For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated: Please read carefully before using a new pack

Oxcarbazepine Oral Suspension USP
VINLEP™Suspension

Composition:
Each 5 ml contains:
Oxcarbazepine I.P. ……300 mg
Flavoured aqueous base ……q.s.

THERAPEUTIC INDICATIONS
Vinlep™ Suspension is indicated in adults and 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 generalized seizures)
- Generalized tonic-clonic seizures

Vinlep™ is indicated as a first-line anti-epileptic for use as monotherapy or adjunctive therapy.

Vinlep™ can replace other anti-epileptic drugs when current therapy provides insufficient seizure control.

DOSAGE & ADMINISTRATION
Dosage
Vinlep is suitable for use either as monotherapy or in combination with other antiepileptic drugs In mono- and adjunctive therapy, treatment with Vinlep 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 drug(s) are replaced by Vinlep, the dose of the concomitant antiepileptic drug(s)should be reduced gradually on initiation of Vinlep 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 Vinlep dose increased more slowly (see section INTERACTIONS).

Vinlep can be taken with or without food.

Therapeutic drug monitoring

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

Plasma level monitoring of oxcarbazepine or MHD is not routinely warranted. However, plasma level monitoring of MHD may be considered during Vinlep 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 section Dosage in renal impairment)
- pregnancy (see Section WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY)
- concomitant use of liver enzyme-inducing drugs (see section INTERACTIONS).
- If any of these situations apply, the dose of Vinlep 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
Vinlep should be initiated with a dose of 600mg/day (8-10 mg/kg/day) given in 2 divided doses.

Maintenance dose
Good therapeutic effects are seen at doses between 600mg/day and 2,400mg/day. If clinically indicated, the dose may be increased by a maximum of 600mg/day increments 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.

There is only limited experience with doses up to 4,200 mg/day.

Special populations

Pediatric Patients

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

Maintenance dose
The target maintenance dose of Vinlep 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 increments at approximately weekly intervals from the starting dose, to a maximum daily dose of 60 mg/kg/day, to achieve the desired clinical response.

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 of 4 to 12 years of age may require a 50% higher oxcarbazapine dose per body weight compared to adults.

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 compared to monotherapy or adjunctive therapy with non-enzyme-inducing antiepileptic drugs. For older children on enzyme-inducing antiepileptic drugs, only a slightly higher dose per body weight may be required than their counterparts on monotherapy.

Vinlep has not been studied in controlled clinical trials in children below 1 month of age.

Geriatric patients (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 <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. Vinlep has not been studied in patients with severe hepatic impairment, therefore, caution should be exercised when dosing such patients (see section WARNINGS AND PRECAUTIONS)

Renal impairment
In patients with impaired renal function (creatinine clearance less than 30 mL/min), Vinlep therapy should be initiated at half the usual starting dose (300 mg/day) and increased slowly to achieve the desired clinical response (see section WARNINGS AND PRECAUTIONS).

CONTRAINDICATIONS
Hypersensitivity to the oxcarbazepine or to any of the excipients.

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 Vinlep. If a patient develops these reactions after treatment with Vinlep, 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 Vinlep (see section ADVERSE DRUG REACTIONS).

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 systemic reaction (see section ADVERSE DRUG REACTIONS). In general, if signs and symptoms suggestive of hypersensitivity reactions occur, Vinlep 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 Vinlep use. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and very rarely be fatal. Vinlep 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 re-challenged with Vinlep were reported. Should a patient develop a skin reaction with Vinlep, consideration should be given to discontinuing Vinlep 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 oxcarbazepine (see below Information for healthcare professionals). The use of Vinlep 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 Vinlep 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 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 between 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 the HLA-A*3101 allele in patients, prior to initiating treatment with oxcarbazepine. Genetic screening is generally not recommended for any current Vinlep 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 appropriate clinical vigilance and patient management. Many Asian patients positive for HLA-B*1502 and treated with oxcarbazepine 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 oxcarbazepine 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 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 Vinlep. The risk of seizure aggravation is seen especially in children but may also occur in adults. In case of seizure aggravation, Vinlep should be discontinued.

