal should be administered as monotherapy. The potential for congenital abnormalities in the offspring of women treated with combination therapies is greater than those receiving monotherapy.

Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

During pregnancy, an effective antiepileptic treatment should not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Monitoring and prevention
Antiepileptic drugs may contribute to folic acid deficiency, a possible contributory cause of foetal abnormality. Folic acid supplementation is recommended before and during pregnancy.

Due to physiological changes during pregnancy, plasma levels of the active metabolite of oxcarbazepine, the 10-monohydroxy derivative (MHD), may gradually decrease throughout pregnancy. It is recommended that clinical response should be monitored carefully in women receiving Trileptal treatment during pregnancy and determination of changes in MHD plasma concentrations should be considered to ensure that adequate seizure control is maintained throughout pregnancy. Postpartum MHD plasma levels may also be considered for monitoring especially in the event that medication was increased during pregnancy.

In the newborn child
Bleeding disorders in the newborn caused by antiepileptic agents have been reported. As a precaution, vitamin K_1 should be administered as a preventive measure in the last few weeks of pregnancy and to the newborn.

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

Animal data
Standard reproductive toxicity studies in rodents and rabbits revealed effects such as increases in the incidence of embryo-fetal 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 fetal malformations in one of the eight embryo-fetal toxicity studies, which were conducted with either oxcarbazepine or MHD, at doses which also caused maternal toxicity. The overall evidence from all animal studies indicates that oxcarbazepine has minor teratogenic potential at doses relevant to humans. However, the animal studies were insufficient to rule out a teratogenic effect of oxcarbazepine.

Lactation
Risk summary
Oxcarbazepine and its active metabolite (MHD) are excreted in human breast milk. Limited data indicate that the breastfed infants' MHD plasma concentrations correspond up to 5 % of the maternal MHD plasma concentration. Although exposure appears to be low, a risk to the infant cannot be excluded. Therefore, a decision whether to continue breastfeeding while using oxcarbazepine should be considered based on 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.

Females and males of reproductive potential
Contraception
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. Trileptal may result in a failure of the therapeutic effect of oral contraceptive drugs containing ethinylestradiol (EE) and levonorgestrel (LNG) (see Warning and precautions and Interactions).

Infertility
There are no human data on fertility.
In rats, fertility in both sexes was unaffected by oxcarbazepine or MHD at oral doses up to 150 and 450 mg/kg/day, respectively. However, disruption of estrous cyclicity and reduced numbers of corpora lutea, implantations and live embryos were observed in female animals at the highest dose of MHD.

4.7 Effects on ability to drive and use machines

The use of Trileptal has been associated with adverse reactions, such as dizziness, somnolence ataxia, diplopia, blurred vision, visual disturbances, hyponatremia and depressed level of consciousness were reported with Trileptal (for the complete list of ADRs see Adverse effects), 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.

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 adverse 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.

Tabulated summary of adverse drug reactions from clinical trials

Adverse reactions from clinical trials (Table 3) are listed by MeDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): *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.*

Table 3

Blood and lymphatic system disorders

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

Immune system disorders

Very rare	Anaphylactic reactions, hypersensitivity (including multi-organ hypersensitivity) characterised by features such as rash, fever. Other organs or systems may be affected such as blood and lymphatic system (e.g. eosinophilia, thrombocytopenia, leukopenia, 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.

Endocrine disorders

Common	Weight increased
Very rare	Hypothyroidism

Metabolism and nutrition disorders

Common	Hyponatraemia.
Very rare	Hyponatraemia associated with signs and symptoms such as seizures, encephalopathy, depressed level of consciousness, confusion, (see also Nervous system disorders for further adverse effects), vision disorders (e.g. blurred vision), hypothyroidism, vomiting, nausea, folic acid deficiency.

Psychiatric disorders

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

Nervous system disorders

Very common	Somnolence, headache, dizziness.
Common	Ataxia, tremor, nystagmus, disturbance in attention, amnesia.

Eye disorders

Very common	Diplopia.
Common	Vision blurred, visual disturbance.

Ear and labyrinth disorders

Common	Vertigo.

Cardiac disorders

Very rare	Atrioventricular block, arrhythmia.

Vascular disorders

Very rare	Hypertension.

Gastrointestinal disorders

Very common	Vomiting, nausea.
Common	Diarrhoea, abdominal pain, constipation.
Very rare	Pancreatitis and/or lipase and/or amylase increase.

Hepatobiliary disorders

Very rare	Hepatitis.

Skin and subcutaneous tissue disorders

Common	Rash, alopecia, acne.
Uncommon	Urticaria.
Very rare	Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), angioedema, erythema multiforme.

Musculoskeletal, connective tissue and bone disorders

Very rare	Systemic lupus erythematosus.

General disorders and administration site conditions

Very common	Fatigue.
Common	Asthenia.

Investigations

Uncommon	Hepatic enzymes increased, blood alkaline phosphatase increased.
Very rare	Amylase increase, lipase increase.

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 serum sodium < 125 mmol/L more than 1 year after initiation of therapy (see **Warnings and 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.

Emergence or worsening of existing depression, suicidal behaviour and suicidal ideation have been reported in patients treated with antiepileptic agents in several indications. The frequency of these events is unknown.

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 categorized 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.

Metabolism and nutrition disorders

Inappropriate ADH secretion like syndrome with signs and symptoms of lethargy, nausea, dizziness, decrease in serum (blood) osmolality, vomiting, headache, confusional state or other neurological signs and symptoms.

Skin and subcutaneous tissue disorders

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Acute Generalized Exanthematous Pustulosis (AGEP)

Injury, poisoning and procedural complications

Fall

Nervous system disorders

Speech disorders (including dysarthria); more frequent during up titration of Trileptal dose.

