APPROVED PROFESSIONAL INFORMATION FOR EIZUREX

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

EIZUREX 150 (film coated tablets)

EIZUREX 300 (film coated tablets)

EIZUREX 600 (film coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

EIZUREX 150

Each film coated tablets contains 150 mg of oxcarbazepine USP

EIZUREX 300

Each film coated tablets contains 300 mg of oxcarbazepine USP

EIZUREX 600

Each film coated tablets contains 600 mg of oxcarbazepine USP

EIZUREX is sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

EIZUREX 150

Brown coloured, oval shaped, biconvex, film coated tablets debossed with ‘V’ on one side and ‘7’ and ‘6’ on another side separated by a score line on both sides.

EIZUREX 300

Brown coloured, oval shaped, biconvex, film coated tablets debossed with 'V' on one side and '7' and '7' on another side separated by a score line on both sides.

EIZUREX 600

Brown coloured, oval shaped, biconvex, film coated tablets debossed with 'V' on one side and '7' and '8' on another side separated by a score line on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

EIZUREX is indicated for the treatment of partial seizures with or without secondary generalised seizures and generalised tonic-clonic seizures, in adults and in children aged 1 month and above.

EIZUREX may be used as monotherapy or adjunctive therapy in adults and in children of 1 month of age and above.

4.2 Posology and method of administration

Posology

EIZUREX is suitable for use either as monotherapy or in combination with other anti-epileptic medicines. In mono- and adjunctive therapy, treatment with EIZUREX 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 medicines (AEMPs) are replaced by EIZUREX, the dose of the concomitant AEMP(s) should be reduced gradually on initiation of EIZUREX therapy. In adjunctive therapy, as the total antiepileptic medicines load of the patient is increased, the dose of

concomitant AEMP(s) may need to be reduced and/or the EIZUREX dose increased more slowly (see section 4.5).

Therapeutic drug monitoring

The therapeutic effect of oxcarbazepine is primarily exerted through the active metabolite 10-monohydroxy derivative (MHD) of oxcarbazepine (see section 5). Plasma level monitoring of oxcarbazepine or MHD is not routinely warranted. However, plasma level monitoring of MHD may be considered during EIZUREX 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 4.2)
- pregnancy (see section 4.6)
- concomitant use of liver enzyme-inducing medicines (see section 4.5)

If any of these situations apply, the dose of EIZUREX may be adjusted (based on plasma levels measured 2 - 4 hours post dose) to maintain peak MHD plasma levels < 35 mg/L.

Adults:

Monotherapy and adjunctive therapy:

Initial dose

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

Maintenance dose

Good therapeutic effects are seen at doses between 600 mg/day and 2400 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.

Maximum recommended dose

In a controlled hospital setting, dose increases up to 2400 mg/day have been achieved over 48 hours. Most adult patients are controlled on dosages of 900-1200 mg/day.

Daily doses from 600 to 2400 mg/day have been shown to be effective in a controlled adjunctive therapy, although most patients were not able to tolerate the 2400 mg/day dose without reduction of concomitant anti-epileptic medicines, mainly because of CNS-related adverse events.
Daily doses above 2400 mg/day have not been studied systematically in clinical trials.

Special populations

Elderly (65 years or above):

Dosages in the elderly may need to be reduced based on decreased renal function. Close monitoring of sodium levels is required in patients at risk of hyponatremia (see section 4.4).

Patients with hepatic impairment:

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

Patients with renal impairment:

In patients with impaired renal function (creatinine clearance less than 30 mL/min) EIZUREX therapy should be initiated at half the usual starting dose (300 mg/day) and increased slowly to achieve the desired clinical response (see section 5.2).

Paediatric population

Children:

Initial dose

In mono- and adjunctive therapy, EIZUREX should be initiated with a dose of 8 - 10 mg/kg/day

given in 2 divided doses.

Maintenance dose

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

In an adjunctive therapy 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 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.

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 paediatric dosage

Under adjunctive therapy and monotherapy, when normalised by body weight, apparent clearance (L/hr/kg) decreased with age such that children 1 month to less than 4 years of age may require twice the EIZUREX dose per body weight compared to adults; and children 4 to 12 years of age may require a 50 % higher oxcarbazepine dose per body weight compared to adults (see section 5.2).

