

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 Tablets IP

**VINLEP®**

**Composition :**

**Vinlep 150**

Each film coated tablet contains

Oxcarbazepine IP 150 mg

**Vinlep 300**

Each film coated tablet contains

Oxcarbazepine IP 300 mg

**Vinlep 450**

Each film coated tablet contains

Oxcarbazepine IP 450 mg

**Vinlep 600**

Each film coated tablet contains:

Oxcarbazepine IP 600 mg

#### **THERAPEUTIC INDICATIONS**

Vinlep® is indicated as a first line anti-epileptic drugs for use as monotherapy and adjunctive therapy in the treatment of partial seizures (which include the seizure subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures) in adult patients with epilepsy.

Vinlep® is indicated as a first-line anti-epileptic for use as monotherapy or adjunctive therapy for the treatment of generalized tonic-clonic seizures in adults and children

As adjunctive therapy in the treatment of partial seizures in children aged 4 -16 years with epilepsy.

As monotherapy in the treatment of partial seizures in children aged 4-16 years

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 adjuvant therapy, treatment with oxcarbazepine is initiated with a clinically effective dose given in two divided doses. The dose may be increased depending on the clinical response of the patient. When other antiepileptic medicinal products are replaced by oxcarbazepine, the dose of the concomitant antiepileptic medicinal products should be reduced gradually on initiation of oxcarbazepine therapy. In adjuvant therapy, as the total antiepileptic medicinal product load of the patient is increased, the dose of concomitant antiepileptic medicinal product(s) may need to be reduced and/or oxcarbazepine 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.

##### **Adjuvant (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

#### Pediatric patients

In mono- and adjuvant (supportive) therapy, Vinlep should be initiated with a dose of 8-10 mg/kg/day given in 2 divided doses. In an adjuvant treatment study, performed in pediatric patients (aged 3 to 17 years) with the purpose to reach target daily dose of 46 mg/kg, the median daily dose has been 31 mg/kg in the range of 6 to 51 mg/kg. In an adjuvant treatment study, performed in pediatric patients (aged less than 4 years) with the purpose to reach target daily dose of 60 mg/kg, final dose of at least 55 mg/kg/day has been reached 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 Vinlep dose per body weight which is two folds of adult dose. And children aged 4 to 12 years may require 50% more Vinlep per body weight compared to adults. (see 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 Vinlep 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 Vinlep is not available in children aged less than 2 years

#### Elderly patients

No difference has been observed in efficacy and safety of Vinlep 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)

### Method of administration

It is for oral use.

The tablets are scored and can be broken in two halves in order to make it easier for the patient to swallow the tablet. For children, who cannot swallow tablets or where the required dose cannot be administered using tablets, Vinlep oral suspension form may be given

## 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 25-30 % of these patients may also experience hypersensitivity reactions with Vinlep (see Section Adverse Reaction).

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 Section Adverse Reaction). 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 persons using Vinlep. 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 rechallenged 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 Vinlep 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 Vinlep treatment in patients from populations at genetic risk due to descent, testing should be considered for detection of HLA-B\*

1502 allele presence. Vinlep 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 Vinlep users.

#### **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 has a prevalence of 2 to 5% in European populations and about 10% in the Japanese population. The prevalence of this allele is estimated to be <5% in the major portion of Australia, Asia, Africa and North America populations with some exceptions within 5 to 12%. It is estimated that the prevalence us above 15% in some ethnic groups in South America (Argentina and Brazil), North America (USA, Navajo and Sioux, and Mexico Sonora Seri) and South India (Tamil Nadu) and that is 10% to 15% in other native ethnicities in these same regions.

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.

Some data is present suggesting that HLA-A\*3101 associated with increased risk of cutaneous adverse drug reactions induced by carbamazepine including SJS, TEN, Drug rash with eosinophilia (DRESS), or less severe acute generalized exanthematous pustulosis (AGEP), or maculopapular rash.

No sufficient data is present to support the recommendation that testing is performed to detect the presence of HLA-A\*3101 in patients

before initiating Vinlep 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 Vinlep, 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 Vinlep, 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 the 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. 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 in this case. As Vinlep 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. When hepatitis is suspected, 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 period (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 also shown a slightly

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 closely monitored for suicidal ideation and behavior.

Patients and caregivers of patients should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

### Hormonal contraceptives

Female patients of childbearing age should be informed that the concurrent use of Vinlep with hormonal contraceptives may reduce the effect of this type of contraceptive (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.

