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 appropriate for use 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 adjuvant therapy, as the total antiepileptic medicinal product 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.

Monotherapy
Vinlep should be initiated with a dose of 600 mg/day (8-10 mg/kg/day for children) given in 2 divided doses. 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 increments at approximately weekly intervals from the starting dose to achieve the desired clinical response. In a controlled hospital setting, dose increases up to 2,400 mg/day have been achieved over 48 hours.

Adjunctive (Supportive) therapy
Vinlep should be initiated with a dose of 600 mg/day (8-10 mg/kg) given in 2 divided doses. 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 increments at weekly intervals from the starting dose to achieve the desired clinical response.
Daily doses above 2,400 mg/day have not been studied systematically in clinical trials.
Experience is limited in relation to dose administration up to 4200 mg/day.

Frequency and duration of administration:
It should not be used without consulting a doctor. Vinlep can be taken with or without food. It is used twice a day both in monotherapy and in combination with other anti-epileptic medicines. The dose may be increased depending on the clinical response of the patient. Plasma oxcarbazepine level monitoring is not necessary during Vinlep treatment.

Special populations
Pediatric Patients
In mono- and adjuvant (supportive) e therapy, Vinlep should be initiated with a dose of 8-10 mg/kg/day given in 2 divided doses.

In an adjuvant treatment study in paediatric patients (aged 3 to 17 years), with the purpose to reach a target daily dose of 46 mg/kg, the median daily dose was 31 mg/kg/with a range of 6 to 51 mg/kg/day.

In an adjuvant (supportive) treatment study in paediatric patients (aged less than 4 years), with the purpose to reach a target daily dose of 60 mg/kg, 56 % of patients reached a final dose of at least 55 mg/kg/day has been reached to in 56% of the patients. 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 dose of 60 mg/kg/day, to achieve the desired clinical response. See Section Pharmacokinetics.

Since clearance (L/hour/kg) decreases by age when normalized by body weight in monotherapy and adjuvant treatment, children aged less than 4 years may require an oxcarbazepine dose per body weight which is two folds of adult dose. And children aged 4 to 12 years may require 50% more oxcarbazepine per body weight compared to adults. (see Section Pharmacokinetics).

Compared to older children, enzyme inducing effect of antiepileptic drugs on weight adjusted normalized clearance appears to be higher for children aged less than 4 years. Compared to combined treatments and monotherapy with antiepileptic drugs without enzyme inducing effect, approximately 60% more oxcarbazepine may be required for administration per body weight at children aged less than 4 years, treated by adjuvant treatment with antiepileptic drugs having enzyme inducing effect. For older children treated with enzyme inducer antiepileptic drugs, dose increase at a lower rate may be required compared to the ones receiving monotherapy or being treated with addition of non-enzyme inducing drugs.
Controlled clinical experience on oxcarbazepine is not available in children aged less than 2 years.

Elderly patients

No difference has been observed in efficacy and safety of oxcarbazepine in patients aged 65 years or over**.**

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 severely impaired patients (see Section Pharmacokinetics).

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 gradually to achieve the desired clinical response (see section Pharmacokinetics).

ADMINISTRATION
It is for oral use.

CONTRAINDICATIONS
Hypersensitivity to the active substance, 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 reported 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 should be started.

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25-30% of these patients may also 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 treatment should be discontinued 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. If patient develops a skin reaction with Vinlep, Vinlep should be discontinued, and consideration should be given to administration of another antiepileptic treatment.

Association with HLA-B*1502
Gradually increasing evidence is present for association of different Human Leukocyte Antigen (HLA) alleles with adverse cutaneous reactions in predisposed patients. Since the chemical structure of oxcarbazepine is similar to that of carbamazepine, it is possible that patients

who are positive for HLA- B*1502 allele may also be at increased risk for SJS/TEN skin reactions during treatment with Vinlep. The prevalence of HLA-B*1502 allele is about 2% to 12% in Han Chinese populations, and about 8% in Thai populations, and above 15% in Philippines and some Malaysian populations. The prevalence of allele has been reported as about 2% in Korea and 6% in India. The prevalence of the HLA-B*1502 allele is negligible in persons of European descent, several African populations, Native Americans, Hispanic populations sampled, and in Japanese (< 1%).