For children 1 month to less than 4 years of age, the influence of enzyme-inducing antiepileptic medicines on their weight- normalised apparent clearance appeared higher compared to older children.

Effect of concomitant enzyme-inducing antiepileptic drugs on paediatric dosage

For children 1 month to less than 4 years of age, about 60 % higher EIZUREX dose per body weight may be required for adjunctive therapy on enzyme-inducing antiepileptic medicines relative to monotherapy or adjunctive therapy with non- enzyme-inducing antiepileptic medicines. For older children on enzyme-inducing antiepileptic medicines, only a slightly higher dose per body weight may be required than their counterparts on monotherapy.

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

Method of administration

For oral use.

The dosing recommendations above apply to all patients, in the absence of impaired renal function (see section 5.2). Drug plasma level monitoring is not necessary to optimize EIZUREX therapy.

The tablets are scored and can be broken in two halves in order to make it easier for the patients to swallow the tablet. If they are unable to swallow tablets an oral suspension must be used.

EIZUREX can be taken with or without food

4.3 Contraindications

Known hypersensitivity to the active substance, oxcarbazepine, eslicarbazepine or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity

Class I (immediate) hypersensitivity reactions including rash, pruritus, urticaria, angioedema and reports of anaphylaxis have been received in the post-marketing period. Cases of anaphylaxis and angioedema involving the larynx, glottis, lips and eyelids have been reported in patients after taking the first or subsequent doses of EIZUREX. If a patient develops these reactions after treatment with EIZUREX, the medicine should be discontinued, and an alternative treatment started.

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25-30 % of these patients may experience hypersensitivity reactions (e.g. severe skin reactions) with EIZUREX (see section 4.8).

Hypersensitivity reactions, including multi-organ hypersensitivity reactions, may also occur in patients without a history of hypersensitivity to carbamazepine. Such reactions can affect the skin, liver, blood and lymphatic system or other organs, either individually or together in the context of a systemic reaction (see section 4.8). In general, if signs and symptoms suggestive of hypersensitivity reactions occur, EIZUREX should be withdrawn immediately.

Dermatological effects

Serious dermatological reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) and erythema multiforme, have been reported very rarely in association with the use of EIZUREX. Patients with serious dermatological reactions may require hospitalisation, as these conditions may be life-threatening and very rarely be fatal.

EIZUREX 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 EIZUREX were reported.

Should a patient develop a skin reaction with EIZUREX, consideration should be given to discontinuing EIZUREX and prescribing another anti-epileptic medicine.

Patients should be made aware of early toxic signs of the above-mentioned reactions, e.g., fever, rash, lesions in the mouth, bruising, purpura. They should be advised to contact their doctor immediately if such a reaction appears.

EIZUREX should not be restarted in patients who discontinued treatment due to a hypersensitivity

reaction (see section 4.3).

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 EIZUREX will not develop SJS/TEN and patients negative for HLA-B*1502 of any ethnicity can still develop SJS/TEN. The same is true for HLA-A*3101 with respect to risk of SJS, TEN, DRESS, AGEP or maculopapular rash. The development of these severe cutaneous adverse reactions and its related morbidity due to other possible factors such as AED dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

Information for healthcare professionals

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

Risk of seizure aggravation

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

Hyponatraemia

Serum sodium levels below 125 mmoL/L, usually asymptomatic and not requiring adjustment of therapy, have been observed in up to 2,7 % of EIZUREX treated patients. Experience shows that

serum sodium levels returned towards normal when the EIZUREX dosage was reduced, discontinued or the patient was treated conservatively (e.g., restricted fluid intake). In patients with pre-existing renal conditions associated with low sodium levels (e.g., inappropriate ADH secretion like syndrome) or in patients treated concomitantly with sodium- lowering medicines (e.g., diuretics, desmopressin) as well as NSAIDs (e.g., indomethacin), 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 EIZUREX therapy when starting on sodium-lowering medicines, the same approach for sodium checks should be followed. In general, if clinical symptoms suggestive of hyponatraemia occur on EIZUREX therapy (see section 4.8), serum sodium measurement may be considered. Other patients may have serum sodium levels assessed as part of their routine laboratory studies.

