ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zebinix 200 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of eslicarbazepine acetate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White oblong tablets, engraved 'ESL 200' on one side and scored on the other side, with a length of 11 mm. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zebinix is indicated as adjunctive therapy in adults, adolescents and children aged above 6 years, with partial-onset seizures with or without secondary generalisation.

4.2 Posology and method of administration

Posology

Adults
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 (see section 5.1).

Special populations

Elderly (over 65 years of age)
No dose adjustment is needed in the elderly population provided that the renal function is not disturbed.

Renal impairment
Caution should be exercised in the treatment of patients, adult and children above 6 years of age, 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.
- CL_{CR} 30-60 ml/min: initial dose of 200 mg (or 5 mg/kg in children above 6 years) once daily or 400 mg (or 10 mg/kg in children above 6 years) every other day for 2 weeks followed by a once daily dose of 400 mg (or 10 mg/kg in children above 6 years). 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.
The pharmacokinetics of eslicarbazepine acetate has not been evaluated in patients with severe hepatic impairment (see sections 4.4 and 5.2) and use in these patients is, therefore, not recommended.

Paediatric population
Children above 6 years of age
The recommended starting dose is 10 mg/kg/day once daily. Dosage should be increased in weekly or bi-weekly increments of 10 mg/kg/day up to 30 mg/kg/day, based on individual response. The maximum dose is 1,200 mg once daily (see section 5.1).

Children with a body weight of ≥60 kg
Children with a body weight of 60 kg or more should be given the same dose as for adults.
The safety and efficacy of eslicarbazepine acetate in children aged 6 years and below has not yet been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Oral use.
Zebinix may be taken with or without food.

Switching preparations
Since comparative bioavailability data for the tablet and the suspension formulation are not available, switching patients from one formulation to the other should be done with caution.

4.3 Contraindications

Hypersensitivity to the active substance, to other carboxamide derivatives (e.g. carbamazepine, oxcarbazepine) or to any of the excipients listed in section 6.1.

Second or third degree atrioventricular (AV) block.

4.4 Special warnings and precautions for use

Suicidal ideation

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic active substances in several indications. A meta-analysis of randomised placebo-controlled trials of antiepileptic 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 disorders

Eslicarbazepine acetate has been associated with some central nervous system adverse reactions, such as dizziness and somnolence, which could increase the occurrence of accidental injury.

Other warnings and precautions

If Zebinix is to be discontinued it is recommended to withdraw it gradually to minimise the potential of increased seizure frequency.
There is no experience regarding the withdrawal of concomitant use of antiepileptic medicinal products during treatment with Zebinix (i.e. switching to monotherapy).

Cutaneous reactions

Rash developed as an adverse reaction in 1.1% of total population treated with Zebinix in placebo-controlled add-on studies in epileptic patients. If signs or symptoms of hypersensitivity develop, eslicarbazepine acetate must be discontinued.

HLA-B* 1502 allele - in Han Chinese, Thai and other Asian populations

HLA-B* 1502 in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing the severe cutaneous reactions known as Stevens Johnson syndrome (SJS) when treated with carbamazepine. The chemical structure of eslicarbazepine acetate is similar to that of carbamazepine, and it is possible that patients who are positive for HLA-B*1502 may also be at risk for SJS after treatment with eslicarbazepine acetate. The prevalence of HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations. Whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine or chemically-related active substances. If patients of these ethnic origins are tested positive for HLA- B*1502 allele, the use of eslicarbazepine acetate may be considered if the benefits are thought to exceed risks.
Because of the prevalence of this allele in other Asian populations (e.g, above 15% in the Philippines and Malaysia), testing genetically at risk populations for the presence of HLA- B*1502 may be considered.

HLA-A*3101 allele- European descent and Japanese populations

There are some data that suggest HLA-A*3101 is associated with an increased risk of carbamazepine induced cutaneous adverse drug reactions including SJS, TEN, Drug rash with eosinophilia (DRESS), or less severe acute generalized exanthematous pustulosis (AGEP) and maculopapular rash in people of European descent and the Japanese.
The frequency of the HLA-A*3101 allele varies widely between ethnic populations. HLA-A*3101 allele has a prevalence of 2 to 5% in European populations and about 10% in Japanese population. The presence of HLA-A*3101 allele may increase the risk for carbamazepine induced cutaneous reactions (mostly less severe) from 5.0% in general population to 26.0% among subjects of European ancestry, whereas its absence may reduce the risk from 5.0% to 3.8%.
There are insufficient data supporting a recommendation for HLA-A*3101 screening before starting carbamazepine or chemically-related compounds treatment.
If patients of European descent or Japanese origin are known to be positive for HLA-A*3101 allele, the use of carbamazepine or chemically-related compounds may be considered if the benefits are thought to exceed risks.

Hyponatraemia

Hyponatraemia has been reported as an adverse reaction in 1.2% of patients treated with Zebinix. Hyponatraemia is asymptomatic in most cases, however, it may be accompanied by clinical symptoms like worsening of seizures, confusion, decreased consciousness. Frequency of hyponatraemia increased with increasing eslicarbazepine acetate 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, carbamazepine), serum sodium levels should be examined before and during treatment with eslicarbazepine acetate. Furthermore, serum sodium levels should be determined if clinical signs of hyponatraemia occur. Apart from this, sodium levels should be determined during routine laboratory examination. If clinically-relevant hyponatraemia develops, eslicarbazepine acetate should be discontinued.

PR interval

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.

Renal impairment

Caution should be exercised in the treatment of patients with renal impairment and the dose should be adjusted according to creatinine clearance (see section 4.2). In patients with CLCR <30 ml/min use is not recommended due to insufficient data.

Hepatic impairment

As clinical data are limited in patients with mild to moderate hepatic impairment and pharmacokinetic and clinical data are missing in patients with severe hepatic impairment, eslicarbazepine acetate should be used with caution in patients with mild to moderate hepatic impairment and is not recommended in patients with severe hepatic impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Eslicarbazepine acetate is extensively converted to eslicarbazepine, which is mainly eliminated by glucuronidation. *In vitro* eslicarbazepine is a weak inducer of CYP3A4 and UDP-glucuronyl transferases. *In vivo* eslicarbazepine showed an inducing effect on the metabolism of medicinal products that are mainly eliminated by metabolism through CYP3A4 (e.g. Simvastatin). Thus, an increase in the dose of the medicinal products that are mainly metabolised through CYP3A4 may be required, when used concomitantly with eslicarbazepine acetate. Eslicarbazepine *in vivo* may have an inducing effect on the metabolism of medicinal products that are mainly eliminated by conjugation through the UDP-glucuronyl transferases. When initiating or discontinuing treatment with Zebinix 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 Zebinix is being used just prior to or in combination with other medicinal products that require dose adjustment when co-administered with Zebinix. Eslicarbazepine has inhibiting properties with respect to CYP2C19. Thus, interactions can arise when co-administering high doses of eslicarbazepine acetate with medicinal products that are mainly metabolised by CYP2C19 (e.g. Phenytoin).

Interactions with other antiepileptic medicinal products

Carbamazepine
In a study in healthy subjects, concomitant administration of eslicarbazepine acetate 800 mg once daily and carbamazepine 400 mg twice daily resulted in an average decrease of 32% in exposure to the active metabolite eslicarbazepine, most likely caused by an induction of glucuronidation. No change in exposure to carbamazepine or its metabolite carbamazepine-epoxide was noted. Based on individual response, the dose of eslicarbazepine acetate may need to be increased if used concomitantly with carbamazepine. Results from patient studies showed that concomitant treatment increased the risk of the following adverse reactions: diplopia, abnormal coordination and dizziness. The risk of increase of other specific adverse reactions caused by co-administration of carbamazepine and eslicarbazepine acetate cannot be excluded.

Phenytoin
In a study in healthy subjects, concomitant administration of eslicarbazepine acetate 1,200 mg once daily and phenytoin resulted in an average decrease of 31-33% in exposure to the active metabolite, eslicarbazepine, most likely caused by an induction of glucuronidation, and an average increase of 31-35% in exposure to phenytoin, most likely caused by an inhibition of CYP2C19. Based on individual response, the dose of eslicarbazepine acetate may need to be increased and the dose of phenytoin may need to be decreased.

Lamotrigine
Glucuronidation is the major metabolic pathway for both eslicarbazepine and lamotrigine and, therefore, an interaction could be expected. A study in healthy subjects with eslicarbazepine acetate

1,200 mg once daily showed a minor average pharmacokinetic interaction (exposure of lamotrigine decreased 15%) between eslicarbazepine acetate and lamotrigine and consequently no dose adjustments are required. However, due to inter-individual variability, the effect may be clinically relevant in some individuals.

Topiramate
In a study in healthy subjects, concomitant administration of eslicarbazepine acetate 1,200 mg once daily and topiramate showed no significant change in exposure to eslicarbazepine but an 18% decrease in exposure to topiramate, most likely caused by a reduced bioavailability of topiramate. No dose adjustment is required.

Valproate and levetiracetam
A population pharmacokinetics analysis of phase III studies in epileptic adult patients indicated that concomitant administration with valproate or levetiracetam did not affect the exposure to eslicarbazepine but this has not been verified by conventional interaction studies.

Oxcarbazepine
Concomitant use of eslicarbazepine acetate with oxcarbazepine is not recommended because this may cause overexposure to the active metabolites.

Other medicinal products

Oral contraceptives
Administration of eslicarbazepine acetate 1,200 mg once daily to female subjects using a combined oral contraceptive showed an average decrease of 37% and 42% in systemic exposure to levonorgestrel and ethinylestradiol, respectively, most likely caused by an induction of CYP3A4. Therefore, women of childbearing potential must use adequate contraception during treatment with Zebinix, and up to the end of the current menstruation cycle after the treatment has been discontinued (see section4.6).

Simvastatin
A study in healthy subjects showed an average decrease of 50% in systemic exposure to simvastatin when co-administered with eslicarbazepine acetate 800 mg once daily, most likely caused by an induction of CYP3A4. An increase of the simvastatin dose may be required when used concomitantly with eslicarbazepine acetate.

Rosuvastatin
There was an average decrease of 36-39% in systemic exposure in healthy subjects when co-administered with eslicarbazepine acetate 1,200 mg once daily. The mechanism for this reduction is unknown, but could be due to interference of transporter activity for rosuvastatin alone or in combination with induction of its metabolism. Since the relationship between exposure and drug activity is unclear, the monitoring of response to therapy (e.g., cholesterol levels) is recommended.

Warfarin
Co-administration of eslicarbazepine acetate 1,200 mg once daily 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 the first weeks after initiation or ending concomitant treatment of warfarin and eslicarbazepine acetate.

Digoxin
A study in healthy subjects showed no effect of eslicarbazepine acetate 1,200 mg once daily on digoxin pharmacokinetics, suggesting that eslicarbazepine acetate has no effect on the transporter P-glycoprotein.

Monoamino Oxidase Inhibitors (MAOIs)

Based on a structural relationship of eslicarbazepine acetate to tricyclic antidepressants, an interaction between eslicarbazepine acetate and MAOIs is theoretically possible.

4.6 Fertility, pregnancy and lactation

Risk related to epilepsy and antiepileptic medicinal products in general

It has been shown that in the offspring of women with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic medicinal product therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practised whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of child-bearing potential. The need for antiepileptic therapy should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both mother and child.

Women of childbearing potential/contraception

Eslicarbazepine acetate adversely interacts with oral contraceptives. Therefore, an alternative, effective and safe method of contraception should be used during treatment and up to the end of the current menstrual cycle after treatment has been stopped.

Pregnancy

There are no data from the use of eslicarbazepine acetate in pregnant women. Studies in animals have shown reproductive toxicity (see Fertility). If women receiving eslicarbazepine acetate become pregnant or plan to become pregnant, the use of Zebinix should be carefully re-evaluated. Minimum effective doses should be given, and monotherapy whenever possible should be preferred at least during the first three months of pregnancy. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity to antenatal screening.

Monitoring and prevention
Antiepileptic medicinal products may contribute to folic acid deficiency, a possible contributory cause of foetal abnormality. Folic acid supplementation is recommended before and during pregnancy. As the efficacy of this supplementation is not proven, a specific antenatal diagnosis can be offered even for women with a supplementary treatment of folic acid.

In the newborn child
Bleeding disorders in the newborn caused by antiepileptic medicinal products 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.

Breast-feeding

It is unknown whether eslicarbazepine acetate is excreted in human milk. Animal studies have shown excretion of eslicarbazepine in breast milk. As a risk to the breast-fed child cannot be excluded breast-feeding should be discontinued during treatment with eslicarbazepine acetate.

Fertility

There are no data on the effects of eslicarbazepine acetate on human fertility. Studies in animals have shown impairment of fertility after treatment with eslicarbazepine acetate (see section 5.3).

4.7 Effects on ability to drive and use machines

Zebinix has minor to moderate influence on the ability to drive and use machines. Some patients might experience dizziness, somnolence or visual disorders, particularly on initiation of treatment. Therefore, patients should be advised that their physical and/or mental abilities needed for operating machinery or driving may be impaired and they are recommended not to do so until it has been established that their ability to perform such activities is not affected.

4.8 Undesirable effects

Summary of the safety profile

In placebo-controlled studies involving 1,842 adult and 427 paediatric patients with partial-onset seizures (1,520 patients treated with eslicarbazepine acetate and 749 treated with placebo), 48.9% of patients treated with eslicarbazepine acetate and 26% of patients treated with placebo experienced adverse reactions.