### Drug discontinuation

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

## INTERACTIONS

### Enzyme inhibition

Vinlep was assessed in human liver microsomes to detect the capacity for inhibiting essential cytochrome P450 enzymes, which account for the metabolism of other drugs. Results demonstrate that Vinlep and its pharmacologically active metabolite (monohydroxy derivative, MHD) inhibit CYP2C19. Therefore, interactions can arise when co-administering high doses of Vinlep with medicinal products that are mainly metabolised by CYP2C19 (e.g. phenobarbital, phenytoin). Reduced dosing of drugs, concomitantly administered, may be required in some patients, concomitantly treated with Vinlep and drugs metabolized by CYP2C19. Vinlep 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

Vinlep 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*, Vinlep and MHD are weak inducers of UDP-glucuronyl transferases, and therefore, *in vivo* Vinlep 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 Vinlep 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 Vinlep therapy, a dose reduction of the concomitant medications may be necessary. Induction studies performed with human hepatocytes have confirmed that Vinlep and MHD are weak inducers of 2B and 3A4 CYP sub-group isoenzymes. Induction potential of Vinlep/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

<i>Co-administered medicinal products</i>	<i>Influence of Vinlep on antiepileptic with drug Concentration</i>	<i>Influence of antiepileptic drug on MHD Concentration</i>
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 Vinlep, 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 Vinlep, 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 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 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 Vinlep 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 medical product 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 Vinlep.

The combination of lithium and Vinlep might cause enhanced neurotoxicity.

## **REPRODUCTION**

### **PREGNANCY**

Pregnancy category is C.

### **Women of child-bearing 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 Vinlep 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 Vinlep use during pregnancy, however, a risk of birth defects for your unborn child cannot be excluded<sup>1</sup>.

### **Neurodevelopment disorders**

Study results related to the risk of neurodevelopmental disorders in children exposed to Vinlep 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, if possible, Vinlep should be administered as 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 must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the fetus.

### **Monitoring and prevention**

Antiepileptic medicinal products may contribute to folic acid deficiency, and this deficiency may lead to increased birth defects in offspring of epileptic women treated. Therefore, folic acid

supplementation is recommended before or during pregnancy. Vitamin B12 deficiency should be prevented or treated.

Plasma levels of the active metabolite of Vinlep, 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 Vinlep 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.

#### Newborn 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.

Vinlep 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<sup>ii</sup>. 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 Vinlep, may reduce the reaction ability of patients (see 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 DRUG 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 were generally of mild and moderate severity, and temporary, 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 Vinlep. 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 ( $\geq 1/10$ ); common ( $\geq 1/100, < 1/10$ ); uncommon ( $\geq 1/1,000, < 1/100$ ); rare ( $\geq 1/10,000, < 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (cannot be estimated from available data).

#### Blood and lymphatic system disorders

Uncommon: Leucopenia

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

#### Metabolism and nutrition disorders

Common: Hyponatraemia

Very rare: Hyponatraemia accompanied with signs and symptoms such as seizure, confusional

state, impaired consciousness, encephalopathy, blurred vision, nausea, vomiting, folate deficiency, hypothyroidism

#### **Psychiatric disorders**

Common: Confusional state, depression, apathy, agitation (e.g. nervousness), affect lability

#### **Nervous system disorders**

Very common: Somnolence, dizziness

Common: Ataxia, tremor, nystagmus, disturbance in attention, amnesia.

#### **Eye disorders:**

Very common: Diplopia

Common: Vision blurred, visual 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: Diarrhoea, 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 hyponatraemia (serum sodium <125 mmol/l) more than 1 year after initiation of therapy. (see Section Warnings/Precaution)

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 ( $\geq 1\%$  -  $< 10\%$ ) 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 Vinlep 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.

#### **Skin and subcutaneous tissue disorders**

Acute generalized exanthematous pustulosis (AGEP). Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

#### **Musculoskeletal, connective tissue and bone disorders**

There have been reports of bone 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.

#### **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  $\mu\text{mol/l}$  (median  $t_{max}$ : 6hours).

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 metabolised 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  $9.3 \pm 1.8$  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 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, 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 at adjuvant 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**

Store protected from moisture at a temperature not exceeding 30°C.

#### **INSTRUCTIONS FOR USE AND HANDLING**

No specific instructions for use.

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

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**Updated:** Mar 2023

**Reference:** Oxcarbazepine CCDS v1 dated 26<sup>th</sup>  
Jan 2023

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