All patients with cardiac insufficiency and secondary heart failure should have regular weight measurements to determine occurrence of fluid retention. In case of fluid retention or worsening of the cardiac condition, serum sodium levels should be checked. If hyponatraemia is observed, water restriction is an important counter- measurement. As oxcarbazepine may, very rarely, lead to impairment of cardiac conduction, patients with pre-existing conduction disturbances (e.g. atrioventricular- block, dysrhythmia) should be followed carefully.

Bone marrow depression

If during treatment, low or decreased white blood cell or platelet counts are observed, the complete blood count and the patient should be monitored closely. EIZUREX should be discontinued if any evidence of significant bone-marrow depression appears.

Hypothyroidism

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

Hepatic function

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

Renal function

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

Haematological effects

Agranulocytosis, aplastic anaemia and pancytopenia have been seen in patients treated with EIZUREX during post-marketing experience (see section 4.8). Discontinuation of the medicines 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 medicines in several indications. A meta- analysis of randomised placebo controlled trials of antiepileptic medicines has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an

increased risk for oxcarbazepine.

Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Hormonal contraceptives

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

Alcohol

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

Withdrawal

As with all antiepileptic medicines, EIZUREX should be withdrawn gradually to minimise the potential of increased seizure frequency. If EIZUREX has to be discontinued abruptly, e.g. owing to severe adverse reactions, the change-over to another anti-epileptic preparation should be effected under cover of suitable medication (e.g. diazepam i.v., rectal; phenytoin i.v.) and under close supervision.

EIZUREX has a low enzyme-inducing potential. If, in patients on adjunctive therapy, carbamazepine or other anti-epileptics with enzyme-inducing properties are withdrawn and replaced by EIZUREX, serum concentrations of the concurrent anti-epileptic medicine should be monitored to avoid possible toxicity; it may be necessary to reduce the dosage of the anti- epileptic co-medication (see section 4.5).

Monitoring of plasma levels

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

- changes in renal function (see renal impairment in section 4.2).
- pregnancy (see sections 4.6 and 5.2).
- concomitant use of liver enzyme-inducing medicines (see section 4.5).

Elderly:

Elderly patients should be carefully monitored as they are at higher risk of adverse reactions.

4.5 Interaction with other medicines and other forms of interaction

Enzyme induction

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

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

discontinuation of EIZUREX therapy, a dose reduction of the concomitant medications may be necessary and should be decided upon by clinical and/or plasma level monitoring.

The induction is likely to gradually decrease over 2 to3 weeks after discontinuation. Hormonal contraceptives: EIZUREX was shown to have an influence on the two components, ethinylestradiol (EE) and (levonorgestrel LNG), of an oral contraceptive. The mean AUC values of EE and LNG were decreased by 48-52 % and 32-52 % respectively. Therefore, concurrent use of EIZUREX with hormonal contraceptives may render these contraceptives ineffective (see section 4.4). Another reliable contraceptive method should be used.

Enzyme inhibition

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

Antiepileptic and enzyme inducing medicines

Potential interactions between EIZUREX and other antiepileptic medicines were assessed in clinical studies. The effect of these interactions on mean AUCs and C_{min} are summarised in the following table.

Summary of antiepileptic medicinal product interactions with EIZUREX

Antiepileptic medicine (AEMP)	Influence of EIZUREX on antiepileptic medicine (AEMP)	Influence of antiepileptic medicine (AEMP) on MHD
Co-administered	Concentration	Concentration

Carbamazepine	0 - 22 % decrease (30 % increase of carbamazepine-epoxide)	40 % decrease
Clobazam	Not studied	No influence
Felbamate	Not studied	No influence
Lamotrigine	No influence	No influence
Phenobarbitone	14 - 15 % increase	30 - 31 % decrease
Phenytoin	0 - 40 % increase	29 - 35 % decrease
Valproic acid	No influence	0 – 18 % decrease

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

Hormonal contraceptives:

EIZUREX 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 EIZUREX with hormonal contraceptives

may render these contraceptives less effective (see section 4.4).