Adverse reactions were usually mild to moderate in intensity and occurred predominantly during the first weeks of treatment with eslicarbazepine acetate.

The risks that have been identified for Zebinix are mainly class-based, dose-dependent undesirable effects. The most common adverse reactions reported in clinical studies with adult epileptic patients, both in placebo and eslicarbazepine acetate groups were dizziness, somnolence, headache, and nausea. The majority of adverse reactions were reported in <3% of subjects in any treatment group.

Tabulated list of adverse reactions

The following convention has been used for the classification of adverse reactions very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and not known (frequency cannot be estimated from available data). Within each frequency category, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions associated with Zebinix obtained from adjunctive therapy in clinical studies and post-marketing surveillance

System Organ Class	**Very common**	**Common**	**Uncommon**		**Not known**
Blood and lymphatic system disorders			Anaemia		Thrombocytopenia, leukopenia
Immune system disorders			Hypersensitivity		
Endocrine disorders			Hypothyroidism		
Metabolism and nutrition disorders		Hyponatraemia, decreased appetite	Electrolyte imbalance, dehydration, hypochloraemia		

Psychiatric disorders		Insomnia	Psychotic disorder, apathy, depression, nervousness, agitation, irritability, attention deficit/ hyperactivity disorder, confusional state, mood swings, crying, psychomotor retardation		
Nervous system disorders	Dizziness, somnolence	Headache, disturbance in attention, tremor, ataxia, balance disorder	Coordination abnormal, memory impairment, amnesia, hypersomnia, sedation, aphasia, dysaesthesia, dystonia, lethargy, parosmia, cerebellar syndrome, convulsion, peripheral neuropathy, nystagmus, speech disorder, dysarthria, burning sensation, paraesthesia, migraine		
Eye disorders		Diplopia, vision blurred	Visual impairment, oscillopsia, binocular eye movement disorder, ocular hyperaemia		
Ear and labyrinth disorders		Vertigo	Hypoacusis, tinnitus		
Cardiac disorders			Palpitations, bradycardia		

Vascular disorders			Hypertension (including hypertensive crisis), hypotension, orthostatic hypotension, flushing, peripheral coldness		
Respiratory, thoracic and mediastinal disorders			Epistaxis, chest pain		
Gastrointestinal disorders		Nausea, vomiting, diarrhoea	Constipation, dyspepsia, gastritis, abdominal pain, dry mouth, abdominal discomfort, abdominal distension, gingivitis, melaena, toothache		Pancreatitis
Hepatobiliary disorders			Liver disorder		
Skin and subcutaneous tissue disorders		Rash	Alopecia, dry skin, hyperhidrosis, erythema, skin disorder, pruritus, dermatitis allergic		Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders			Myalgia, bone metabolism disorder, muscular weakness, pain in extremity		
Renal and urinary disorders			Urinary tract infection		
General disorders and administration site conditions		Fatigue, gait disturbance, asthenia	Malaise, chills, oedema peripheral		

Investigations			Blood pressure decreased, weight decreased, blood pressure increased, blood sodium decreased, blood chloride decreased, osteocalcin increased, haematocrit decreased, haemoglobin decreased, transaminases increased		
Injury, poisoning and procedural complications			Drug toxicity, fall, thermal burn		

Description of selected adverse reactions

Eye and nervous system disorders
In patients concomitantly treated with carbamazepine and eslicarbazepine acetate in placebo-controlled studies, the following adverse reactions were observed: diplopia (11.4% of subjects with concomitant carbamazepine, 2.4% of subjects without concomitant carbamazepine), abnormal coordination (6.7% with concomitant carbamazepine, 2.7% without concomitant carbamazepine), and dizziness (30.0% with concomitant carbamazepine, 11.5% without concomitant carbamazepine), see section 4.5.

PR interval
The use of eslicarbazepine acetate is associated with increase in the PR interval. Adverse reactions associated with PR interval prolongation (e.g. AV block, syncope, bradycardia) may occur.

Class related adverse reactions
Rare adverse reactions such as bone marrow depression, anaphylactic reactions, severe cutaneous reactions (e.g. Stevens-Johnson Syndrome), systemic lupus erythematosus or serious cardiac arrhythmias did not occur during the placebo-controlled studies of the epilepsy program with eslicarbazepine acetate. However, they have been reported with oxcarbazepine. Therefore, their occurrence after treatment with eslicarbazepine acetate cannot be excluded.

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with the structurally related antiepileptic drugs carbamazepine and oxcarbazepine. The mechanism by which bone metabolism is affected has not been identified.

Paediatric population

In placebo-controlled studies involving patients aged from 2 to 18 years with partial-onset seizures (238 patients treated with eslicarbazepine acetate and 189 with placebo), 35.7% of patients treated with eslicarbazepine acetate and 19% of patients treated with placebo experienced adverse reactions. The most common adverse reaction in the group treated with eslicarbazepine acetate were diplopia (5.0%), somnolence (8.0%) and vomiting (4.6%).

The adverse reaction profile of eslicarbazepine acetate is generally similar across age goups. In the age group from 6 to 11 years of age, the most common adverse reactions observed in more than two patients treated with eslicarbazepine acetate were diplopia (9.5%), somnolence (7.4%), diziness (6.3%), convulsion (6.3%) and nausea (3.2%); in the age group from 12 to 18 years were somnolence (7.4%), vomiting (4.2%), diplopia (3.2%) and fatigue (3.2%). The safety of Zebinix in children aged 6 years and below has not yet been established.

The safety profile of eslicarbazepine acetate was generally similar between adult and paediatric patients, except for agitation (common, 1.3%) and abdominal pain (common, 2.1%) which were more common in children than in adults. Dizziness; somnolence; vertigo; asthenia; gait disturbance; tremor; ataxia; balance disorder; vision blurred; diarrhoea and rash were less common in children than in adults. Hyponatraemia was only reported in adult population. Dermatitis allergic (uncommon, 0.8%) was reported only in the paediatric population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Central nervous symptoms such as vertigo, walking instability and hemi-paresis have been observed with accidental eslicarbazepine acetate overdose. There is no known specific antidote. Symptomatic and supportive treatment should be administered as appropriate. Eslicarbazepine acetate metabolites can effectively be cleared by haemodialysis, if necessary (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, carboxamide derivatives, ATC code: N03AF04

Mechanism of action

The precise mechanisms of action of eslicarbazepine acetate are unknown. However, *in vitro* electrophysiological studies indicate that both eslicarbazepine acetate and its metabolites stabilise the inactivated state of voltage-gated sodium channels, preventing their return to the activated state and thereby sustaining repetitive neuronal firing.

Pharmacodynamic effect

Eslicarbazepine acetate and its active metabolites prevented the development of seizures in nonclinical models predictive of anticonvulsant efficacy in man. In humans, the pharmacological activity of eslicarbazepine acetate is primarily exerted through the active metabolite eslicarbazepine.

Clinical efficacy and safety

Adult population
The efficacy and safety of eslicarbazepine acetate has been demonstrated in four phase III double-blind placebo-controlled studies in 1,703 randomized adult patients with partial epilepsy refractory to treatment with one to three concomitant antiepileptic medicinal products. Oxcarbazepine and felbamate were not allowed as concomitant medicinal products in these studies. Eslicarbazepine acetate was tested at doses of 400 mg (in -301 and -302 studies only), 800 mg and 1,200 mg, once

daily. Eslicarbazepine acetate 800 mg once daily and 1,200 mg once daily were significantly more effective than placebo in reducing seizure frequency over a 12-week maintenance period. The percentage of subjects with ≥50% reduction (1581 analyzed) in seizure frequency in the phase III studies was 19.3% for placebo, 20.8% for eslicarbazepine acetate 400 mg, 30.5% for eslicarbazepine acetate 800 mg and 35.3% for eslicarbazepine acetate 1,200 mg daily.

Elderly population
The safety and efficacy of eslicarbazepine acetate as adjunctive therapy for partial seizures in elderly patients were evaluated in one non-controlled study, with a duration of 26 weeks, in 72 elderly (aged ≥ 65 years). The data shows that the incidence of adverse reactions in this population (65.3 %) is similar to the general population enrolled in the double-blind epilepsy studies (66.8%).The most frequent individual adverse reactions were dizziness (12.5% of subjects), somnolence (9.7%), fatigue, convulsion and hyponatraemia (8.3%, each), nasopharyngitis (6.9%) and upper respiratory tract infection (5.6%). A total of 50 of the 72 subjects starting the study completed the 26-week treatment period that corresponds to a retention rate of 69.4% (see section 4.2 for information on elderly use).

Paediatric population
The efficacy and safety of eslicarbazepine acetate as adjunctive therapy for partial-onset seizures in children was evaluated in one phase II study in children aged from 6 to 16 years (N=123) and one phase III study in children aged from 2 to 18 years (N=304). Both studies were double-blind and placebo controlled with a duration of maintenance of 8 weeks (study 208) and 12 weeks (study 305), respectively. Eslicarbazepine acetate was tested at doses of 20 and 30 mg/kg/day, up to a maximum of 1,200 mg/day. The target dose was 30 mg/kg/day in study 208 and 20 mg/kg/day in study 305. Doses could be adjusted based on tolerability and treatment response.

In the phase II study, evaluation of efficacy was a secondary objective. The least square mean reduction in standardised seizure frequency from baseline to maintenance period was significantly ($p<0.001$) higher with eslicarbazepine acetate (-34.8%) compared to placebo (-13.8%). Forty-two patients (50.6%) in the eslicarbazepine acetate group compared to 10 patients (25.0%) in the placebo group were responders (≥50% reduction of standardised seizure frequency), resulting in a significant difference ($p=0.009$).

In the phase III study, the least square mean reduction in standardised seizure frequency with eslicarbazepine acetate (-18.1% versus baseline) was different to placebo (-8.6% versus baseline) but not statistically significant ($p=0.2490$). Forty-one patients (30.6%) in the eslicarbazepine acetate group compared to 40 patients (31.0%) in the placebo group were responders (≥50% reduction of standardised seizure frequency), resulting in a non-significant difference ($p=0.9017$). *Post-hoc* subgroup analyses for the phase III study were conducted by age strata and above 6 years, as well as by dose.. In children above 6 years, 36 patients (35.0%) in the eslicarbazepine acetate group compared to 29 patients (30.2%) in the placebo group were responders ($p=0.4759$) and the least square mean reduction in standardised seizure frequency was higher in the eslicarbazepine acetate group compared to placebo (-24.4% versus -10.5%); however, the difference of 13.9% was not statistically significant ($p=0.1040$). A total of 39% patients in study 305 were up titrated to the maximum possible dose (30 mg/kg/day). Amongst these, when excluding patients aged 6 years and younger, 14 (48.3%) and 11 (30.6%) of patients in the eslicarbazepine acetate and placebo group, respectively, were responders ($p=0.1514$). Although the robustness of these *post-hoc* subgroup analyses is limited, the data suggest an age and dose dependent increase in effect size.

The European Medicines Agency has deferred the obligation to submit the results of studies with Zebinix in one or more subsets of the paediatric population in the treatment of epilepsy with partial onset seizures (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Eslicarbazepine acetate is extensively converted to eslicarbazepine. Plasma levels of eslicarbazepine acetate usually remain below the limit of quantification, following oral administration. Eslicarbazepine C_{max} is attained at 2 to 3 hours post-dose (t_{max}). Bioavailability may be assumed as high because the amount of metabolites recovered in urine corresponded to more than 90% of an eslicarbazepine acetate dose.

Distribution

The binding of eslicarbazepine to plasma proteins is relatively low (<40%) and independent from concentration. *In vitro* studies have shown that plasma protein binding was not relevantly affected by the presence of warfarin, diazepam, digoxin, phenytoin and tolbutamide. The binding of warfarin, diazepam, digoxin, phenytoin and tolbutamide was not significantly affected by the presence of eslicarbazepine.

Biotransformation

Eslicarbazepine acetate is rapidly and extensively biotransformed to its major active metabolite eslicarbazepine by hydrolytic first-pass metabolism. The steady state plasma concentrations are attained after 4 to 5 days of once daily dosing, consistent with an effective half-life in the order of 20-24 hours. In studies in healthy subjects and epileptic adult patients, the apparent half-life of eslicarbazepine was 10-20 hours and 13-20 hours, respectively. Minor metabolites in plasma are R-licarbazepine and oxcarbazepine, which were shown to be active, and the glucuronic acid conjugates of eslicarbazepine acetate, eslicarbazepine, R-licarbazepine and oxcarbazepine.

Eslicarbazepine acetate does not affect its own metabolism or clearance.

Eslicarbazepine is a weak inducer of CYP3A4 and has inhibiting properties with respect to CYP2C19 (as stated in section 4.5).

In studies with eslicarbazepine in fresh human hepatocytes a mild induction of UGT1A1 mediated glucuronidation was observed.

Elimination

Eslicarbazepine acetate metabolites are eliminated from the systemic circulation primarily by renal excretion, in the unchanged and glucuronide conjugate forms. In total, eslicarbazepine and its glucuronide correspond to more than 90% of total metabolites excreted in urine, approximately two thirds in the unchanged form and one third as glucuronide conjugate.

Linearity/non-linearity

The pharmacokinetics of eslicarbazepine acetate is linear and dose-proportional in the range 400-1,200 mg both in healthy subjects and patients.

Elderly (over 65 years of age)

The pharmacokinetic profile of eslicarbazepine acetate is unaffected in the elderly patients with creatinine clearance >60 ml/min (see section 4.2).