Allele prevalences, mentioned here, indicate the percentage of chromosomes carrying the said allele in the population specified. That is to say that percentage of patients carrying a copy of the allele at minimum one of two chromosomes (i.e., "carrier prevalence") is about two folds of allele prevalence. Therefore, the percentage of patients at risk is almost twice the allele prevalence.

Before starting oxcarbazepine treatment in patients from populations at genetic risk due to descent, testing should be considered for detection of HLA-B* 1502 allele presence. oxcarbazepine should not be used in patients testing positive for HLA-B*1502 test if the benefits do not clearly outweigh the risks. HLA-B* 1502 may be a risk factor for SJS/TEN development in Chinese patients receiving other antiepileptic drugs (AED) associated with SJS/TEN. Therefore, in cases when alternative treatments are equally acceptable, use of other drugs associated with SJS/TEN should be avoided in HLA-B* 1502 positive patients. Since SJS/TEN risk is largely limited to first few months of the treatment irrespective of HLA-B*1502 status, screening is not generally recommended for patients with low HLA-B* 1502 prevalence or for current oxcarbazepine users.

Association with HLA-A*3101

Human Leukocyte Antigen (HLA)-A*3101 may be a risk factor for the development of adverse cutaneous 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 prevalence 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 prevalences mentioned here indicate the percentage of chromosomes in the population specified That is to say that the percentage of patients who carry a copy of the allele at minimum one of their two chromosomes (i.e., the “carrier frequency”) is about two folds of allele prevalence. Therefore, the percentage of patients who may be at risk is almost twice the allele prevalence.

Some data is suggesting that 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.

No sufficient data to support a recommendation that testing is performed to detect the presence of the HLA-A*3101 allele in patients, before initiating oxcarbazepine treatment. Since SJS/TEN, AGEP, DRESS, and maculopapular rash risk is largely limited to first few months of the treatment irrespective of HLA-A*3101 status, genetic screening is not generally recommended for current Vinlep users.

Genetic screening limitation

Genetic screening results should never be used to replace appropriate clinical vigilance and patient management. While SJS/TEN do not develop in many HLA-B* 1502 positive Asian patients treated with oxcarbazepine, SJS/TEN may develop in HLA-B* 1502 negative patients with any ethnic origin. Similarly, while SJS, TEN, DRESS, AGEP, or maculopapular rash do not develop in many HLA-A*3101 positive patients treated with oxcarbazepine, these severe cutaneous adverse reactions may develop in HLA-A*3101 negative patients with any ethnic origin. The role of other possible factors such as AED dose, adherence, concomitant drugs, comorbidities, and dermatological follow up level has not been examined in the development of these severe cutaneous adverse reactions or at morbidity due to these.

Information for healthcare professionals
If testing is required for detection of HLA-B*1502 presence, high resolution “HLA-B*1502 genotyping “ is recommended. If one or two HLA-B*1502 allele are detected, test result is positive. If no HLA-B*1502 allele is detected, test result is negative. Similarly, if testing is required for the detection of HLA-A*3101 presence, high resolution "HLA-A*3101 genotyping" is recommended. If one or two HLA-A*3101 allele are detected, test result is positive. If no HLA-A*3101 allele is detected, test result is negative.

Hyponatraemia
Serum sodium levels below 125 mmol/L, usually asymptomatic and not requiring adjustment of therapy have been observed in about 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 renal impairment associated with low sodium (e.g. diuretics, inappropriate ADH secretion like syndrome) or in patients treated concomitantly with sodium-lowering drugs (e.g., diuretics, drugs leading to non- appropriate 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 measure which may be taken. As oxcarbazepine may, very rarely, lead to impairment of cardiac conduction, patients with pre-existing conduction disturbances (e.g. AV-block, arrhythmia) should be followed carefully.

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.