Calcium antagonists:

After repeated co-administration of EIZUREX, the AUC values of felodipine were lowered by 28 %. However, the plasma levels remained in the recommended therapeutic range. On the other hand, verapamil produced a decrease of 20 % of the plasma levels of MHD. This decrease in plasma levels of MHD is not considered to be of clinical relevance.

Other medicines 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 EIZUREX.

The interaction between oxcarbazepine and MAOIs is theoretically possible based on a structural relationship of oxcarbazepine to tricyclic antidepressants.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential and contraceptive measures

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

Pregnancy

Data on a limited number of pregnancies indicate that EIZUREX may cause serious birth defects (e.g. cleft palate) when administered during pregnancy. In animal studies, increased embryo mortality, delayed growth and malformations were observed.

Taking these data into consideration:

- If women receiving EIZUREX become pregnant, plan to become pregnant or if the need to initiate treatment with EIZUREX arises during pregnancy, the medicines' potential benefits must be carefully weighed against the potential risk of foetal malformations, (e.g., cleft palate). This is particularly important during the first three months of pregnancy.
- Minimum effective doses should be given, and monotherapy whenever possible should be preferred at least during the first three months of pregnancy in women of childbearing age.
- Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.
- During pregnancy, antiepileptic treatment must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Monitoring and prevention:

Antiepileptic medicines such as EIZUREX 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 EIZUREX treatment during pregnancy and determination of changes in MHD plasma concentrations should be considered to ensure that adequate seizure control is maintained throughout pregnancy. Determination of changes in MHD plasma concentrations should be considered. If dosages have been increased during pregnancy, postpartum MHD plasma levels may also be considered for monitoring.

In the newborn child:

Bleeding disorders in the newborn caused by antiepileptic medicines have been reported. As a precaution, vitamin K1 should be administered as a preventive measure in the last few weeks of

pregnancy and to the newborn.

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

Breastfeeding

Oxcarbazepine as contained in EIZUREX and its active metabolite (MHD) are excreted in breast milk. A milk-to-plasma concentration ratio of 0,5 was found for both. The effects on the infant exposed to EIZUREX by this route are not known. Therefore, EIZUREX is not recommended to be used during breastfeeding.

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 oestrous cyclicity and reduced numbers of corpora lutea, implantations and live embryos were observed in female animals at the highest dose of MHD.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Blood and lymphatic system disorders	Less frequent	Leucopenia, bone marrow depression, aplastic anemia, agranulocytosis, pancytopenia, neutropenia, thrombocytopenia
Immune system disorders	Less frequent	Anaphylactic reactions, hypersensitivity[#]
Endocrine disorders	Frequent	Weight increased
	Less frequent	Hypothyroidism
Metabolism and nutrition disorders	Frequent	Hyponatraemia[†]
	Less frequent	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, folic acid deficiency
Psychiatric disorders	Frequent	Agitation (e.g. nervousness), affect lability, confusional state, depression, apathy
Nervous system disorders	Frequent	Somnolence, headache, dizziness, ataxia, tremor, nystagmus, disturbance in attention, amnesia, Speech disorders (including dysarthria); more frequent during up titration of EIZUREX dose
Eye disorders	Frequent	Diplopia, vision blurred, visual

		disturbance
Ear and labyrinth disorders	Frequent	Vertigo
Cardiac disorders	Less frequent	Atrioventricular block, dysrhythmia
Vascular disorders	Less frequent	Hypertension
Gastrointestinal disorders	Frequent	Vomiting, nausea, diarrhoea, abdominal pain, constipation
	Less frequent	Pancreatitis and/or lipase and/or amylase increase
Hepato-biliary disorders	Less frequent	Hepatitis
Skin and subcutaneous tissue disorders	Frequent	Rash, alopecia, acne
	Less frequent	Urticaria, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Acute Generalised Exanthematous Pustulosis (AGEP), Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), angioedema, erythema multiforme (see section 4.4)
Musculoskeletal, connective tissue and bone disorders	Less frequent	There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with EIZUREX. The mechanism by which EIZUREX affects bone metabolism has

		not been identified, systemic lupus erythematosus
General disorders and administration site conditions	Frequent	Fatigue, asthenia
Investigations	Less frequent	Hepatic enzymes increased, blood alkaline phosphatase increased, decrease in T4 (with unclear clinical significance)
Injury, poisoning and procedural complications	Less frequent	Fall