Renal impairment

Eslicarbazepine acetate metabolites are eliminated from the systemic circulation primarily by renal excretion. A study in adult patients with mild to severe renal impairment showed that clearance is dependent on renal function. During treatment with Zebinix dose adjustment is recommended in patients, adult and children above 6 years of age with creatinine clearance <60 ml/min (see section 4.2).

In children from 2 to 6 years of age, the use of eslicarbazepine acetate is not recommended. At this age the intrinsic activity of the elimination process has not yet reached maturation.

Haemodialysis removes eslicarbazepine acetate metabolites from plasma.

Hepatic impairment

The pharmacokinetics and metabolism of eslicarbazepine acetate were evaluated in healthy subjects and moderately liver-impaired patients after multiple oral doses. Moderate hepatic impairment did not affect the pharmacokinetics of eslicarbazepine acetate. No dose adjustment is recommended in patients with mild to moderate liver impairment (see section 4.2).
The pharmacokinetics of eslicarbazepine acetate has not been evaluated in patients with severe hepatic impairment.

Gender

Studies in healthy subjects and patients showed that pharmacokinetics of eslicarbazepine acetate were not affected by gender.

Paediatric population

Similar to adults, eslicarbazepine acetate is extensively converted to eslicarbazepine. Plasma levels of eslicarbazepine acetate usually remain below the limit of quantification, following oral administration. Eslicarbazepine C_{max} is attained at 2 to 3 hours post-dose (t_{max}). Body weight was shown to have an effect on volume of distribution and clearance. Furthermore, a role of age independently of weight with regards to clearance of eslicarbazepine acetate could not be excluded, in particular for the youngest age group (2-6 years).

Children aged 6 years and below

Population pharmacokinetics indicate that in the subgroup of children aged from 2 to 6 years, doses of 27.5 mg/kg/day and 40 mg/kg/day are required in order to achieve exposures that are equivalent to the therapeutic doses of 20 and 30 mg/kg/day in children above 6 years of age.

Children above 6 years of age

Population pharmacokinetics indicate that comparable eslicarbazepine exposure is observed between 20 and 30 mg/kg/day in children above 6 years old and adults with 800 and 1200 mg of eslicarbazepine acetate once-daily, respectively (see section 4.2).

5.3 Preclinical safety data

Adverse reactions observed in animal studies occurred at exposure levels appreciably lower than the clinical exposure levels to eslicarbazepine (the principal and pharmacologically active metabolite of eslicarbazepine acetate). Safety margins based on comparative exposure have thus not been established.

Evidence of nephrotoxicity was observed in repeated dose-toxicity studies in the rat, but was not seen in studies in mice or dogs, and is consistent with an exacerbation of spontaneous chronic progressive nephropathy in this species.

Liver centrilobular hypertrophy was seen in repeated-dose toxicity studies in mice and rats and an increased incidence of liver tumours was observed in the carcinogenicity study in mice; these findings are consistent with an induction of hepatic microsomal enzymes, an effect which has not been observed in patients receiving eslicarbazepine acetate.

Juvenile animals studies

In repeat-dose studies in juvenile dogs, the toxicity profile was comparable to that observed in adult animals. In the 10-month study decreases in bone mineral content, bone area and/or bone mineral density in lumbar vertebrae and/or femur were observed in high-dose female animals at exposure levels lower than the clinical exposure levels to eslicarbazepine in children.

Genotoxicity studies with eslicarbazepine acetate indicate no special hazards for humans.

Impairment of fertility was observed in female rats; decreases in implantations and live embryos seen in the mouse fertility study may also indicate effects on female fertility, however, corpora lutea counts were not evaluated. Eslicarbazepine acetate was not teratogenic in the rat or rabbit, but did induce skeletal abnormalities in the mouse. Ossification delays, reduced foetal weights, an increase in minor skeletal and visceral anomalies were observed at maternal toxic doses in embryotoxicity studies in mice, rats and rabbits. A delay in the sexual development of the F1 generation was observed in peri/postnatal studies in mice and rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K 29/32
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Aluminium blisters placed into cardboard boxes containing 20 or 60 tablets.

HDPE bottles with polypropylene child resistant closure, inside a cardboard box, containing 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BIAL - Portela & Cª, SA
À Av. da Siderurgia Nacional

4745-457 S. Mamede do Coronado - Portugal
tel: +351 22 986 61 00
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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/514/021-023

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21.04.2009

Date of latest renewal: 22.01.2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Zebinix 400 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg of eslicarbazepine acetate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White circular biconvex tablets, engraved 'ESL 400'on one side and scored on the other side, with a diameter of 11 mm.. The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zebinix is indicated as adjunctive therapy in adults, adolescents and children aged above 6 years, with partial-onset seizures with or without secondary generalisation.

4.2 Posology and method of administration

Posology

Adults
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 (see section 5.1).

Special populations

Elderly (over 65 years of age)
No dose adjustment is needed in the elderly population provided that the renal function is not disturbed.

Renal impairment
Caution should be exercised in the treatment of patients, adult and children above 6 years of age, 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.
- CL_{CR} 30-60 ml/min: initial dose of 200 mg (or 5 mg/kg in children above 6 years) once daily or 400 mg (or 10 mg/kg in children above 6 years) every other day for 2 weeks followed by a once daily dose of 400 mg (or 10 mg/kg in children above 6 years). 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.

The pharmacokinetics of eslicarbazepine acetate has not been evaluated in patients with severe hepatic impairment (see sections 4.4 and 5.2) and use in these patients is, therefore, not recommended.

Paediatric population
Children above 6 years of age
The recommended starting dose is 10 mg/kg/day once daily. Dosage should be increased in weekly or bi-weekly increments of 10 mg/kg/day up to 30 mg/kg/day, based on individual response. The maximum dose is 1,200 mg once daily (see section 5.1).

Children with a body weight of ≥60 kg
Children with a body weight of 60 kg or more should be given the same dose as for adults.
The safety and efficacy of eslicarbazepine acetate in children aged 6 years and below has not yet been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Oral use.
Zebinix may be taken with or without food.

Switching preparations
Since comparative bioavailability data for the tablet and the suspension formulation are not available, switching patients from one formulation to the other should be done with caution.

4.3 Contraindications

Hypersensitivity to the active substance, to other carboxamide derivatives (e.g. carbamazepine, oxcarbazepine) or to any of the excipients listed in section 6.1.

Second or third degree atrioventricular (AV) block.

4.4 Special warnings and precautions for use

Suicidal ideation

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic active substances in several indications. A meta-analysis of randomised placebo-controlled trials of antiepileptic 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 disorders

Eslicarbazepine acetate has been associated with some central nervous system adverse reactions, such as dizziness and somnolence, which could increase the occurrence of accidental injury.

Other warnings and precautions

If Zebinix is to be discontinued it is recommended to withdraw it gradually to minimise the potential of increased seizure frequency.
There is no experience regarding the withdrawal of concomitant use of antiepileptic medicinal products during treatment with Zebinix (i.e. switching to monotherapy).

Cutaneous reactions

Rash developed as an adverse reaction in 1.1% of total population treated with Zebinix in placebo-controlled add-on studies in epileptic patients. If signs or symptoms of hypersensitivity develop, eslicarbazepine acetate must be discontinued.

HLA-B* 1502 allele - in Han Chinese, Thai and other Asian populations

HLA-B* 1502 in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing the severe cutaneous reactions known as Stevens Johnson syndrome (SJS) when treated with carbamazepine. The chemical structure of eslicarbazepine acetate is similar to that of carbamazepine, and it is possible that patients who are positive for HLA-B*1502 may also be at risk for SJS after treatment with eslicarbazepine acetate. The prevalence of HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations. Whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine or chemically-related active substances. If patients of these ethnic origins are tested positive for HLA- B*1502 allele, the use of eslicarbazepine acetate may be considered if the benefits are thought to exceed risks.
Because of the prevalence of this allele in other Asian populations (e.g, above 15% in the Philippines and Malaysia), testing genetically at risk populations for the presence of HLA- B*1502 may be considered.

HLA-A*3101 allele- European descent and Japanese populations

There are some data that suggest HLA-A*3101 is associated with an increased risk of carbamazepine induced cutaneous adverse drug reactions including SJS, TEN, Drug rash with eosinophilia (DRESS), or less severe acute generalized exanthematous pustulosis (AGEP) and maculopapular rash in people of European descent and the Japanese.
The frequency of the HLA-A*3101 allele varies widely between ethnic populations. HLA-A*3101 allele has a prevalence of 2 to 5% in European populations and about 10% in Japanese population. The presence of HLA-A*3101 allele may increase the risk for carbamazepine induced cutaneous reactions (mostly less severe) from 5.0% in general population to 26.0% among subjects of European ancestry, whereas its absence may reduce the risk from 5.0% to 3.8%.
There are insufficient data supporting a recommendation for HLA-A*3101 screening before starting carbamazepine or chemically-related compounds treatment.
If patients of European descent or Japanese origin are known to be positive for HLA-A*3101 allele, the use of carbamazepine or chemically-related compounds may be considered if the benefits are thought to exceed risks.

Hyponatraemia

Hyponatraemia has been reported as an adverse reaction in 1.2% of patients treated with Zebinix. Hyponatraemia is asymptomatic in most cases, however, it may be accompanied by clinical symptoms like worsening of seizures, confusion, decreased consciousness. Frequency of hyponatraemia increased with increasing eslicarbazepine acetate 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, carbamazepine), serum sodium levels should be examined before and during treatment with eslicarbazepine acetate. Furthermore, serum sodium levels should be determined if clinical signs of hyponatraemia occur. Apart from this, sodium levels should be determined during routine laboratory examination. If clinically-relevant hyponatraemia develops, eslicarbazepine acetate should be discontinued.

PR interval

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.

Renal impairment

Caution should be exercised in the treatment of patients with renal impairment and the dose should be adjusted according to creatinine clearance (see section 4.2). In patients with CL_{CR} <30 ml/min use is not recommended due to insufficient data.

Hepatic impairment

As clinical data are limited in patients with mild to moderate hepatic impairment and pharmacokinetic and clinical data are missing in patients with severe hepatic impairment, eslicarbazepine acetate should be used with caution in patients with mild to moderate hepatic impairment and is not recommended in patients with severe hepatic impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Eslicarbazepine acetate is extensively converted to eslicarbazepine, which is mainly eliminated by glucuronidation. *In vitro* eslicarbazepine is a weak inducer of CYP3A4 and UDP-glucuronyl transferases. *In vivo* eslicarbazepine showed an inducing effect on the metabolism of medicinal products that are mainly eliminated by metabolism through CYP3A4 (e.g. Simvastatin). Thus, an increase in the dose of the medicinal products that are mainly metabolised through CYP3A4 may be required, when used concomitantly with eslicarbazepine acetate. Eslicarbazepine *in vivo* may have an inducing effect on the metabolism of medicinal products that are mainly eliminated by conjugation through the UDP-glucuronyl transferases.When initiating or discontinuing treatment with Zebinix 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 Zebinix is being used just prior to or in combination with other medicinal products that require dose adjustment when co-administered with Zebinix. Eslicarbazepine has inhibiting properties with respect to CYP2C19. Thus, interactions can arise when co-administering high doses of eslicarbazepine acetate with medicinal products that are mainly metabolised by CYP2C19 (e.g. Phenytoin).

Interactions with other antiepileptic medicinal products

Carbamazepine
In a study in healthy subjects, concomitant administration of eslicarbazepine acetate 800 mg once daily and carbamazepine 400 mg twice daily resulted in an average decrease of 32% in exposure to the active metabolite eslicarbazepine, most likely caused by an induction of glucuronidation. No change in exposure to carbamazepine or its metabolite carbamazepine-epoxide was noted. Based on individual response, the dose of eslicarbazepine acetate may need to be increased if used concomitantly with carbamazepine. Results from patient studies showed that concomitant treatment increased the risk of the following adverse reactions: diplopia, abnormal coordination and dizziness. The risk of increase of other specific adverse reactions caused by co-administration of carbamazepine and eslicarbazepine acetate cannot be excluded.

Phenytoin
In a study in healthy subjects, concomitant administration of eslicarbazepine acetate 1,200 mg once daily and phenytoin resulted in an average decrease of 31-33% in exposure to the active metabolite, eslicarbazepine, most likely caused by an induction of glucuronidation, and an average increase of 31-35% in exposure to phenytoin, most likely caused by an inhibition of CYP2C19. Based on individual response, the dose of eslicarbazepine acetate may need to be increased and the dose of phenytoin may need to be decreased.

Lamotrigine
Glucuronidation is the major metabolic pathway for both eslicarbazepine and lamotrigine and therefore, an interaction could be expected. A study in healthy subjects with eslicarbazepine acetate 1,200 mg once daily showed a minor average pharmacokinetic interaction (exposure of lamotrigine decreased 15%) between eslicarbazepine acetate and lamotrigine and consequently no dose adjustments are required. However, due to inter-individual variability, the effect may be clinically relevant in some individuals.

Topiramate
In a study in healthy subjects, concomitant administration of eslicarbazepine acetate 1,200 mg once daily and topiramate showed no significant change in exposure to eslicarbazepine but an 18% decrease in exposure to topiramate, most likely caused by a reduced bioavailability of topiramate. No dose adjustment is required.

Valproate and levetiracetam
A population pharmacokinetics analysis of phase III studies in epileptic adult patients indicated that concomitant administration with valproate or levetiracetam did not affect the exposure to eslicarbazepine but this has not been verified by conventional interaction studies.