Haematological effects
Very rare reports of agranulocytosis, aplastic anemia and pancytopenia have been seen in patients treated with Vinlep during post-marketing experience (see section Adverse drug reactions). Nevertheless, since the incidence of these conditions is very low and since concomitant confounding factors (for example, underlying disease, concomitant drug treatment) are present, causality relation cannot be detected. Discontinuation of the medicinal product 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.

Suicidal ideation and behavior have been reported in patients treated with this drug. Therefore patients should be monitored for signs of suicidal ideation and behaviour Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

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

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

INTERACTIONS
Enzyme inhibition
Oxcarbazepine was assessed in human liver microsomes to detect the inhibiting essential cytochrome P450 enzymes, which account for the metabolism of other drugs. . Results demonstrate that oxcarbazepine and its pharmacologically active metabolite (monohydroxy derivative,

MHD) inhibit CYP2C19. Therefore, interactions can arise when co-administering high doses of Vinlep with drugs that are metabolized CYP2C19 (e.g. phenobarbital, phenytoin,). Reduced dosing of drugs, concomitantly administered, may be required in some patients, concomitantly treated with oxcarbazepine and drugs metabolized by CYP2C19. Oxcarbazepine and MHD have either no or very low functioning capacity as inhibitors of CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP4A9, and CYP4A11 enzymes in human liver microsomes.

Enzyme induction
Oxcarbazepine and MHD may cause reduced plasma concentrations for dihydropyridine calcium antagonists, oral contraceptives, and antiepileptics such as carbamazepine by stimulating CYP3A4 and CYP3A5 in vitro and in vivo, responsible for the metabolism of these drugs. This level of reduction in plasma concentrations may also be observed in other drugs largely metabolized by CYP3A4 and CYP3A5 (for example, immunosuppressants such as ciclosporin, tacrolimus).

In vitro, oxcarbazepine and MHD are weak inducers of UDP-glucuronyl transferase. Therefore, in vivo oxcarbazepine and MHD may not possibly have an effect on medicinal products which are mainly eliminated by conjugation through the UDP-glucuronyl transferases (for example, valproic acid, lamotrigine). Although it is considered that oxcarbazepine and MHD have weak inducing potential, higher dosing for concomitantly used drugs, which are metabolized by CYP3A4 or conjugation (UDPGT), may be required. In case of discontinuation of oxcarbazepine therapy, a dose reduction of the concomitant medications may be necessary.
Induction studies performed with human hepatocytes have confirmed that oxcarbazepine and MHD are weak inducers of 2B and 3A4 CYP sub-group isoenzymes. Induction potential of oxcarbazaepine/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 below

Co-administered medicinal product	Influence of Vinlep on antiepileptic drug *Concentration*	Influence of antiepileptic drug 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

Since oxcarbazepine, used at doses above 1,200 mg/day, increase plasma levels of concomitantly administered phenytoin by about 40%, reduction of phenytoin dose may be required (See Section Dosage and method of administration). When phenobarbital is concomitantly used with oxcarbazepine, a slight increase (15%) is observed at phenobarbital level.Strong inducers of cytochrome P450 system, i.e., carbamazepine, phenytoin and phenobarbital, decrease the plasma levels of MHD by 29-40 %.
No autoinduction has been observed with oxcarbazepine.

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 were not performed with other oral or implant contraceptives. Therefore, concurrent use of Vinlep with hormonal contraceptives may render these contraceptives ineffective (see sections Warnings and Precautions, and Reproduction)

Calcium antagonists
Following concomitant administrations with oxcarbazepine repetitively, AUC levels of felodipine were reduced
by 28%. Nevertheless, plasma levels remained in therapeutic range recommended. On the other hand, verapamil caused a reduction of 20% in plasma levels of MHD. This reduction occurring in plasma levels of MHD is not considered to be clinically significant.

Other drug interactions

Cimetidine, erythromycin and dextropropoxyphene had no effect on the pharmacokinetics of MHD, viloxazine caused slight changes in plasma levels of MHD (in case of repetitive concomitant use, approximately 10% increase).
No interaction was detected between warfarin and oxcarbazepine.
The combination of lithium and oxcarbazepine might cause enhanced neurotoxicity.