Description of selected adverse reactions

Hypersensitivity (including multi-organ hypersensitivity) characterised by features such as rash, fever. Other organs or systems may be affected such as blood and lymphatic system (e.g. eosinophilia, thrombocytopenia, leucopenia, lymphadenopathy, splenomegaly), liver (e.g. hepatitis, abnormal liver function tests), muscles and joints (e.g. joint swelling, myalgia, arthralgia), nervous system (e.g. hepatic encephalopathy), kidneys (e.g. renal failure, nephritis interstitial, proteinuria), lungs (e.g. pulmonary oedema, asthma, bronchospasms, interstitial lung disease, dyspnoea), angioedema.

†Serum sodium levels below 125 mmol/l have been observed in up to 2,7 % of EIZUREX treated patients with frequency common (see section 4.4). In most cases, the hyponatraemia is asymptomatic and does not require adjustment of therapy. Less frequently, the hyponatraemia is associated with signs and symptoms such as seizures, encephalopathy, depressed level of consciousness, confusion, (see also nervous system disorders for further undesirable effects), vision disorders (e.g. blurred vision), hypothyroidism, vomiting, and nausea. Low serum sodium levels generally occurred during the first 3 months of treatment with EIZUREX, although there were

patients who first developed a serum sodium level <125 mmoL/more than 1 year after initiation of therapy (see section 4.4).

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 categorised 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.

Immune system disorders:

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).

Skin and subcutaneous tissue disorders:

Acute Generalised Exanthematous Pustulosis (AGEP).

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

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of EIZUREX is important. It allows continued monitoring of the benefit/risk balance of EIZUREX. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to the Holder of certificate of registration through the mail: **pvg.cdma@hererodrugs.com**

4.9 Overdose

Symptoms

Symptoms of overdose include somnolence, dizziness, nausea, vomiting, hyperkinesia, hyponatraemia, ataxia and nystagmus.

Management

There is no specific antidote. Symptomatic and supportive treatment should be administered as appropriate. Removal of the medicine by inactivation by administering activated charcoal should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC code: N03A F 02

PHARMACOLOGICAL CLASSIFICATION

A 2.5 Anticonvulsants, including anti-epileptics

Oxcarbazepine and its active, 10-monohydroxy metabolite (monohydroxy derivative), are anticonvulsants.

The pharmacological activity of oxcarbazepine is primarily exerted through the metabolite

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

5.2 Pharmacokinetic properties

Absorption

Following oral administration of EIZUREX, oxcarbazepine is completely absorbed and extensively metabolised to its pharmacologically active metabolite (10- monohydroxy, derivative). After single dose administration of 600 mg EIZUREX to healthy male volunteers under fasted conditions, the mean C_{max} value of MHD was 34 µmol/L, with a corresponding median t_{max} of 4,5 hours. In a mass balance study in man, only 2 % of total radioactivity in plasma was due to unchanged oxcarbazepine, approximately 70 % was due to MHD, and the remainder attributable to minor secondary metabolites which were rapidly eliminated.

Food has no effect on the rate and extent of absorption of oxcarbazepine, therefore, oxcarbazepine can be taken with or without food.

Distribution

The apparent volume of distribution of MHD is 49 liters. Approximately 40 % of the active metabolite, the monohydroxy derivative, 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.

Biotransformation

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

Elimination

Oxcarbazepine is cleared from the body mostly in the form of metabolites which are predominantly excreted by the kidneys. More than 95 % of the dose appears in the urine, with less than 1 % as unchanged oxcarbazepine. Faecal excretion accounts for less than 4 % of the administered dose. Approximately 80 % of the dose is excreted in the urine either as glucuronides of MHD (49 %) or as unchanged MHD (27 %), whereas the inactive DHD accounts for approximately 3 % and conjugates of oxcarbazepine account for 13 % of the dose.