Oxcarbazepine
Concomitant use of eslicarbazepine acetate with oxcarbazepine is not recommended because this may cause overexposure to the active metabolites.

<u>Other medicinal products</u>

Oral contraceptives
Administration of eslicarbazepine acetate 1,200 mg once daily to female subjects using a combined oral contraceptive showed an average decrease of 37% and 42% in systemic exposure to levonorgestrel and ethinylestradiol, respectively, most likely caused by an induction of CYP3A4. Therefore, women of childbearing potential must use adequate contraception during treatment with Zebinix, and up to the end of the current menstruation cycle after the treatment has been discontinued (see section 4.6).

Simvastatin
A study in healthy subjects showed an average decrease of 50% in systemic exposure to simvastatin when co-administered with eslicarbazepine acetate 800 mg once daily, most likely caused by an induction of CYP3A4. An increase of the simvastatin dose may be required when used concomitantly with eslicarbazepine acetate.

Rosuvastatin
There was an average decrease of 36-39% in systemic exposure in healthy subjects when co-administered with eslicarbazepine acetate 1,200 mg once daily. The mechanism for this reduction is unknown, but could be due to interference of transporter activity for rosuvastatin alone or in combination with induction of its metabolism. Since the relationship between exposure and drug activity is unclear, the monitoring of response to therapy (e.g., cholesterol levels) is recommended.

Warfarin

Co-administration of eslicarbazepine acetate 1,200 mg once daily 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 the first weeks after initiation or ending concomitant treatment of warfarin and eslicarbazepine acetate.

Digoxin
A study in healthy subjects showed no effect of eslicarbazepine acetate 1,200 mg once daily on digoxin pharmacokinetics, suggesting that eslicarbazepine acetate has no effect on the transporter P-glycoprotein.

Monoamino Oxidase Inhibitors (MAOIs)
Based on a structural relationship of eslicarbazepine acetate to tricyclic antidepressants, an interaction between eslicarbazepine acetate and MAOIs is theoretically possible.

4.6 Fertility, pregnancy and lactation

Risk related to epilepsy and antiepileptic medicinal products in general
It has been shown that in the offspring of women with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic medicinal product therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practised whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of child-bearing potential. The need for antiepileptic therapy should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both mother and child.

Women of childbearing potential/contraception
Eslicarbazepine acetate adversely interacts with oral contraceptives. Therefore, an alternative, effective and safe method of contraception should be used during treatment and up to the end of the current menstrual cycle after treatment has been stopped.

Pregnancy
There are no data from the use of eslicarbazepine acetate in pregnant women. Studies in animals have shown reproductive toxicity (see Fertility). If women receiving eslicarbazepine acetate become pregnant or plan to become pregnant, the use of Zebinix should be carefully re-evaluated. Minimum effective doses should be given, and monotherapy whenever possible should be preferred at least during the first three months of pregnancy. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity to antenatal screening.

Monitoring and prevention
Antiepileptic medicinal products may contribute to folic acid deficiency, a possible contributory cause of foetal abnormality. Folic acid supplementation is recommended before and during pregnancy. As the efficacy of this supplementation is not proven, a specific antenatal diagnosis can be offered even for women with a supplementary treatment of folic acid.

In the newborn child
Bleeding disorders in the newborn caused by antiepileptic medicinal products 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.

Breast-feeding

It is unknown whether eslicarbazepine acetate is excreted in human milk. Animal studies have shown excretion of eslicarbazepine in breast milk. As a risk to the breast-fed child cannot be excluded breast-feeding should be discontinued during treatment with eslicarbazepine acetate.

Fertility
There are no data on the effects of eslicarbazepine acetate on human fertility. Studies in animals have shown impairment of fertility after treatment with eslicarbazepine acetate (see section 5.3).

4.7 Effects on ability to drive and use machines

Zebinix has minor to moderate influence on the ability to drive and use machines. Some patients might experience dizziness, somnolence or visual disorders, particularly on initiation of treatment. Therefore, patients should be advised that their physical and/or mental abilities needed for operating machinery or driving may be impaired and they are recommended not to do so until it has been established that their ability to perform such activities is not affected.

4.8 Undesirable effects

Summary of the safety profile
In placebo-controlled studies involving 1,842 adult and 427 paediatric patients with partial-onset seizures (1,520 patients treated with eslicarbazepine acetate and 749 treated with placebo), 48.9% of patients treated with eslicarbazepine acetate and 26% of patients treated with placebo experienced adverse reactions.

Adverse reactions were usually mild to moderate in intensity and occurred predominantly during the first weeks of treatment with eslicarbazepine acetate.

The risks that have been identified for Zebinix are mainly class-based, dose-dependent undesirable effects. The most common adverse reactions reported in clinical studies with adult epileptic patients, both in placebo and eslicarbazepine acetate groups were dizziness, somnolence, headache, and nausea. The majority of adverse reactions were reported in <3% of subjects in any treatment group.

Tabulated list of adverse reactions

The following convention has been used for the classification of adverse reactions very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and not known (frequency cannot be estimated from available data). Within each frequency category, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions associated with Zebinix obtained from adjunctive therapy in clinical studies and post-marketing surveillance

System Organ Class	**Very common**	**Common**	**Uncommon**		**Not known**
Blood and lymphatic system disorders			Anaemia		Thrombocytopenia, leukopenia
Immune system disorders			Hypersensitivity		
Endocrine disorders			Hypothyroidism		
Metabolism and nutrition disorders		Hyponatraemia, decreased appetite	Electrolyte imbalance, dehydration, hypochloraemia		

Psychiatric disorders		Insomnia	Psychotic disorder, apathy, depression, nervousness, agitation, irritability, attention deficit/ hyperactivity disorder, confusional state, mood swings, crying, psychomotor retardation		
Nervous system disorders	Dizziness, somnolence	Headache, disturbance in attention, tremor, ataxia, balance disorder	Coordination abnormal, memory impairment, amnesia, hypersomnia, sedation, aphasia, dysaesthesia, dystonia, lethargy, parosmia, cerebellar syndrome, convulsion, peripheral neuropathy, nystagmus, speech disorder, dysarthria, burning sensation, paraesthesia, migraine		
Eye disorders		Diplopia, vision blurred	Visual impairment, oscillopsia, binocular eye movement disorder, ocular hyperaemia		
Ear and labyrinth disorders		Vertigo	Hypoacusis, tinnitus		
Cardiac disorders			Palpitations, bradycardia		

Vascular disorders			Hypertension (including hypertensis crisis), hypotension, orthostatic hypotension, flushing, peripheral coldness		
Respiratory, thoracic and mediastinal disorders			Epistaxis, chest pain		
Gastrointestinal disorders		Nausea, vomiting, diarrhoea	Constipation, dyspepsia, gastritis, abdominal pain, dry mouth, abdominal discomfort, abdominal distension, gingivitis, melaena, toothache		Pancreatitis
Hepatobiliary disorders			Liver disorder		
Skin and subcutaneous tissue disorders		Rash	Alopecia, dry skin, hyperhidrosis, erythema, skin disorder, pruritus, dermatitis allergic		Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders			Myalgia, bone metabolism disorder, muscular weakness, pain in extremity		
Renal and urinary disorders			Urinary tract infection		
General disorders and administration site conditions		Fatigue, gait disturbance, asthenia	Malaise, chills, oedema peripheral		

Investigations			Blood pressure decreased, weight decreased, blood pressure increased, blood sodium decreased, blood chloride decreased, osteocalcin increased, haematocrit decreased, haemoglobin decreased, transaminases increased		
Injury, poisoning and procedural complications			Drug toxicity, fall, thermal burn		

Description of selected adverse reactions

Eye and nervous system disorders
In patients concomitantly treated with carbamazepine and eslicarbazepine acetate in placebo-controlled studies, the following adverse reactions were observed: diplopia (11.4% of subjects with concomitant carbamazepine, 2.4% of subjects without concomitant carbamazepine), abnormal coordination (6.7% with concomitant carbamazepine, 2.7% without concomitant carbamazepine), and dizziness (30.0% with concomitant carbamazepine, 11.5% without concomitant carbamazepine), see section 4.5.

PR interval
The use of eslicarbazepine acetate is associated with increase in the PR interval. Adverse reactions associated with PR interval prolongation (e.g. AV block, syncope, bradycardia) may occur.

Class related adverse reactions
Rare adverse reactions such as bone marrow depression, anaphylactic reactions, severe cutaneous reactions (e.g. Stevens-Johnson Syndrome), systemic lupus erythematosus or serious cardiac arrhythmias did not occur during the placebo-controlled studies of the epilepsy program with eslicarbazepine acetate. However, they have been reported with oxcarbazepine. Therefore, their occurrence after treatment with eslicarbazepine acetate cannot be excluded.

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with the structurally related antiepileptic drugs carbamazepine and oxcarbazepine. The mechanism by which bone metabolism is affected has not been identified.

Paediatric population

In placebo-controlled studies involving patients aged from 2 to 18 years with partial-onset seizures (238 patients treated with eslicarbazepine acetate and 189 with placebo), 35.7% of patients treated with eslicarbazepine acetate and 19% of patients treated with placebo experienced adverse reactions. The most common adverse reaction in the group treated with eslicarbazepine acetate were diplopia (5.0%), somnolence (8.0%) and vomiting (4.6%).

The adverse reaction profile of eslicarbazepine acetate is generally similar across age goups. In the age group from 6 to 11 years of age, the most common adverse reactions observed in more than two patients treated with eslicarbazepine acetate were diplopia (9.5%), somnolence (7.4%), diziness (6.3%), convulsion (6.3%) and nausea (3.2%); in the age group from 12 to 18 years were somnolence (7.4%), vomiting (4.2%), diplopia (3.2%) and fatigue (3.2%). The safety of Zebinix in children aged 6 years and below has not yet been established.

The safety profile of eslicarbazepine acetate was generally similar between adult and paediatric patients, except for agitation (common, 1.3%) and abdominal pain (common, 2.1%) which were more common in children than in adults. Dizziness; somnolence; vertigo; asthenia; gait disturbance; tremor; ataxia; balance disorder; vision blurred; diarrhoea and rash were less common in children than in adults. Hyponatraemia was only reported in adult population. Dermatitis allergic (uncommon, 0.8%) was reported only in the paediatric population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Central nervous symptoms such as vertigo, walking instability and hemi-paresis have been observed with accidental eslicarbazepine acetate overdose. There is no known specific antidote. Symptomatic and supportive treatment should be administered as appropriate. Eslicarbazepine acetate metabolites can effectively be cleared by haemodialysis, if necessary (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, carboxamide derivatives, ATC code: N03AF04

Mechanism of action

The precise mechanisms of action of eslicarbazepine acetate are unknown. However, *in vitro* electrophysiological studies indicate that both eslicarbazepine acetate and its metabolites stabilise the inactivated state of voltage-gated sodium channels, preventing their return to the activated state and thereby sustaining repetitive neuronal firing.

Pharmacodynamic effect

Eslicarbazepine acetate and its active metabolites prevented the development of seizures in nonclinical models predictive of anticonvulsant efficacy in man. In humans, the pharmacological activity of eslicarbazepine acetate is primarily exerted through the active metabolite eslicarbazepine.

Clinical efficacy and safety

Adult population
The efficacy and safety of eslicarbazepine acetate has been demonstrated in four phase III double-blind placebo-controlled studies in 1,703 randomized adult patients with partial epilepsy refractory to treatment with one to three concomitant antiepileptic medicinal products. Oxcarbazepine and felbamate were not allowed as concomitant medicinal products in these studies. Eslicarbazepine acetate was tested at doses of 400 mg (in -301 and -302 studies only), 800 mg and 1,200 mg, once

daily. Eslicarbazepine acetate 800 mg once daily and 1,200 mg once daily were significantly more effective than placebo in reducing seizure frequency over a 12-week maintenance period. The percentage of subjects with ≥50% reduction (1581 analyzed) in seizure frequency in the phase III studies was 19.3% for placebo, 20.8% for eslicarbazepine acetate 400 mg, 30.5% for eslicarbazepine acetate 800 mg and 35.3% for eslicarbazepine acetate 1,200 mg daily.

Elderly population
The safety and efficacy of eslicarbazepine acetate as adjunctive therapy for partial seizures in elderly patients were evaluated in one non-controlled study, with a duration of 26 weeks, in 72 elderly (aged ≥ 65 years). The data shows that the incidence of adverse reactions in this population (65.3 %) is similar to the general population enrolled in the double-blind epilepsy studies (66.8%).The most frequent individual adverse reactions were dizziness (12.5% of subjects), somnolence (9.7%), fatigue, convulsion and hyponatraemia (8.3%, each), nasopharyngitis (6.9%) and upper respiratory tract infection (5.6%). A total of 50 of the 72 subjects starting the study completed the 26-week treatment period that corresponds to a retention rate of 69.4% (see section 4.2 for information on elderly use).

Paediatric population
The efficacy and safety of eslicarbazepine acetate as adjunctive therapy for partial-onset seizures in children was evaluated in one phase II study in children aged from 6 to 16 years (N=123) and one phase III study in children aged from 2 to 18 years (N=304). Both studies were double-blind and placebo controlled with a duration of maintenance of 8 weeks (study 208) and 12 weeks (study 305), respectively. Eslicarbazepine acetate was tested at doses of 20 and 30 mg/kg/day, up to a maximum of 1,200 mg/day. The target dose was 30 mg/kg/day in study 208 and 20 mg/kg/day in study 305. Doses could be adjusted based on tolerability and treatment response.