Hyponatraemia

Serum sodium levels below 125 mmol/L, usually asymptomatic and not requiring adjustment of therapy have been observed in upto 2.7% of Vinlep treated patients. Experience from clinical trials show that serum sodium levels returned towards normal when the Vinlep 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 (e.g. inappropriate ADH secretion like syndrome) or in patients treated concomitantly with sodium-lowering drugs (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 Vinlep therapy when starting on sodium-lowering drugs, the same approach for sodium checks should be followed. In general, if clinical symptoms

suggestive of hyponatraemia occur on Vinlep therapy (see section ADVERSE DRUG REACTIONS), serum sodium measurement may be considered. Other patients may have serum sodium assessed as part of their routine laboratory studies.
All patients with cardiac insufficiency and secondary heart failure should have regular weight measurements to determine occurrence of fluid retention. In case of fluid retention or worsening of the cardiac condition, serum sodium should be checked. If hyponatraemia is observed, water restriction is an important counter-measure. 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 Vinlep 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 Vinlep therapy.

Hepatic function
Very rare cases of hepatitis have been reported, which in most cases resolved favorably. In case of suspected hepatitis, discontinuation of Vinlep should be considered.

Caution should be exercised when treating patients with severe hepatic impairment (see section DOSAGE & ADMINISTRATION)

Renal function

In patients with impaired renal function (creatinine clearance less than 30 mL/min), caution should be exercised during Vinlep treatment especially with regard to the starting dose and up titration of the dose (see section DOSAGE & ADMINISTRATION)

Haematological effects
Very rare reports of agranulocytosis, aplastic anemia and pancytopenia have been seen in patients treated with Vinlep during post-marketing experience (see sectionADVERSE DRUG REACTIONS). 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.

Interactions

Hormonal contraceptives
Female patients of childbearing age should be warned that the concurrent use of Vinlep with hormonal contraceptives may render this type of contraceptive ineffective (see section INTERACTIONS AND WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY). Additional non-hormonal forms of contraception are recommended when using Vinlep.

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

Withdrawal effects
As with all antiepileptic drugs, Vinlep should be withdrawn gradually to minimise the potential of increased seizure frequency.

INTERACTIONS
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 Vinlep with drugs that are metabolized CYP2C19 (e.g.

phenobarbital, phenytoin, see below). In some patients treated with Vinlep and drugs metabolized via CYP2C19 dose 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 . A decrease in plasma concentrations may also be observed for other drugs mainly metabolized by CYP3A4 and CYP3A5, for example immunosuppressant (e.g. ciclosporin)

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 Vinlep therapy, a dose reduction of 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
Potential interactions between Vinlep and other antiepileptic drugs were assessed in clinical studies. The effect of these interactions on mean AUCs and C_{min} are summarized in the following table.

Summary of antiepileptic drug interactions with Vinlep

Antiepileptic drug	**Influence of Vinlep on antiepileptic drug**	**Influence of antiepileptic drug on MHD**
Co-administered	*Concentration*	*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 Vinlep was given at doses above 1,200 mg/day. Therefore, when using doses of Vinlep greater than 1,200 mg/day during adjunctive therapy, a decrease in the dose of phenytoin may be required (see section DOSAGE AND ADMINISTRATION). The increase in the phenobarbital level, however, is small (15%) when given with Vinlep. Strong inducers of cytochrome P450 enzymes (i.e carbamazepine, phenytoin and phenobarbital) have been shown to decrease the plasma levels of MHD (29-40%). No autoinduction has been observed with Vinlep.

Hormonal contraceptives
Vinlep was shown to have an influence on the two components, ethinylestradiol (EE) and levonorgestrel (LNG), of an oral contraceptive. The mean AUC values of EE and LNG were decreased by 48-52% and 32 -52% respectively. Studies with other oral or implant contraceptives have not been conducted. Therefore, concurrent use of Vinlep with hormonal contraceptives may render these contraceptives ineffective (see sections WARNINGS AND PRECAUTIONS, and WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY).)

Calcium antagonists
After repeated co-administration of Vinlep, 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% in the plasma levels of MHD. This decrease in MHD plasma levels is not considered to be of clinical relevance.