Oxcarbazepine is rapidly eliminated from the plasma with apparent half-life values between 1,3 and 2,3 hours. In contrast, the apparent plasma half-life of MHD averaged 9,3 ± 1,8 h.

Upon repeated oral dosing of oxcarbazepine, the pharmacokinetics of the unchanged medicine and its active metabolite do not change, indicating absence of auto-induction and accumulation characteristics.

Linearity

Steady-state plasma concentrations of MHD are reached within 2 - 3 days in patients when oxcarbazepine is given twice a day. At steady-state, the pharmacokinetics of MHD is linear and show dose proportionality across the dose range of 300 to 2400 mg/day.

Special populations

Patients with hepatic impairment

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

Patients with renal impairment

There is a linear correlation between creatinine clearance and the renal clearance of MHD. When EIZUREX is administered as a single 300 mg dose, in renally impaired patients (creatinine clearance < 30 mL/min) the elimination half-life of MHD is prolonged by 60-90 % (16 to 19 hours) with a two-fold increase in AUC compared to adults with normal renal function (10 hours).

Pregnancy

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

Elderly

Following administration of single (300 mg) and multiple doses (600 mg/day) of EIZUREX in elderly volunteers (60 – 82 years of age), the maximum plasma concentrations and AUC values of MHD were 30 % - 60 % higher than in younger volunteers (18 - 32 years of age). Comparisons of creatinine clearances in young and elderly volunteers indicate that the difference was due to age-related reductions in creatinine clearance. No special dose recommendations are necessary because therapeutic doses are individually adjusted.

Gender

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

Paediatric population

Children

Weight-adjusted MHD clearance decreases as age and weight increases approaching that of adults. The mean weight-adjusted clearance in children 1 month to less than 4 years of age is 93 % higher than that of adults. Therefore, MHD exposure in these children is expected to be about one-half that of adults when treated with a similar weight-adjusted dose. The mean weight-adjusted clearance in children 4 to 12 years of age is approximately 43 % higher than that of adults. Therefore, MHD exposure in these children is expected to be about two-thirds that of adults when treated with a similar weight-adjusted dose. As weight increases, for patients 13 years of age and above, the weight-adjusted MHD clearance is expected to reach that of adults.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Oxcarbazepine
- Microcrystalline cellulose
- Hypromellose
- Colloidal silicon dioxide
- Crospovidone
- Magnesium Stearate,

Composition of Opadry II Brown 85F565266

- Polyvinyl alcohol-part hydrolyzed E1203
- Macrogol/PEG E1521
- Talc E553b
- Titanium dioxide E171
- Iron oxide yellow E172
- Iron oxide red E172
- Ferrosoferric oxide NF/ Black iron oxide E172

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C

Protect from moisture.

Keep the tablets in the original container until required for

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

EIZUREX 150

100's count

High Density Polyethylene Container 60 cc with 33 mm Neck (Heavy weight) with child resistant plastic caps with pulp liners 33 mm

10's count

Clear (250 µ PVC/25 µ PE/90 GSM PVdC) width 172 mm (ACG) ,with plain aluminium foil 0,025 x 168 mm -7GSM HSL coat

EIZUREX 300

100's count

High Density Polyethylene Container 100 cc with 38 mm Neck (Heavy weight) with child resistant plastic caps with pulp liners 38 mm

14's count

Clear film width 251 mm (250 µ PVC/25 µ PE/90 GSM PVdC), with 25µ plain aluminium foil (Hard Tempered) with 7GSM HSL coating on bright side width 245 mm

EIZUREX 600

100's count

High Density Polyethylene Container 150 cc with 38 mm Neck (Heavy weight) with child resistant plastic caps with pulp liners 38 mm

10's count

Clear triplex film width 222 mm (250 µ PVC/25 µ PE/90 GSM PVdC), with plain aluminium foil 0,025 x 216 mm -7GSM HSL coat

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Hetero Drugs South Africa (Pty) Ltd

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8 REGISTRATION NUMBER(S)

EIZUREX 150: 57/2.5/0209

EIZUREX 300: 57/2.5/0210

EIZUREX 600: 57/2.5/0211

9 DATE OF FIRST AUTHORISATION

25 March 2025

10 DATE OF REVISION OF THE TEXT