In the phase II study, evaluation of efficacy was a secondary objective. The least square mean reduction in standardised seizure frequency from baseline to maintenance period was significantly ($p<0.001$) higher with eslicarbazepine acetate (-34.8%) compared to placebo (-13.8%). Forty-two patients (50.6%) in the eslicarbazepine acetate group compared to 10 patients (25.0%) in the placebo group were responders (≥50% reduction of standardised seizure frequency), resulting in a significant difference ($p=0.009$).

In the phase III study, the least square mean reduction in standardised seizure frequency with eslicarbazepine acetate (-18.1% versus baseline) was different to placebo (-8.6% versus baseline) but not statistically significant ($p=0.2490$). Forty-one patients (30.6%) in the eslicarbazepine acetate group compared to 40 patients (31.0%) in the placebo group were responders (≥50% reduction of standardised seizure frequency), resulting in a non-significant difference ($p=0.9017$). *Post-hoc* subgroup analyses for the phase III study were conducted by age strata and above 6 years, as well as by dose. In children above 6 years, 36 patients (35.0%) in the eslicarbazepine acetate group compared to 29 patients (30.2%) in the placebo group were responders ($p=0.4759$) and the least square mean reduction in standardised seizure frequency was higher in the eslicarbazepine acetate group compared to placebo (-24.4% versus -10.5%); however, the difference of 13.9% was not statistically significant ($p=0.1040$). A total of 39% patients in study 305 were up titrated to the maximum possible dose (30 mg/kg/day). Amongst these, when excluding patients aged 6 years and younger, 14 (48.3%) and 11 (30.6%) of patients in the eslicarbazepine acetate and placebo group, respectively, were responders ($p=0.1514$). Although the robustness of these *post-hoc* subgroup analyses is limited, the data suggest an age and dose dependent increase in effect size.

The European Medicines Agency has deferred the obligation to submit the results of studies with Zebinix in one or more subsets of the paediatric population in the treatment of epilepsy with partial onset seizures (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Eslicarbazepine acetate is extensively converted to eslicarbazepine. Plasma levels of eslicarbazepine acetate usually remain below the limit of quantification, following oral administration. Eslicarbazepine C_{max} is attained at 2 to 3 hours post-dose (t_{max}). Bioavailability may be assumed as high because the amount of metabolites recovered in urine corresponded to more than 90% of an eslicarbazepine acetate dose.

Distribution
The binding of eslicarbazepine to plasma proteins is relatively low (<40%) and independent from concentration. *In vitro* studies have shown that plasma protein binding was not relevantly affected by the presence of warfarin, diazepam, digoxin, phenytoin and tolbutamide. The binding of warfarin, diazepam, digoxin, phenytoin and tolbutamide was not significantly affected by the presence of eslicarbazepine.

Biotransformation
Eslicarbazepine acetate is rapidly and extensively biotransformed to its major active metabolite eslicarbazepine by hydrolytic first-pass metabolism. The steady state plasma concentrations are attained after 4 to 5 days of once daily dosing, consistent with an effective half-life in the order of 20-24 hours. In studies in healthy subjects and epileptic adult patients, the apparent half-life of eslicarbazepine was 10-20 hours and 13-20 hours, respectively. Minor metabolites in plasma are R-licarbazepine and oxcarbazepine, which were shown to be active, and the glucuronic acid conjugates of eslicarbazepine acetate, eslicarbazepine, R-licarbazepine and oxcarbazepine.

Eslicarbazepine acetate does not affect its own metabolism or clearance.

Eslicarbazepine is a weak inducer of CYP3A4 and has inhibiting properties with respect to CYP2C19 (as stated in section 4.5).

In studies with eslicarbazepine in fresh human hepatocytes a mild induction of UGT1A1 mediated glucuronidation was observed.

Elimination
Eslicarbazepine acetate metabolites are eliminated from the systemic circulation primarily by renal excretion, in the unchanged and glucuronide conjugate forms. In total, eslicarbazepine and its glucuronide correspond to more than 90% of total metabolites excreted in urine, approximately two thirds in the unchanged form and one third as glucuronide conjugate.

Linearity/non-linearity
The pharmacokinetics of eslicarbazepine acetate is linear and dose-proportional in the range 400-1,200 mg both in healthy subjects and patients.

Elderly (over 65 years of age)
The pharmacokinetic profile of eslicarbazepine acetate is unaffected in the elderly patients with creatinine clearance >60 ml/min (see section 4.2).

Renal impairment
Eslicarbazepine acetate metabolites are eliminated from the systemic circulation primarily by renal excretion. A study in adult patients with mild to severe renal impairment showed that clearance is dependent on renal function. During treatment with Zebinix dose adjustment is recommended in patients, adult and children above 6 years of age with creatinine clearance <60 ml/min (see section 4.2).
In children from 2 to 6 years of age, the use of eslicarbazepine acetate is not recommended. At this age the intrinsic activity of the elimination process has not yet reached maturation.

Haemodialysis removes eslicarbazepine acetate metabolites from plasma.

Hepatic impairment

The pharmacokinetics and metabolism of eslicarbazepine acetate were evaluated in healthy subjects and moderately liver-impaired patients after multiple oral doses. Moderate hepatic impairment did not affect the pharmacokinetics of eslicarbazepine acetate. No dose adjustment is recommended in patients with mild to moderate liver impairment (see section 4.2).
The pharmacokinetics of eslicarbazepine acetate has not been evaluated in patients with severe hepatic impairment.

Gender
Studies in healthy subjects and patients showed that pharmacokinetics of eslicarbazepine acetate were not affected by gender.

Paediatric population

Similar to adults, eslicarbazepine acetate is extensively converted to eslicarbazepine. Plasma levels of eslicarbazepine acetate usually remain below the limit of quantification, following oral administration. Eslicarbazepine C_{max} is attained at 2 to 3 hours post-dose (t_{max}). Body weight was shown to have an effect on volume of distribution and clearance. Furthermore, a role of age independently of weight with regards to clearance of eslicarbazepine acetate could not be excluded, in particular for the youngest age group (2-6 years).

Children aged 6 years and below
Population pharmacokinetics indicate that in the subgroup of children aged from 2 to 6 years, doses of 27.5 mg/kg/day and 40 mg/kg/day are required in order to achieve exposures that are equivalent to the therapeutic doses of 20 and 30 mg/kg/day in children above 6 years of age.

Children above 6 years of age
Population pharmacokinetics indicate that comparable eslicarbazepine exposure is observed between 20 and 30 mg/kg/day in children above 6 years old and adults with 800 and 1200 mg of eslicarbazepine acetate once-daily, respectively (see section 4.2).

5.3 Preclinical safety data

Adverse reactions observed in animal studies occurred at exposure levels appreciably lower than the clinical exposure levels to eslicarbazepine (the principal and pharmacologically active metabolite of eslicarbazepine acetate). Safety margins based on comparative exposure have thus not been established.

Evidence of nephrotoxicity was observed in repeated dose-toxicity studies in the rat, but was not seen in studies in mice or dogs, and is consistent with an exacerbation of spontaneous chronic progressive nephropathy in this species.

Liver centrilobular hypertrophy was seen in repeated-dose toxicity studies in mice and rats and an increased incidence of liver tumours was observed in the carcinogenicity study in mice; these findings are consistent with an induction of hepatic microsomal enzymes, an effect which has not been observed in patients receiving eslicarbazepine acetate.

Juvenile animals studies
In repeat-dose studies in juvenile dogs, the toxicity profile was comparable to that observed in adult animals. In the 10-month study decreases in bone mineral content, bone area and/or bone mineral density in lumbar vertebrae and/or femur were observed in high-dose female animals at exposure levels lower than the clinical exposure levels to eslicarbazepine in children.

Genotoxicity studies with eslicarbazepine acetate indicate no special hazards for humans.

Impairment of fertility was observed in female rats; decreases in implantations and live embryos seen in the mouse fertility study may also indicate effects on female fertility, however, corpora lutea counts

were not evaluated. Eslicarbazepine acetate was not teratogenic in the rat or rabbit, but did induce skeletal abnormalities in the mouse. Ossification delays, reduced foetal weights, an increase in minor skeletal and visceral anomalies were observed at maternal toxic doses in embryotoxicity studies in mice, rats and rabbits. A delay in the sexual development of the F1 generation was observed in peri/postnatal studies in mice and rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K 29/32
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/Aluminium or PVC/Aluminium blisters placed into cardboard boxes containing 7, 14 or 28 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BIAL - Portela & Cª, SA
À Av. da Siderurgia Nacional 4745-457 S. Mamede do Coronado - Portugal
tel: +351 22 986 61 00
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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/514/001-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21.04.2009

Date of latest renewal: 22.01.2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Zebinix 600 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 600 mg of eslicarbazepine acetate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White oblong tablets, engraved 'ESL 600'on one side and scored on the other side, with a length of 17.3 mm. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zebinix is indicated as adjunctive therapy in adults, adolescents and children aged above 6 years, with partial-onset seizures with or without secondary generalisation.

4.2 Posology and method of administration

Posology

Adults
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 (see section 5.1).

Special populations

Elderly (over 65 years of age)
No dose adjustment is needed in the elderly population provided that the renal function is not disturbed.

Renal impairment
Caution should be exercised in the treatment of patients, adult and children above 6 years of age, 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.
- CL_{CR} 30-60 ml/min: initial dose of 200 mg (or 5 mg/kg in children above 6 years) once daily or 400 mg (or 10 mg/kg in children above 6 years) every other day for 2 weeks followed by a once daily dose of 400 mg (or 10 mg/kg in children above 6 years). 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.
The pharmacokinetics of eslicarbazepine acetate has not been evaluated in patients with severe hepatic impairment (see sections 4.4 and 5.2) and use in these patients is, therefore, not recommended.

Paediatric population
Children above 6 years of age
The recommended starting dose is 10 mg/kg/day once daily. Dosage should be increased in weekly or bi-weekly increments of 10 mg/kg/day up to 30 mg/kg/day, based on individual response. The maximum dose is 1,200 mg once daily (see section 5.1).

Children with a body weight of ≥60 kg
Children with a body weight of 60 kg or more should be given the same dose as for adults.
The safety and efficacy of eslicarbazepine acetate in children aged 6 years and below has not yet been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.
Method of administration

Oral use.
Zebinix may be taken with or without food.

Switching preparations
Since comparative bioavailability data for the tablet and the suspension formulation are not available, switching patients from one formulation to the other should be done with caution.

4.3 Contraindications

Hypersensitivity to the active substance, to other carboxamide derivatives (e.g. carbamazepine, oxcarbazepine) or to any of the excipients listed in section 6.1.

Second or third degree atrioventricular (AV) block.

4.4 Special warnings and precautions for use

Suicidal ideation

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic active substances in several indications. A meta-analysis of randomised placebo-controlled trials of antiepileptic 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 disorders

Eslicarbazepine acetate has been associated with some central nervous system adverse reactions, such as dizziness and somnolence, which could increase the occurrence of accidental injury.

Other warnings and precautions

If Zebinix is to be discontinued it is recommended to withdraw it gradually to minimise the potential of increased seizure frequency.
There is no experience regarding the withdrawal of concomitant use of antiepileptic medicinal products during treatment with Zebinix (i.e. switching to monotherapy).

Cutaneous reactions

Rash developed as an adverse reaction in 1.1% of total population treated with Zebinix in placebo-controlled add-on studies in epileptic patients. If signs or symptoms of hypersensitivity develop, eslicarbazepine acetate must be discontinued.

HLA-B* 1502 allele - in Han Chinese, Thai and other Asian populations

HLA-B* 1502 in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing the severe cutaneous reactions known as Stevens Johnson syndrome (SJS) when treated with carbamazepine. The chemical structure of eslicarbazepine acetate is similar to that of carbamazepine, and it is possible that patients who are positive for HLA-B*1502 may also be at risk for SJS after treatment with eslicarbazepine acetate. The prevalence of HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations. Whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine or chemically-related active substances. If patients of these ethnic origins are tested positive for HLA- B*1502 allele, the use of eslicarbazepine acetate may be considered if the benefits are thought to exceed risks.
Because of the prevalence of this allele in other Asian populations (e.g, above 15% in the Philippines and Malaysia), testing genetically at risk populations for the presence of HLA- B*1502 may be considered.

HLA-A*3101 allele- European descent and Japanese populations

There are some data that suggest HLA-A*3101 is associated with an increased risk of carbamazepine induced cutaneous adverse drug reactions including SJS, TEN, Drug rash with eosinophilia (DRESS), or less severe acute generalized exanthematous pustulosis (AGEP) and maculopapular rash in people of European descent and the Japanese.
The frequency of the HLA-A*3101 allele varies widely between ethnic populations. HLA-A*3101 allele has a prevalence of 2 to 5% in European populations and about 10% in Japanese population. The presence of HLA-A*3101 allele may increase the risk for carbamazepine induced cutaneous reactions (mostly less severe) from 5.0% in general population to 26.0% among subjects of European ancestry, whereas its absence may reduce the risk from 5.0% to 3.8%.
There are insufficient data supporting a recommendation for HLA-A*3101 screening before starting carbamazepine or chemically-related compounds treatment.
If patients of European descent or Japanese origin are known to be positive for HLA-A*3101 allele, the use of carbamazepine or chemically-related compounds may be considered if the benefits are thought to exceed risks.