Other drug 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 Vinlep.

WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY

PREGNANCY

Offspring of epileptic mothers are known to be more prone to developmental disorders, including malformations. Data on a limited number of pregnancies indicate that oxcarbazepine may cause serious birth defects when administered during pregnancy. The most frequent congenital malformations seen with oxcarbazepine therapy 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.
Based on data in a North American pregnancy registry, the rate of major congenital malformations, defined as a structural abnormality with surgical, medical, or cosmetic importance, diagnosed within 12 weeks of birth was 2.0% (95% CI 0.6 to 5.1%) 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 congenital abnormality in pregnant women on oxcarbazepine is (RR) 1.6, 95% CI 0.46 to 5.7.

Taking this data into consideration

- If women receiving Vinlep become pregnant or plan to become pregnant, or if the need to initiate treatment with Vinlep arises during pregnancy, the drugs potential benefits must be carefully weighed against the potential risk of foetal malformations. This is particularly important during the first three months of pregnancy.
- Minimum effective doses should be given
- In women of childbearing age, Vinlep should be administered as monotherapy, whenever possible.
- Patients should be counseled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.
- During pregnancy, an effective antiepileptic treatment should not be interrupted, since the aggravation of the illness is detrimental to both the mother and the fetus.

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 Vinlep treatment during pregnancy and determination of changes in MHD plasma concentrations should be considered to ensure that adequate seizure control is maintained throughout pregnancy (see section DOSAGE AND ADMINISTRATION). 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.

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

Women of child-bearing potential and contraceptive measures

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

(see sections WARNINGS AND PRECAUTIONS and INTERACTIONS).

Breast-feeding
Oxcarbazepine and its active metabolite (MHD) are excreted in human breast milk. A milk-to-plasma concentration ratio of 0.5 was found for both. The effects on the infant exposed to Vinlep by this route are unknown. Therefore, Vinlep should not be used during breast-feeding.

Fertility

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.

Driving and using machines

Adverse reactions such as dizziness, somnolence, ataxia, diplopia, blurred vision, visual disturbances, hyponatremia and depressed level of consciousness were reported with Vinlep (for the complete list of ADRs see section ADVERSE DRUG REACTIONS), 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.

ADVERSE DRUG REACTIONS
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.

Summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials are listed by MedDRA 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 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Blood and lymphatic system disorders
Uncommon : Leucopenia
Very rare: Bone marrow depression, aplastic anemia, agranulocytosis, pancytopenia, neutropenia, thrombocytopenia.

Immune system disorders
Very rare: Anaphylactic reactions, hypersensitivity (including multi-organ hypersensitivity) characterized 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,

Endocrine disorders
Very rare: Hypothyrodism

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

Hepato- biliary 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 Vinlep use. It generally occurred during the first 3 months of treatment with Vinlep, although there were patients who first developed a serum sodium < 125 mmol/L more than 1 year after initiation of therapy (see section 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.

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 Oxcarbazepine 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 Vinlep 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 oxcarbazepine. The mechanism by which oxcarbazepine affects bone metabolism has not been identified.

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

EXCIPIENTS
Xantural 75 (Xanthan Gum), Propylene Glycol, Sorbitol 70 PCT Solution, Nutrinova Sorbic acid Pharma Grade, Benzoic acid, DL Malic acid, Saccharine Sodium 40-80 Mesh, Simethicone Emulsion USP-30%, Yellow plum Lemon FL FT-5399, Purified Water

INCOMPATIBILITIES
Not known

STORAGE
Preserve in light resistant container.
Store at controlled room temperature.
Do not freeze

INSTRUCTIONS FOR USE AND HANDLING
Shake well before use.

Use within 7 weeks of first opening the bottle

Shelf life: See Outer Carton

Note: Vinlep should be kept out of the reach and sight of children

Manufactured by:
Sanofi Healthcare India Private Limited
At : Plot No. 3, MIDC Shiroli
Kolhapur 416122

Created: March 2022

Reference: Trioptal suspension India package insert dated 28th Aug 2017 based on the international package leaflet dated 17th July 2017 (accessed on 8th March 2022)