REPRODUCTION
PREGNANCY
Pregnancy category is C.

Women of childbearing potential/contraception:
Vinlep interacts with oral contraceptives. Therefore, an alternative, efficient, and reliable contraception method should be administered during the treatment.

Pregnancy
Data obtained from limited number of pregnancies demonstrate that oxcarbazepine may lead to serious birth defects when administered during pregnancy. In animal studies, increased embryo mortality, delayed growth, and malformations were observed at maternally toxic dose levels.

Birth defects
Studies have not shown an increased risk of birth defects associated with oxcarbazepine use during pregnancy, however, a risk of birth defects for your unborn child cannot be excluded.

Neurodevelopment disorders
Study results related to the risk of neurodevelopmental disorders in children exposed to oxcarbazepine during pregnancy are conflicting and the risk cannot be excluded.

If women receiving Vinlep become pregnant or plan to become pregnant, or initiation of Vinlep treatment is required during pregnancy, potential fetal malformation risk should be carefully assessed against potential benefits of the medicinal product. This condition is important especially during the first three months of pregnancy

• Minimum effective doses should be given. If drug treatment is certainly required, and if a more reliable alternative is not available, the lowest dose of Vinlep for sufficient treatment should be administered.
• In fertile women, Vinlep should be administered as monotherapy,
• 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 must 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. Vitamin B12 deficiency should be prevented or treated.
Plasma levels of the active metabolite of oxcarbazepine, the 10-monohydroxy derivative (MHD), may gradually decrease throughout pregnancy due to physiological changes during pregnancy. It is recommended that clinical response should be monitored carefully in women receiving oxcarbazepine treatment during pregnancy. Changes in MHD plasma levels should be carefully observed to ensure that

adequate seizure control is maintained. In cases dosages have been increased especially during pregnancy, postpartum MHD plasma levels may also be considered for monitoring.

New born babies
Since bleeding disorders have been reported in newborn babies of mothers using antiepileptic agents, as a precaution, vitamin K1 should be administered as a preventive measure to the mother in the last few weeks of pregnancy and to the newborn after the delivery.
Oxcarbazapine and its active metabolite (MHD) are transferred across the placenta. In a case, plasma MHD concentrations were found similar in the newborn baby and the mother.

LACTATION
Vinlep 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, lactation is not recommended during Vinlep administration.

Fertility
In a fertility study performed with oral MHD administration (50, 150, or 450 mg/kg) to rats before or during mating and early gestation, the number of corpus luteum, implantation, and live embryo decreased, and estrous cycle was impaired in female rats receiving the highest dose.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS
Dizziness or somnolence, which may be associated with oxcarbazepine, may reduce the reaction ability of patients (see Section adverse drug reactions). Patients should be advised that their physical and/or mental abilities required for operating machinery or driving a car might be impaired.

ADVERSE REACTIONS
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 and were observed mostly at the initiation of the treatment. Analysis of the undesirable effect profile by body system is based on adverse events from clinical trials assessed as related to oxcarbazepine. In addition, clinically meaningful reports on adverse events from named patient programs and postmarketing experience were taken into account.
The distribution of side effects is as follows in accordance with systems and their frequencies. The following CIOMS frequency rating is used, when applicable:
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) not known (cannot be estimated from available data).

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

Immune system disorders
Very rare: 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, liver function test abnormal, hepatitis), muscles and joints (e.g. joint swelling, myalgia, arthralgia), nervous system (e.g. hepatic encephalopathy), kidneys (e.g renal failure, , tubulointerstitial nephritis, proteinuria), lungs (e.g., pulmonary oedema, asthma, bronchospasms, interstitial lung disease, dyspnea).Angioedema, anaphylactic reactions.

Metabolism and nutrition disorders
Common: Hyponatraemia
Very rare: Hyponatraemia* accompanied with signs and symptoms such as seizures, encephalopathy, impaired consciousness, confusional state, blurred vision, vomiting, nausea, folate c deficiency, hypothryroidism.