Hyponatraemia

Hyponatraemia has been reported as an adverse reaction in 1.2% of patients treated with Zebinix. Hyponatraemia is asymptomatic in most cases, however, it may be accompanied by clinical symptoms like worsening of seizures, confusion, decreased consciousness. Frequency of hyponatraemia increased with increasing eslicarbazepine acetate 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, carbamazepine), serum sodium levels should be examined before and during treatment with eslicarbazepine acetate. Furthermore, serum sodium levels should be determined if clinical signs of hyponatraemia occur. Apart from this, sodium levels should be determined during routine laboratory examination. If clinically-relevant hyponatraemia develops, eslicarbazepine acetate should be discontinued.

PR interval

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.

Renal impairment

Caution should be exercised in the treatment of patients with renal impairment and the dose should be adjusted according to creatinine clearance (see section 4.2). In patients with CL_{CR} <30 ml/min use is not recommended due to insufficient data.

Hepatic impairment

As clinical data are limited in patients with mild to moderate hepatic impairment and pharmacokinetic and clinical data are missing in patients with severe hepatic impairment, eslicarbazepine acetate should be used with caution in patients with mild to moderate hepatic impairment and is not recommended in patients with severe hepatic impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Eslicarbazepine acetate is extensively converted to eslicarbazepine, which is mainly eliminated by glucuronidation. *In vitro* eslicarbazepine is a weak inducer of CYP3A4 and UDP-glucuronyl transferases. *In vivo* eslicarbazepine showed an inducing effect on the metabolism of medicinal products that are mainly eliminated by metabolism through CYP3A4 (e.g. Simvastatin). Thus, an increase in the dose of the medicinal products that are mainly metabolised through CYP3A4 may be required, when used concomitantly with eslicarbazepine acetate. Eslicarbazepine *in vivo* may have an inducing effect on the metabolism of medicinal products that are mainly eliminated by conjugation through the UDP-glucuronyl transferases. When initiating or discontinuing treatment with Zebinix 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 Zebinix is being used just prior to or in combination with other medicinal products that require dose adjustment when co-administered with Zebinix. Eslicarbazepine has inhibiting properties with respect to CYP2C19. Thus, interactions can arise when co-administering high doses of eslicarbazepine acetate with medicinal products that are mainly metabolised by CYP2C19 (e.g. Phenytoin).

Interactions with other antiepileptic medicinal products

Carbamazepine
In a study in healthy subjects, concomitant administration of eslicarbazepine acetate 800 mg once daily and carbamazepine 400 mg twice daily resulted in an average decrease of 32% in exposure to the active metabolite eslicarbazepine, most likely caused by an induction of glucuronidation. No change in exposure to carbamazepine or its metabolite carbamazepine-epoxide was noted. Based on individual response, the dose of eslicarbazepine acetate may need to be increased if used concomitantly with carbamazepine. Results from patient studies showed that concomitant treatment increased the risk of the following adverse reactions: diplopia, abnormal coordination and dizziness. The risk of increase of other specific adverse reactions caused by co-administration of carbamazepine and eslicarbazepine acetate cannot be excluded.

Phenytoin
In a study in healthy subjects, concomitant administration of eslicarbazepine acetate 1,200 mg once daily and phenytoin resulted in an average decrease of 31-33% in exposure to the active metabolite, eslicarbazepine, most likely caused by an induction of glucuronidation, and an average increase of 31-35% in exposure to phenytoin, most likely caused by an inhibition of CYP2C19. Based on individual response, the dose of eslicarbazepine acetate may need to be increased and the dose of phenytoin may need to be decreased.

Lamotrigine
Glucuronidation is the major metabolic pathway for both eslicarbazepine and lamotrigine and therefore, an interaction could be expected. A study in healthy subjects with eslicarbazepine acetate

1,200 mg once daily showed a minor average pharmacokinetic interaction (exposure of lamotrigine decreased 15%) between eslicarbazepine acetate and lamotrigine and consequently no dose adjustments are required. However, due to inter-individual variability, the effect may be clinically relevant in some individuals.

Topiramate
In a study in healthy subjects, concomitant administration of eslicarbazepine acetate 1,200 mg once daily and topiramate showed no significant change in exposure to eslicarbazepine but an 18% decrease in exposure to topiramate, most likely caused by a reduced bioavailability of topiramate. No dose adjustment is required.

Valproate and levetiracetam
A population pharmacokinetics analysis of phase III studies in epileptic adult patients indicated that concomitant administration with valproate or levetiracetam did not affect the exposure to eslicarbazepine but this has not been verified by conventional interaction studies.

Oxcarbazepine
Concomitant use of eslicarbazepine acetate with oxcarbazepine is not recommended because this may cause overexposure to the active metabolites.

Other medicinal products

Oral contraceptives
Administration of eslicarbazepine acetate 1,200 mg once daily to female subjects using a combined oral contraceptive showed an average decrease of 37% and 42% in systemic exposure to levonorgestrel and ethinylestradiol, respectively, most likely caused by an induction of CYP3A4. Therefore, women of childbearing potential must use adequate contraception during treatment with Zebinix, and up to the end of the current menstruation cycle after the treatment has been discontinued (see section 4.6).

Simvastatin
A study in healthy subjects showed an average decrease of 50% in systemic exposure to simvastatin when co-administered with eslicarbazepine acetate 800 mg once daily, most likely caused by an induction of CYP3A4. An increase of the simvastatin dose may be required when used concomitantly with eslicarbazepine acetate.

Rosuvastatin
There was an average decrease of 36-39% in systemic exposure in healthy subjects when co-administered with eslicarbazepine acetate 1,200 mg once daily. The mechanism for this reduction is unknown, but could be due to interference of transporter activity for rosuvastatin alone or in combination with induction of its metabolism. Since the relationship between exposure and drug activity is unclear, the monitoring of response to therapy (e.g., cholesterol levels) is recommended.

Warfarin
Co-administration of eslicarbazepine acetate 1,200 mg once daily 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 the first weeks after initiation or ending concomitant treatment of warfarin and eslicarbazepine acetate.

Digoxin
A study in healthy subjects showed no effect of eslicarbazepine acetate 1,200 mg once daily on digoxin pharmacokinetics, suggesting that eslicarbazepine acetate has no effect on the transporter P-glycoprotein.

Monoamino Oxidase Inhibitors (MAOIs)

Based on a structural relationship of eslicarbazepine acetate to tricyclic antidepressants, an interaction between eslicarbazepine acetate and MAOIs is theoretically possible.

4.6 Fertility, pregnancy and lactation

Risk related to epilepsy and antiepileptic medicinal products in general
It has been shown that in the offspring of women with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic medicinal product therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practised whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of child-bearing potential. The need for antiepileptic therapy should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both mother and child.

Women of childbearing potential/contraception
Eslicarbazepine acetate adversely interacts with oral contraceptives. Therefore, an alternative, effective and safe method of contraception should be used during treatment and up to the end of the current menstrual cycle after treatment has been stopped.

Pregnancy
There are no data from the use of eslicarbazepine acetate in pregnant women. Studies in animals have shown reproductive toxicity (see Fertility). If women receiving eslicarbazepine acetate become pregnant or plan to become pregnant, the use of Zebinix should be carefully re-evaluated. Minimum effective doses should be given, and monotherapy whenever possible should be preferred at least during the first three months of pregnancy. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity to antenatal screening.

Monitoring and prevention
Antiepileptic medicinal products may contribute to folic acid deficiency, a possible contributory cause of foetal abnormality. Folic acid supplementation is recommended before and during pregnancy. As the efficacy of this supplementation is not proven, a specific antenatal diagnosis can be offered even for women with a supplementary treatment of folic acid.

In the newborn child
Bleeding disorders in the newborn caused by antiepileptic medicinal products 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.

Breast-feeding
It is unknown whether eslicarbazepine acetate is excreted in human milk. Animal studies have shown excretion of eslicarbazepine in breast milk. As a risk to the breast-fed child cannot be excluded breast-feeding should be discontinued during treatment with eslicarbazepine acetate.

Fertility
There are no data on the effects of eslicarbazepine acetate on human fertility. Studies in animals have shown impairment of fertility after treatment with eslicarbazepine acetate (see section 5.3).

4.7 Effects on ability to drive and use machines

Zebinix has minor to moderate influence on the ability to drive and use machines. Some patients might experience dizziness, somnolence or visual disorders, particularly on initiation of treatment. Therefore, patients should be advised that their physical and/ or mental abilities needed for operating machinery

or driving may be impaired and they are recommended not to do so until it has been established that their ability to perform such activities is not affected.

4.8 Undesirable effects

Summary of the safety profile

In placebo-controlled studies involving 1.842 adult and 427 paediatric patients with partial-onset seizures (1,520 patients treated with eslicarbazepine acetate and 749 treated with placebo), 48.9% of patients treated with eslicarbazepine acetate and 26% of patients treated with placebo experienced adverse reactions.

Adverse reactions were usually mild to moderate in intensity and occurred predominantly during the first weeks of treatment with eslicarbazepine acetate.

The risks that have been identified for Zebinix are mainly class-based, dose-dependent undesirable effects. The most common adverse reactions reported in clinical studies with adult epileptic patients, both in placebo and eslicarbazepine acetate groups were dizziness, somnolence, headache, and nausea. The majority of adverse reactions were reported in <3% of subjects in any treatment group.

Tabulated list of adverse reactions

The following convention has been used for the classification of adverse reactions very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and not known (frequency cannot be estimated from available data). Within each frequency category, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions associated with Zebinix obtained from adjunctive therapy in clinical studies and post-marketing surveillance

System Organ Class	**Very common**	**Common**	**Uncommon**		**Not known**
Blood and lymphatic system disorders			Anaemia		Thrombocytopenia,leukopenia
Immune system disorders			Hypersensitivity		
Endocrine disorders			Hypothyroidism		
Metabolism and nutrition disorders		Hyponatraemia, decreased appetite	Electrolyte imbalance, dehydration, hypochloraemia		
Psychiatric disorders		Insomnia	Psychotic disorder, apathy, depression, nervousness, agitation, irritability, attention deficit/ hyperactivity disorder, confusional state, mood swings, crying, psychomotor retardation		

Nervous system disorders	Dizziness, somnolence	Headache, disturbance in attention, tremor, ataxia, balance disorder	Coordination abnormal, memory impairment, amnesia, hypersomnia, sedation, aphasia, dysaesthesia, dystonia, lethargy, parosmia, cerebellar syndrome, convulsion, peripheral neuropathy, nystagmus, speech disorder, dysarthria, burning sensation, paraesthesia, migraine		
Eye disorders		Diplopia, vision blurred	Visual impairment, oscillopsia, binocular eye movement disorder, ocular hyperaemia		
Ear and labyrinth disorders		Vertigo	Hypoacusis, tinnitus		
Cardiac disorders			Palpitations, bradycardia		
Vascular disorders			Hypertension (including hypertensive crisis), hypotension, orthostatic hypotension, flushing, peripheral coldness		
Respiratory, thoracic and mediastinal disorders			Epistaxis, chest pain		

Gastrointestinal disorders		Nausea, vomiting, diarrhoea	Constipation, dyspepsia, gastritis, abdominal pain, dry mouth, abdominal discomfort, abdominal distension, gingivitis, melaena, toothache		Pancreatitis
Hepatobiliary disorders			Liver disorder		
Skin and subcutaneous tissue disorders		Rash	Alopecia, dry skin, hyperhidrosis, erythema, skin disorder, pruritus, dermatitis allergic		Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders			Myalgia, bone metabolism disorder, muscular weakness, pain in extremity		
Renal and urinary disorders			Urinary tract infection		
General disorders and administration site conditions		Fatigue, gait disturbance, asthenia	Malaise, chills, oedema peripheral		
Investigations			Blood pressure decreased, weight decreased, blood pressure increased, blood sodium decreased, blood chloride decreased, osteocalcin increased, haematocrit decreased, haemoglobin decreased, transaminases increased		

Injury, poisoning and procedural complications			Drug toxicity, fall, thermal burn		

Description of selected adverse reactions

Eye and nervous system disorders
In patients concomitantly treated with carbamazepine and eslicarbazepine acetate in placebo-controlled studies, the following adverse reactions were observed: diplopia (11.4% of subjects with concomitant carbamazepine, 2.4% of subjects without concomitant carbamazepine), abnormal coordination (6.7% with concomitant carbamazepine, 2.7% without concomitant carbamazepine), and dizziness (30.0% with concomitant carbamazepine, 11.5% without concomitant carbamazepine), see section 4.5.

PR interval
The use of eslicarbazepine acetate is associated with increase in the PR interval. Adverse reactions associated with PR interval prolongation (e.g. AV block, syncope, bradycardia) may occur.

Class related adverse reactions
Rare adverse reactions such as bone marrow depression, anaphylactic reactions, severe cutaneous reactions (e.g. Stevens-Johnson Syndrome), systemic lupus erythematosus or serious cardiac arrhythmias did not occur during the placebo-controlled studies of the epilepsy program with eslicarbazepine acetate. However, they have been reported with oxcarbazepine. Therefore, their occurrence after treatment with eslicarbazepine acetate cannot be excluded.

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with the structurally related antiepileptic drugs carbamazepine and oxcarbazepine. The mechanism by which bone metabolism is affected has not been identified.

Paediatric population

In placebo-controlled studies involving patients aged from 2 to 18 years with partial-onset seizures (238 patients treated with eslicarbazepine acetate and 189 with placebo), 35.7% of patients treated with eslicarbazepine acetate and 19% of patients treated with placebo experienced adverse reactions. The most common adverse reaction in the group treated with eslicarbazepine acetate were diplopia (5.0%), somnolence (8.0%) and vomiting (4.6%).