Musculoskeletal, connective tissue and bone disorders

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with Trileptal. The mechanism by which oxcarbazepine affects bone metabolism has not been identified.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions
https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

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

Signs and Symptoms
Electrolyte and fluid balance conditions: hyponatremia

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, 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.

For information on the management of overdose, contact the New Zealand National Poisons Centre (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC code: N03A F02

Mechanism of action (MOA)
The pharmacological activity of Trileptal (oxcarbazepine) is primarily exerted through the metabolite (MHD) of oxcarbazepine (see **Pharmacokinetics – Biotransformation/Metabolism**). 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.

Pharmacodynamics
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 studies
A total of 10 double blind, well controlled trials, 2 in adjunctive therapy and 8 in monotherapy were conducted in patients with partial seizures which included the seizure subtypes of simple, complex and partial seizures evolving to secondarily generalised seizures. All comparative trials also included patients with generalised tonic-clonic seizures. Two dose-control monotherapy substitution trials in which patients received a variety of concomitant antiepileptic drugs which included carbamazepine, gabapentin, lamotrigine, phenytoin, and valproate confirm efficacy when these antiepileptic drugs were substituted by Trileptal. Two trials were conducted in children (aged 3 to 17 years), one in adjunctive therapy versus placebo, the other a monotherapy comparison with phenytoin. Efficacy was demonstrated with doses ranging from 600 mg/day to 2,400 mg/day in all the primary efficacy parameters which included mean or percentage change in seizure frequency from baseline in the adjunctive trials and time to meeting pre-defined exit criteria or the percentage of patients meeting exit criteria in the monotherapy trials.

An adjunctive therapy, rater-blind, trial in children (aged 1 month to less than 4 years) with inadequately-controlled partial seizures on one to two concomitant antiepileptic drugs was conducted, comparing two doses of oxcarbazepine. The primary measure of effectiveness was a between group comparison of the absolute change in study specific seizure frequency per 24 hours compared to the seizure frequency at baseline. This comparison was statistically significant in favour of Trileptal 60 mg/kg/day. A monotherapy, rater-blind, trial in children (aged 1 month to 16 years) with inadequately controlled or new-onset partial seizures was conducted comparing two doses of oxcarbazepine. The primary measure of effectiveness was a between group comparison of the time to meet exit criteria which was not statistically significant. The majority of patients in both treatment groups did not experience any video EEG-confirmed seizures during the study and completed this 5-day study without exiting.

It has been shown that Trileptal has similar efficacy to other first line antiepileptic drugs (i.e. valproic acid, phenytoin and carbamazepine) with a statistically significantly better tolerability profile than phenytoin as judged by withdrawals due to adverse events and, a statistically significant longer retention rate (i.e. proportion of patients who stayed on treatment). Similar proportions of patients with partial and

generalised tonic-clonic seizures, who were treated with Trileptal, were seizure free over the 12 month treatment period of these trials.

5.2 Pharmacokinetics (PK)

Absorption
Following oral administration of Trileptal tablets, oxcarbazepine is completely absorbed and extensively metabolised to its pharmacologically active metabolite (10-monohydroxy derivative, MHD). After single dose administration of 600 mg Trileptal tablet to healthy male volunteers under fasted conditions, the mean C_{max} value of MHD was 34 micromol/L, 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 (see Dosage and administration).

Distribution
The apparent volume of distribution of MHD is 49 litres.

Approximately 40 % of MHD, is bound to serum proteins, predominately to albumin. Binding was independent of the serum concentration within the therapeutically relevant range. Oxcarbazepine and MHD do not bind to alpha-1-acid glycoprotein.

Biotransformation/Metabolism
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 hours.

Linearity/non-linearity
Steady-state plasma concentrations of MHD are reached within 2 to 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

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.

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 up to 19 hours, with a two fold increase in AUC.

Paediatric patients (below 18 years)
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.

Pregnancy
Due to physiological changes during pregnancy, MHD plasma levels may gradually decrease throughout pregnancy (see **Dosage regimen and administration** and **Pregnancy, lactation, females and males of reproductive potential**).

Geriatric patients (65 years or above)
Following administration of single (300 mg) and multiple doses (600 mg/day) of Trileptal in elderly volunteers (60 to 82 years of age), the maximum plasma concentrations and AUC values of MHD were 30 to 60 % higher than in younger volunteers (18 to 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 Non-clinical safety data

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

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.

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

Trileptal film-coated tablets

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

Tablet coating:
Hypromellose; talc; titanium dioxide (E171);

150 mg tablet coating only:
Macrogol 4000; iron oxide, yellow (E 172); iron oxide red (E 172); iron oxide black (E 172).

600 mg tablet coating only:
Macrogol 4000; iron oxide red (E 172); iron oxide black (E 172).

Ethanol is a component of the flavour.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C in the original package.

Trileptal must be kept out of the reach and sight of children.

6.5 Nature and content of container

*Tablets**
Blister packs containing 100 tablets* . Blister material: PVC/PE/PVDC with aluminium foil backing.

*Not all presentations are available.

6.6 Special precautions for disposal

No special requirements.

7. SPONSOR

Novartis New Zealand Limited
PO Box 99102
Newmarket
Auckland 1149

Telephone: 0800 354 335

8. MEDICINE CLASSIFICATION

Prescription Medicine

9. DATE OF FIRST APPROVAL

FILM COATED TABLETS: 10/8/2000

10. DATE OF PREPARATION

20 September 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Removal of 4,200mg statement
4.9	Gastric lavage/activated charcoal removal; addition of poison centre number

(Internal code: tri260924iNZ based on CDS dated 28 May 2024)