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

Nervous system disorders
Very common: Somnolence, , dizziness
Common: Ataxia, tremor, nystagmus, disturbance in attention, amnesia.

Eye disorders:
Very common: Diplopia
Common: Vision blurred, impairment.

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: Diarrhea, abdominal pain, constipation.
Very rare: Pancreatitis and/or lipase increased and/or amylase increased

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 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).

The adverse effect most commonly reported in clinical studies conducted with children aged less than four years and over 1 month, somnolence, was observed in 11% of patients. Commonly (≥ 1% - < 10%) observed adverse effects were ataxia, irritability, vomiting, lethargy, fatigue, nystagmus, tremor, decreased appetite, and increased blood uric acid.

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.

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

Skin and subcutaneous tissue disorders
Drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP).

OVERDOSE
The maximum dose taken was approximately 24.000 mg in isolated cases of overdose reported. All patients recovered with symptomatic treatment.

Signs and symptoms
Symptoms of overdose include somnolence, dizziness, nausea, vomiting, hyperkinesia, hyponatraemia, ataxia, and nystagmus. There is no specific antidote. Symptomatic and supportive treatment should be administered as appropriate

Management

The medicinal product should be removed by gastric lavage and/or inactivation by administering activated charcoal.

Pharmacology
MECHANISM OF ACTION
The pharmacological activity of oxcarbazepine is primarily exerted through the metabolite (monohydroxy derivative, MHD) (see Section Pharmacokinetics). The mechanism of action of oxcarbazepine and MHD is thought to be mainly based on blockade of voltage-sensitive sodium channels, thus resulting in stabilisation of 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 of the drug. No significant interactions with brain neurotransmitter or modulator receptor sites were found.

Pharmacodynamics
Pharmacotherapeutic group: Antiepileptics
ATC code: N03A F02

Pharmacodynamic effects
Oxcarbazepine and its active metabolite (MHD) are potent and efficacious anticonvulsants in animal models. 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.

PHARMACOKINETICS
General properties
Absorption
Following oral administration of oxcarbazepine, oxcarbazepine is completely absorbed and extensively metabolised to its pharmacologically active metabolite (MHD).

After single dose administration of 600 mg oxcarbazepine oral suspension to healthy male volunteers under fasted conditions, the mean C_{max} value of MHD was 24,9 µmol/l (median t_{max}: 6 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, oxcarbazepine 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.

Metabolism
Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to MHD, which is primarily responsible for the pharmacological effect of oxcarbazepine. MHD is 9etabolized further by conjugation with glucuronic acid. Minor amounts (4 % of the dose) are oxidized 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. Fecal 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 %). The inactive DHD accounts for approximately 3 %, and conjugates of oxcarbazepine account for 13 % of the dose excreted by urine.
Oxcarbazepine is rapidly eliminated from the plasma. Apparent half-life values range between 1.3 and 2.3 hours. On the other hand, 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 oxcarbazepine is given to patients twice a day. At steady-state, the pharmacokinetics of MHD are linear, and show dose proportionality across the dose range of 300 to 2400 mg/day.

Special populations
Gender
No gender related pharmacokinetic differences have been observed in children, adults, or the elderly.

Elderly
Following administration of single (300 mg) and multiple doses (600 mg/day) of oxcarbazepine in elderly volunteers at 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 adjustments are necessary because therapeutic doses are individually adjusted.

Pediatric
Weight-adjusted MHD clearance decreases by increased age and weight, approaching adult values. Mean weight-adjusted clearance is 93% higher than that of adults in children aged below 4 years and over 1 month. Therefore, when treated with a similar weight-adjusted dose, the MHD exposure in these children is expected to be about half that of the adults. The mean weight clearance in children 4 to 12 years of age is 43% higher 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, weight-adjusted MHD clearance is expected to reach that of adults.

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

Renal Impairment
There is a linear correlation between creatinine clearance of the drug user and the renal clearance of MHD. When oxcarbazepine is administered as a single 300 mg dose, in renally impaired patients (creatinine clearance < 30mL/min), the elimination half-life of MHD is prolonged up to 19 hours with a twofold increase in area under the curve (AUC).