The adverse reaction profile of eslicarbazepine acetate is generally similar across age goups. In the age group from 6 to 11 years of age, the most common adverse reactions observed in more than two patients treated with eslicarbazepine acetate were diplopia (9.5%), somnolence (7.4%), diziness (6.3%), convulsion (6.3%) and nausea (3.2%); in the age group from 12 to 18 years were somnolence (7.4%), vomiting (4.2%), diplopia (3.2%) and fatigue (3.2%). The safety of Zebinix in children aged 6 years and below has not yet been established.

The safety profile of eslicarbazepine acetate was generally similar between adult and paediatric patients, except for agitation (common, 1.3%) and abdominal pain (common, 2.1%) which were more common in children than in adults. Dizziness; somnolence; vertigo; asthenia; gait disturbance; tremor; ataxia; balance disorder; vision blurred; diarrhoea and rash were less common in children than in adults. Hyponatraemia was only reported in adult population. Dermatitis allergic (uncommon, 0.8%) was reported only in the paediatric population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Central nervous symptoms such as vertigo, walking instability and hemi-paresis have been observed with accidental eslicarbazepine acetate overdose. There is no known specific antidote. Symptomatic and supportive treatment should be administered as appropriate. Eslicarbazepine acetate metabolites can effectively be cleared by haemodialysis, if necessary (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, carboxamide derivatives, ATC code: N03AF04

Mechanism of action

The precise mechanisms of action of eslicarbazepine acetate are unknown. However, in vitro electrophysiological studies indicate that both eslicarbazepine acetate and its metabolites stabilise the inactivated state of voltage-gated sodium channels, preventing their return to the activated state and thereby sustaining repetitive neuronal firing.

Pharmacodynamic effect

Eslicarbazepine acetate and its active metabolites prevented the development of seizures in nonclinical models predictive of anticonvulsant efficacy in man. In humans, the pharmacological activity of eslicarbazepine acetate is primarily exerted through the active metabolite eslicarbazepine.

Clinical efficacy and safety

Adult population
The efficacy and safety of eslicarbazepine acetate has been demonstrated in four phase III double-blind placebo-controlled studies in 1,703 randomized adult patients with partial epilepsy refractory to treatment with one to three concomitant antiepileptic medicinal products. Oxcarbazepine and felbamate were not allowed as concomitant medicinal products in these studies. Eslicarbazepine acetate was tested at doses of 400 mg (in -301 and -302 studies only), 800 mg and 1,200 mg, once daily. Eslicarbazepine acetate 800 mg once daily and 1,200 mg once daily were significantly more effective than placebo in reducing seizure frequency over a 12-week maintenance period. The percentage of subjects with ≥50% reduction (1581 analyzed) in seizure frequency in the phase III studies was 19.3% for placebo, 20.8% for eslicarbazepine acetate 400 mg, 30.5% for eslicarbazepine acetate 800 mg and 35.3% for eslicarbazepine acetate 1,200 mg daily.

Elderly population
The safety and efficacy of eslicarbazepine acetate as adjunctive therapy for partial seizures in elderly patients were evaluated in one non-controlled study, with a duration of 26 weeks, in 72 elderly (aged ≥ 65 years). The data shows that the incidence of adverse reactions in this population (65.3 %) is similar to the general population enrolled in the double-blind epilepsy studies (66.8%).The most frequent individual adverse reactions were dizziness (12.5% of subjects), somnolence (9.7%), fatigue, convulsion and hyponatraemia (8.3%, each), nasopharyngitis (6.9%) and upper respiratory tract infection (5.6%). A total of 50 of the 72 subjects starting the study completed the 26-week treatment period that corresponds to a retention rate of 69.4% (see section 4.2 for information on elderly use).

Paediatric population

The efficacy and safety of eslicarbazepine acetate as adjunctive therapy for partial-onset seizures in children was evaluated in one phase II study in children aged from 6 to 16 years (N=123) and one phase III study in children aged from 2 to 18 years (N=304). Both studies were double-blind and placebo controlled with a duration of maintenance of 8 weeks (study 208) and 12 weeks (study 305), respectively. Eslicarbazepine acetate was tested at doses of 20 and 30 mg/kg/day, up to a maximum of 1,200 mg/day. The target dose was 30 mg/kg/day in study 208 and 20 mg/kg/day in study 305. Doses could be adjusted based on tolerability and treatment response.

In the phase II study, evaluation of efficacy was a secondary objective. The least square mean reduction in standardised seizure frequency from baseline to maintenance period was significantly ($p<0.001$) higher with eslicarbazepine acetate (-34.8%) compared to placebo (-13.8%). Forty-two patients (50.6%) in the eslicarbazepine acetate group compared to 10 patients (25.0%) in the placebo group were responders (≥50% reduction of standardised seizure frequency), resulting in a significant difference ($p=0.009$).

In the phase III study, the least square mean reduction in standardised seizure frequency with eslicarbazepine acetate (-18.1% versus baseline) was different to placebo (-8.6% versus baseline) but not statistically significant ($p=0.2490$). Forty-one patients (30.6%) in the eslicarbazepine acetate group compared to 40 patients (31.0%) in the placebo group were responders (≥50% reduction of standardised seizure frequency), resulting in a non-significant difference ($p=0.9017$). *Post-hoc* subgroup analyses for the phase III study were conducted by age strata and above 6 years, as well as by dose. In children above 6 years, 36 patients (35.0%) in the eslicarbazepine acetate group compared to 29 patients (30.2%) in the placebo group were responders ($p=0.4759$) and the least square mean reduction in standardised seizure frequency was higher in the eslicarbazepine acetate group compared to placebo (-24.4% versus -10.5%); however, the difference of 13.9% was not statistically significant ($p=0.1040$). A total of 39% patients in study 305 were up titrated to the maximum possible dose (30 mg/kg/day). Amongst these, when excluding patients aged 6 years and younger, 14 (48.3%) and 11 (30.6%) of patients in the eslicarbazepine acetate and placebo group, respectively, were responders ($p=0.1514$). Although the robustness of these *post-hoc* subgroup analyses is limited, the data suggest an age and dose dependent increase in effect size.

The European Medicines Agency has deferred the obligation to submit the results of studies with Zebinix in one or more subsets of the paediatric population in the treatment of epilepsy with partial onset seizures (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Eslicarbazepine acetate is extensively converted to eslicarbazepine. Plasma levels of eslicarbazepine acetate usually remain below the limit of quantification, following oral administration. Eslicarbazepine C_{max} is attained at 2 to 3 hours post-dose (t_{max}). Bioavailability may be assumed as high because the amount of metabolites recovered in urine corresponded to more than 90% of an eslicarbazepine acetate dose.

Distribution

The binding of eslicarbazepine to plasma proteins is relatively low (<40%) and independent from concentration. *In vitro* studies have shown that plasma protein binding was not relevantly affected by the presence of warfarin, diazepam, digoxin, phenytoin and tolbutamide. The binding of warfarin, diazepam, digoxin, phenytoin and tolbutamide was not significantly affected by the presence of eslicarbazepine.

Biotransformation

Eslicarbazepine acetate is rapidly and extensively biotransformed to its major active metabolite eslicarbazepine by hydrolytic first-pass metabolism. The steady state plasma concentrations are attained after 4 to 5 days of once daily dosing, consistent with an effective half-life in the order of 20-24 hours. In studies in healthy subjects and epileptic adult patients, the apparent half-life of

eslicarbazepine was 10-20 hours and 13-20 hours, respectively. Minor metabolites in plasma are R-licarbazepine and oxcarbazepine, which were shown to be active, and the glucuronic acid conjugates of eslicarbazepine acetate, eslicarbazepine, R-licarbazepine and oxcarbazepine.

Eslicarbazepine acetate does not affect its own metabolism or clearance.

Eslicarbazepine is a weak inducer of CYP3A4 and has inhibiting properties with respect to CYP2C19 (as stated in section 4.5).

In studies with eslicarbazepine in fresh human hepatocytes a mild induction of UGT1A1 mediated glucuronidation was observed.

Elimination
Eslicarbazepine acetate metabolites are eliminated from the systemic circulation primarily by renal excretion, in the unchanged and glucuronide conjugate forms. In total, eslicarbazepine and its glucuronide correspond to more than 90% of total metabolites excreted in urine, approximately two thirds in the unchanged form and one third as glucuronide conjugate.

Linearity/non-linearity
The pharmacokinetics of eslicarbazepine acetate is linear and dose-proportional in the range 400-1,200 mg both in healthy subjects and patients.

Elderly (over 65 years of age)
The pharmacokinetic profile of eslicarbazepine acetate is unaffected in the elderly patients with creatinine clearance >60 ml/min (see section 4.2).

Renal impairment
Eslicarbazepine acetate metabolites are eliminated from the systemic circulation primarily by renal excretion. A study in adult patients with mild to severe renal impairment showed that clearance is dependent on renal function. During treatment with Zebinix dose adjustment is recommended in patients,adult and children above 6 years of age with creatinine clearance <60 ml/min (see section 4.2).
In children from 2 to 6 years of age, the use of eslicarbazepine acetate is not recommended. At this age the intrinsic activity of the elimination process has not yet reached maturation.

Haemodialysis removes eslicarbazepine acetate metabolites from plasma.

Hepatic impairment
The pharmacokinetics and metabolism of eslicarbazepine acetate were evaluated in healthy subjects and moderately liver-impaired patients after multiple oral doses. Moderate hepatic impairment did not affect the pharmacokinetics of eslicarbazepine acetate. No dose adjustment is recommended in patients with mild to moderate liver impairment (see section 4.2).
The pharmacokinetics of eslicarbazepine acetate has not been evaluated in patients with severe hepatic impairment.

Gender
Studies in healthy subjects and patients showed that pharmacokinetics of eslicarbazepine acetate were not affected by gender.

Paediatric population

Similar to adults, eslicarbazepine acetate is extensively converted to eslicarbazepine. Plasma levels of eslicarbazepine acetate usually remain below the limit of quantification, following oral administration. Eslicarbazepine C_{max} is attained at 2 to 3 hours post-dose (t_{max}). Body weight was shown to have an effect on volume of distribution and clearance. Furthermore, a role of age independently of weight

with regards to clearance of eslicarbazepine acetate could not be excluded, in particular for the youngest age group (2-6 years).

Children aged 6 years and below
Population pharmacokinetics indicate that in the subgroup of children aged from 2 to 6 years, doses of 27.5 mg/kg/day and 40 mg/kg/day are required in order to achieve exposures that are equivalent to the therapeutic doses of 20 and 30 mg/kg/day in children above 6 years of age.

Children above 6 years of age
Population pharmacokinetics indicate that comparable eslicarbazepine exposure is observed between 20 and 30 mg/kg/day in children above 6 years old and adults with 800 and 1200 mg of eslicarbazepine acetate once-daily, respectively (see section 4.2).

5.3 Preclinical safety data

Adverse reactions observed in animal studies occurred at exposure levels appreciably lower than the clinical exposure levels to eslicarbazepine (the principal and pharmacologically active metabolite of eslicarbazepine acetate). Safety margins based on comparative exposure have thus not been established.

Evidence of nephrotoxicity was observed in repeated dose-toxicity studies in the rat, but was not seen in studies in mice or dogs, and is consistent with an exacerbation of spontaneous chronic progressive nephropathy in this species.

Liver centrilobular hypertrophy was seen in repeated-dose toxicity studies in mice and rats and an increased incidence of liver tumours was observed in the carcinogenicity study in mice; these findings are consistent with an induction of hepatic microsomal enzymes, an effect which has not been observed in patients receiving eslicarbazepine acetate.

Juvenile animals studies
In repeat-dose studies in juvenile dogs, the toxicity profile was comparable to that observed in adult animals. In the 10-month study decreases in bone mineral content, bone area and/or bone mineral density in lumbar vertebrae and/or femur were observed in high-dose female animals at exposure levels lower than the clinical exposure levels to eslicarbazepine in children.

Genotoxicity studies with eslicarbazepine acetate indicate no special hazards for humans.

Impairment of fertility was observed in female rats; decreases in implantations and live embryos seen in the mouse fertility study may also indicate effects on female fertility, however, corpora lutea counts were not evaluated. Eslicarbazepine acetate was not teratogenic in the rat or rabbit, but did induce skeletal abnormalities in the mouse. Ossification delays, reduced foetal weights, an increase in minor skeletal and visceral anomalies were observed at maternal toxic doses in embryotoxicity studies in mice, rats and rabbits. A delay in the sexual development of the F1 generation was observed in peri/postnatal studies in mice and rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K 29/32
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium /Aluminium or PVC/Aluminium blisters placed into cardboard boxes containing 30 or 60 tablets.

HDPE bottles with polypropylene child resistant closure, placed into cardboard boxes, containing 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BIAL - Portela & Cª, SA
À Av. da Siderurgia Nacional
4745-457 S. Mamede do Coronado - Portugal
tel: +351 22 986 61 00
fax: +351 22 986 61 99
e-mail: info@bial.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/514/007-011

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21.04.2009

Date of latest renewal: 22.01.2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Zebinix 800 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 800 mg of eslicarbazepine acetate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White oblong tablets, engraved ‘ESL 800’on one side and scored on the other side, with a length of 19 mm. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zebinix is indicated as adjunctive therapy in adults, adolescents and children aged above 6 years with partial-onset seizures with or without secondary generalisation.

