Specialist Initiated Drugs

Prescribing Information Sheet September 2014

Eslicarbazepine (Zebinix®) - Adjunctive treatment of partial-onset seizures

Formulary Status

Eslicarbazepine acetate for the adjunctive treatment of partial-onset seizures should be initiated by a specialist who will prescribe the initial supply.

The specialist will titrate the dose until the patient is stable. This usually takes 1 -2 months but will vary per patient.

On-going prescribing can be continued by a GP.

The responsibility for increasing/decreasing the dose or stopping treatment due to lack of effect or side effects remains with the specialist. They should be consulted if a change in treatment is required.

Full prescribing guidance – Summary of Product Characteristics www.emc.medicines.org.uk

Indication and Dosage

Indication- Eslicarbazepine is indicated for the adjunctive treatment of partial-onset seizures with or without secondary generalised seizures in adult patients.

Presentation- Scored tablets 800mg. The tablet can be divided into equal doses.

Dosage and Administration – Eslicarbazepine is taken once daily with or without food,

The recommended starting dose is 400 mg once daily which should be increased to 800 mg once daily after one or two weeks. Based on individual response, the dose may be increased to 1,200 mg once daily

Elderly (over 65 years of age) Caution should be exercised in the treatment of elderly patients as there is limited safety information on the use of eslicarbazepine acetate in these patients

Renal impairment - Caution should be exercised in the treatment of patients with renal impairment and the dose should be adjusted according to creatinine clearance (CL_{CR}) as follows:
- CL_{CR} >60 ml/min: no dose adjustment required.

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- CL_{CR} 30-60 ml/min: initial dose of 200 mg once daily or 400 mg every other day for 2 weeks followed by a once daily dose of 400 mg. However, based on individual response, the dose may be increased.
- CL_{CR} <30 ml/min: use is not recommended in patients with severe renal impairment due to insufficient data.

Hepatic impairment - No dose adjustment is needed in patients with mild to moderate hepatic impairment. Use in patients with severe hepatic impairment is not recommended.

Monitoring
No routine monitoring is required. Serum sodium levels may need to be assessed if clinically indicated (*see below for more details*).
Hyponatraemia has been reported as an adverse reaction in less than 1% of patients treated with eslicarbazepine. Hyponatraemia is asymptomatic in most cases; however, it may be accompanied by clinical symptoms such as worsening of seizures, confusion and/or decreased consciousness. The incidence of hyponatraemia appears to increase with increasing eslicarbazepine dose. In patients with pre-existing renal disease leading to hyponatraemia, or in patients concomitantly treated with medicinal products which may themselves lead to hyponatraemia (e.g. diuretics, desmopressin), serum sodium levels should be examined before and, where clinically indicated, during treatment with eslicarbazepine.
Serum sodium levels should be determined if clinical signs of hyponatraemia occur.
If clinically relevant hyponatraemia develops consideration should be given to discontinuation of eslicarbazepine.

End of treatment
As with other anti-epileptic medicinal products, if eslicarbazepine is to be discontinued it is recommended to withdraw it gradually to minimise the potential of increased seizure frequency.

Adverse effects, special warnings and precautions for use (consult SPC for full list)

Contraindicated in second or third degree atrioventricular (AV) block

Prolongations in PR interval have been observed in clinical studies with eslicarbazepine acetate. Caution should be exercised in patients with medical conditions (e.g. low levels of thyroxine, cardiac conduction abnormalities), or when taking concomitant medicinal products known to be associated with PR prolongation.

Suicidal ideation
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic active substances in several indications. A meta-analysis of randomized placebo-controlled trials of anti-epileptic medicinal products 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 eslicarbazepine acetate. 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

Nervous system and gastrointestinal disorders
Eslicarbazepine has a similar adverse effect profile to oxcarbazepine. The most common adverse effects are dizziness, somnolence, headache, diplopia, nausea and abnormal coordination. These adverse effects occur mainly during the first six weeks of treatment. These are more frequent in patients treated concurrently with carbamazepine than those who are not (dizziness 30% vs. 11.5%, diplopia 11.4% vs. 2.4%, abnormal coordination 6.7% vs. 2.7%).

Skin reactions

Rash occurred in 1.1% of patients in clinical trials. There were no reports of severe skin reactions such as Stevens-Johnson syndrome (SJS), but there have been reports with oxcarbazepine. The SPC for eslicarbazepine states that people of Han Chinese and Thai origin should be screened for allele HLAB* 1502 before starting treatment as this is a risk factor for SJS. If this is indicated then assessment and/or testing will be carried out by the initiating Consultant.

Drug Interactions (consult SPC for full list)

Interactions listed in BNF 67 (March 2014) are with medications that antagonise the effects of anti-epileptics such as antidepressants, antimalarials, antipsychotics and orlistat.

Eslicarbazepine is a weak inducer of CYP3A4 and an inhibitor of CYP2C19 hepatic enzymes. Dose adjustments may be needed if eslicarbazepine is given concurrently with medicines metabolised by these enzymes. When initiating or discontinuing treatment with eslicarbazepine or changing the dose, it may take 2 to 3 weeks to reach the new level of enzyme activity. This time delay must be taken into account when eslicarbazepine is being used just prior to or in combination with other medicines that require dose adjustment when co-administered with eslicarbazepine.

Interactions with other antiepileptic medicinal products

Carbamazepine - based on individual response the dose of eslicarbazepine may need to be increased. The risk of an increase of adverse reactions caused by co-administration of carbamazepine and eslicarbazepine cannot be excluded

Phenytoin - based on individual response, the dose of eslicarbazepine may need to be increased and the dose of phenytoin may need to be decreased.

Lamotrigine - in some patients a clinically relevant reduction in lamotrigine exposure may necessitate a lamotrigine dose increase.

Topiramate - a reduction in topiramate exposure may occur. The manufacturers advise no dose adjustment is required

Valproate and levetiracetam - no clinically significant interactions expected to occur.

Oral contraceptives

Eslicarbazepine may decrease the effectiveness of hormonal contraceptives. Additional non-hormonal forms of contraception are recommended.

Simvastatin

A study in healthy subjects showed an average decrease of 50% in systemic exposure to simvastatin, most likely caused by an induction of CYP3A4.

Rosuvastatin

There was an average decrease of 36-39% in systemic exposure in healthy subjects when co-administered with eslicarbazepine.

Warfarin

Co-administration of eslicarbazepine with warfarin showed a small (23%) but statistically significant decrease in exposure to S-warfarin. There was no effect on the R-warfarin pharmacokinetics or on coagulation. However, due to inter-individual variability in the interaction, special attention on monitoring of INR should be performed in the first weeks after initiation or ending concomitant treatment.

Monoamine Oxidase Inhibitors (MAOIs)
Based on structural relationships, an interaction between eslicarbazepine acetate and MAOIs is theoretically possible.

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References

Summary of Product Characteristics Zebinix®, Eisai Ltd. Last updated 28 May 2014 www.emc.medicines.org.uk

National Institute of Clinical Excellence Clinical Guideline (CG137) Epilepsy. January 2012. Accessed via http://www.nice.org.uk