Pregnancy
Plasma levels of the active metabolite of oxcarbazepine, the 10-monohydroxy derivative (MHD), may gradually decrease throughout pregnancy due to physiological changes during pregnancy. (See Section Pregnancy).

PHARMACOGENOMICS
CLINICAL EFFICACY/CLINICAL STUDIES
A total of 10 double-blind, controlled studies (two of them were adjuvant treatment, and eight of them were monotherapy) were performed with partial seizures including sub-types of partial seizures progressing to simple, complex, and secondary generalized seizures. Patients with generalized tonic-clonic seizures were also included in all comparative studies.

In two dose controlled monotherapy studies, in which patients were switched from various antiepileptic drugs such as carbamazepine, gabapentin, lamotrigine, phenytoin, and valproate to oxcarbazepine use, oxcarbazepine efficacy was confirmed. Two studies were performed in children (aged 3 to 17 years), one for adjuvant therapy compared with placebo, and other for monotherapy compared with phenytoin. At doses ranging at 600 - 2400 mg/day, efficacy was demonstrated in all primary efficacy parameters, including mean or percentage change from baseline in seizure frequency atadjuvant treatment studies, and time of meeting pre-specified exit criteria or percentage of patients fulfilling exit criteria in monotherapy studies.

In children (aged 1 month to 4 years) with insufficiently controlled partial seizures, a study was performed, comparing two doses of oxcarbazepine for adjuvant therapy, and in which one to two antiepileptic drugs were used concomitantly, and the person, reviewing the results, was blinded. The primary efficacy measure was to compare the absolute change from baseline seizure frequency in study specific seizure frequency observed in 24 hours. This comparison was statistically significant in favor of oxcarbazepine 60 mg/kg/day. In children (aged 1 month to 4 years) with insufficiently controlled or new onset of partial seizures, a study was performed, comparing two doses of oxcarbazepine for monotherapy, and the person, reviewing the results, was blinded. The primary efficacy criteria was to compare the time to meet study exit criteria, and no statistically significant difference was found between two groups. Most of the patients in both treatment groups had no video-EEG confirmed seizures throughout the study, and completed this 5-day study without study discontinuation.

It has been shown that oxcarbazepine had similar efficacy compared to other first line antiepileptic drugs (for example, valproic acid, phenytoin, and carbamazepine), and as it was assessed by rates of study discontinuation due to adverse events, and by longer duration of treatment (i.e., the rate of patients continuing the treatment), it has been demonstrated statistically that oxcarbazepine had a better tolerability profile compared to phenytoin. In these studies, the rates of patients, treated with oxcarbazepine for partial and generalized tonic-clonic seizures, were found similar for not having seizures during the treatment period over 12 months.

NONCLINICAL SAFETY DATA
Preclinical data indicated no special hazard for humans based on repeated dose toxicity, safety pharmacology and mutagenicity and carcinogenicity studies with oxcarbazepine and the pharmacologically active metabolite (MHD).

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

Single dose toxicity
None

Repeat Dose toxicity
Evidence of nephrotoxicity was noted in repeated dose toxicity rat studies, but not in dog or mice studies. As there are no reports of such changes in patients, the clinical relevance of this finding in rats remains unknown.

Genotoxicity
None

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 may be attributed to the induction of hepatic microsomal enzymes in rats and mice administered oxcarbazepine. An inductive effect which, although it cannot be excluded, is weak or absent in patients treated with oxcarbazepine. 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 levels. The mechanism for the development of these tumours has not been elucidated. Thus, the clinical relevance of these tumours is unknown.

Reproductive and Developmental Toxicity
Animal studies revealed effects such as increases in the incidence of embryo mortality and some delay in antenatal and/or postnatal growth at maternally toxic dose levels. There was an increase in rat fetal malformations in one of the eight embryo toxicity studies, which were conducted with either oxcarbazepine or the pharmacologically active metabolite (MHD), at a dose which also showed maternal toxicity (see Section Reproduction).

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:
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