4.2 Posology and method of administration

Posology

Adults
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 (see section 5.1).
Special populations
Elderly (over 65 years of age)
No dose adjustment is needed in the elderly population provided that the renal function is not disturbed.

Renal impairment
Caution should be exercised in the treatment of patients, adult and children above 6 years of age, 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.
- CL_{CR} 30-60 ml/min: initial dose of 200 mg (or 5 mg/kg in children above 6 years) once daily or 400 mg (or 10 mg/kg in children above 6 years) every other day for 2 weeks followed by a once daily dose of 400 mg (or 10 mg/kg in children above 6 years). 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.
The pharmacokinetics of eslicarbazepine acetate has not been evaluated in patients with severe hepatic impairment (see sections 4.4 and 5.2) and use in these patients is, therefore, not recommended.

Paediatric population
Children above 6 years of age
The recommended starting dose is 10 mg/kg/day once daily. Dosage should be increased in weekly or bi-weekly increments of 10 mg/kg/day up to 30 mg/kg/daybased on individual response. the maximum dose is 1,200 mg once daily (see section 5.1).

Children with a body weight of ≥60 kg
Children with a body weight of 60 kg or more should be given the same dose as for adults.

The safety and efficacy of eslicarbazepine acetate in children aged 6 years and below has not yet been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Oral use.
Zebinix may be taken with or without food.

Switching preparations
Since comparative bioavailability data for the tablet and the suspension formulation are not available, switching patients from one formulation to the other should be done with caution.

4.3 Contraindications

Hypersensitivity to the active substance, to other carboxamide derivatives (e.g. carbamazepine, oxcarbazepine) or to any of the excipients listed in section 6.1.

Second or third degree atrioventricular (AV) block.

4.4 Special warnings and precautions for use

Suicidal ideation

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic active substances in several indications. A meta-analysis of randomised placebo-controlled trials of antiepileptic 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 disorders

Eslicarbazepine acetate has been associated with some central nervous system adverse reactions, such as dizziness and somnolence, which could increase the occurrence of accidental injury.

Other warnings and precautions

If Zebinix is to be discontinued it is recommended to withdraw it gradually to minimise the potential of increased seizure frequency.
There is no experience regarding the withdrawal of concomitant use of antiepileptic medicinal products during treatment with Zebinix (i.e. switching to monotherapy).

Cutaneous reactions

Rash developed as an adverse reaction in 1.1% of total population treated with Zebinix in placebo-controlled add-on studies in epileptic patients. If signs or symptoms of hypersensitivity develop, eslicarbazepine acetate must be discontinued.

HLA-B* 1502 allele - in Han Chinese, Thai and other Asian populations

HLA-B* 1502 in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing the severe cutaneous reactions known as Stevens Johnson syndrome (SJS) when treated with carbamazepine. The chemical structure of eslicarbazepine acetate is similar to that of carbamazepine, and it is possible that patients who are positive for HLA-B*1502 may also be at risk for SJS after treatment with eslicarbazepine acetate. The prevalence of HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations. Whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine or chemically-related active substances. If patients of these ethnic origins are tested positive for HLA- B*1502 allele, the use of eslicarbazepine acetate may be considered if the benefits are thought to exceed risks.
Because of the prevalence of this allele in other Asian populations (e.g, above 15% in the Philippines and Malaysia), testing genetically at risk populations for the presence of HLA- B*1502 may be considered.

HLA-A*3101 allele- European descent and Japanese populations

There are some data that suggest HLA-A*3101 is associated with an increased risk of carbamazepine induced cutaneous adverse drug reactions including SJS, TEN, Drug rash with eosinophilia (DRESS), or less severe acute generalized exanthematous pustulosis (AGEP) and maculopapular rash in people of European descent and the Japanese.
The frequency of the HLA-A*3101 allele varies widely between ethnic populations. HLA-A*3101 allele has a prevalence of 2 to 5% in European populations and about 10% in Japanese population. The presence of HLA-A*3101 allele may increase the risk for carbamazepine induced cutaneous reactions (mostly less severe) from 5.0% in general population to 26.0% among subjects of European ancestry, whereas its absence may reduce the risk from 5.0% to 3.8%.
There are insufficient data supporting a recommendation for HLA-A*3101 screening before starting carbamazepine or chemically-related compounds treatment.
If patients of European descent or Japanese origin are known to be positive for HLA-A*3101 allele, the use of carbamazepine or chemically-related compounds may be considered if the benefits are thought to exceed risks.

Hyponatraemia

Hyponatraemia has been reported as an adverse reaction in 1.2% of patients treated with Zebinix. Hyponatraemia is asymptomatic in most cases, however, it may be accompanied by clinical symptoms like worsening of seizures, confusion, decreased consciousness. Frequency of hyponatraemia increased with increasing eslicarbazepine acetate 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, carbamazepine), serum sodium levels should be examined before and during treatment with eslicarbazepine acetate. Furthermore, serum sodium levels should be determined if clinical signs of hyponatraemia occur. Apart from this, sodium levels should be determined during routine laboratory examination. If clinically-relevant hyponatraemia develops, eslicarbazepine acetate should be discontinued.

PR interval

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.

Renal impairment

Caution should be exercised in the treatment of patients with renal impairment and the dose should be adjusted according to creatinine clearance (see section 4.2). In patients with CL_{CR} <30 ml/min use is not recommended due to insufficient data.

Hepatic impairment

As clinical data are limited in patients with mild to moderate hepatic impairment and pharmacokinetic and clinical data are missing in patients with severe hepatic impairment, eslicarbazepine acetate should be used with caution in patients with mild to moderate hepatic impairment and is not recommended in patients with severe hepatic impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Eslicarbazepine acetate is extensively converted to eslicarbazepine, which is mainly eliminated by glucuronidation. *In vitro* eslicarbazepine is a weak inducer of CYP3A4 and UDP-glucuronyl transferases. *In vivo* eslicarbazepine showed an inducing effect on the metabolism of medicinal products that are mainly eliminated by metabolism through CYP3A4 (e.g. Simvastatin). Thus, an increase in the dose of the medicinal products that are mainly metabolised through CYP3A4 may be required, when used concomitantly with eslicarbazepine acetate. Eslicarbazepine *in vivo* may have an inducing effect on the metabolism of medicinal products that are mainly eliminated by conjugation through the UDP-glucuronyl transferases. When initiating or discontinuing treatment with Zebinix 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 Zebinix is being used just prior to or in combination with other medicinal products that require dose adjustment when co-administered with Zebinix. Eslicarbazepine has inhibiting properties with respect to CYP2C19. Thus, interactions can arise when co-administering high doses of eslicarbazepine acetate with medicinal products that are mainly metabolised by CYP2C19 (e.g. Phenytoin).

Interactions with other antiepileptic medicinal products

Carbamazepine
In a study in healthy subjects, concomitant administration of eslicarbazepine acetate 800 mg once daily and carbamazepine 400 mg twice daily resulted in an average decrease of 32% in exposure to the active metabolite eslicarbazepine, most likely caused by an induction of glucuronidation. No change in exposure to carbamazepine or its metabolite carbamazepine-epoxide was noted. Based on individual response, the dose of eslicarbazepine acetate may need to be increased if used concomitantly with carbamazepine. Results from patient studies showed that concomitant treatment increased the risk of the following adverse reactions: diplopia, abnormal coordination and dizziness. The risk of increase of other specific adverse reactions caused by co-administration of carbamazepine and eslicarbazepine acetate cannot be excluded.

Phenytoin
In a study in healthy subjects, concomitant administration of eslicarbazepine acetate 1,200 mg once daily and phenytoin resulted in an average decrease of 31-33% in exposure to the active metabolite, eslicarbazepine, most likely caused by an induction of glucuronidation, and an average increase of 31-35% in exposure to phenytoin, most likely caused by an inhibition of CYP2C19. Based on individual response, the dose of eslicarbazepine acetate may need to be increased and the dose of phenytoin may need to be decreased.

Lamotrigine
Glucuronidation is the major metabolic pathway for both eslicarbazepine and lamotrigine and therefore, an interaction could be expected. A study in healthy subjects with eslicarbazepine acetate

1,200 mg once daily showed a minor average pharmacokinetic interaction (exposure of lamotrigine decreased 15%) between eslicarbazepine acetate and lamotrigine and consequently no dose adjustments are required. However, due to inter-individual variability, the effect may be clinically relevant in some individuals.

Topiramate
In a study in healthy subjects, concomitant administration of eslicarbazepine acetate 1,200 mg once daily and topiramate showed no significant change in exposure to eslicarbazepine but an 18% decrease in exposure to topiramate, most likely caused by a reduced bioavailability of topiramate. No dose adjustment is required.

Valproate and levetiracetam
A population pharmacokinetics analysis of phase III studies in epileptic adult patients indicated that concomitant administration with valproate or levetiracetam did not affect the exposure to eslicarbazepine but this has not been verified by conventional interaction studies.

Oxcarbazepine
Concomitant use of eslicarbazepine acetate with oxcarbazepine is not recommended because this may cause overexposure to the active metabolites.

Other medicinal products

Oral contraceptives
Administration of eslicarbazepine acetate 1,200 mg once daily to female subjects using a combined oral contraceptive showed an average decrease of 37% and 42% in systemic exposure to levonorgestrel and ethinylestradiol, respectively, most likely caused by an induction of CYP3A4. Therefore, women of childbearing potential must use adequate contraception during treatment with Zebinix, and up to the end of the current menstruation cycle after the treatment has been discontinued (see section and 4.6).

Simvastatin
A study in healthy subjects showed an average decrease of 50% in systemic exposure to simvastatin when co-administered with eslicarbazepine acetate 800 mg once daily, most likely caused by an induction of CYP3A4. An increase of the simvastatin dose may be required when used concomitantly with eslicarbazepine acetate.

Rosuvastatin
There was an average decrease of 36-39% in systemic exposure in healthy subjects when co-administered with eslicarbazepine acetate 1,200 mg once daily. The mechanism for this reduction is unknown, but could be due to interference of transporter activity for rosuvastatin alone or in combination with induction of its metabolism. Since the relationship between exposure and drug activity is unclear, the monitoring of response to therapy (e.g., cholesterol levels) is recommended.

Warfarin
Co-administration of eslicarbazepine acetate 1,200 mg once daily 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 the first weeks after initiation or ending concomitant treatment of warfarin and eslicarbazepine acetate.

Digoxin
A study in healthy subjects showed no effect of eslicarbazepine acetate 1,200 mg once daily on digoxin pharmacokinetics, suggesting that eslicarbazepine acetate has no effect on the transporter P-glycoprotein.

Monoamino Oxidase Inhibitors (MAOIs)

Based on a structural relationship of eslicarbazepine acetate to tricyclic antidepressants, an interaction between eslicarbazepine acetate and MAOIs is theoretically possible.

4.6 Fertility, pregnancy and lactation

Risk related to epilepsy and antiepileptic medicinal products in general
It has been shown that in the offspring of women with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic medicinal product therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practised whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of child-bearing potential. The need for antiepileptic therapy should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both mother and child.

Women of childbearing potential/contraception
Eslicarbazepine acetate adversely interacts with oral contraceptives. Therefore, an alternative, effective and safe method of contraception should be used during treatment and up to the end of the current menstrual cycle after treatment has been stopped.

Pregnancy
There are no data from the use of eslicarbazepine acetate in pregnant women. Studies in animals have shown reproductive toxicity (see Fertility). If women receiving eslicarbazepine acetate become pregnant or plan to become pregnant, the use of Zebinix should be carefully re-evaluated. Minimum effective doses should be given, and monotherapy whenever possible should be preferred at least during the first three months of pregnancy. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity to antenatal screening.

Monitoring and prevention
Antiepileptic medicinal products may contribute to folic acid deficiency, a possible contributory cause of foetal abnormality. Folic acid supplementation is recommended before and during pregnancy. As the efficacy of this supplementation is not proven, a specific antenatal diagnosis can be offered even for women with a supplementary treatment of folic acid.

In the newborn child
Bleeding disorders in the newborn caused by antiepileptic medicinal products 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.

Breast-feeding
It is unknown whether eslicarbazepine acetate is excreted in human milk. Animal studies have shown excretion of eslicarbazepine in breast milk. As a risk to the breast-fed child cannot be excluded breast-feeding should be discontinued during treatment with eslicarbazepine acetate.

Fertility
There are no data on the effects of eslicarbazepine acetate on human fertility. Studies in animals have shown impairment of fertility after treatment with eslicarbazepine acetate (see section 5.3).

4.7 Effects on ability to drive and use machines

Zebinix has minor to moderate influence on the ability to drive and use machines. Some patients might experience dizziness, somnolence or visual disorders, particularly on initiation of treatment. Therefore, patients should be advised that their physical and/or mental abilities needed for operating machinery or

driving may be impaired and they are recommended not to do so until it has been established that their ability to perform such activities is not affected.

4.8 Undesirable effects

Summary of the safety profile

In placebo-controlled studies involving 1,842 adult and 427 paediatric patients with partial-onset seizures (1,520 patients treated with eslicarbazepine acetate and 749 treated with placebo), 48.9% of patients treated with eslicarbazepine acetate and 26% of patients treated with placebo experienced adverse reactions.

Adverse reactions were usually mild to moderate in intensity and occurred predominantly during the first weeks of treatment with eslicarbazepine acetate.

The risks that have been identified for Zebinix are mainly class-based, dose-dependent undesirable effects. The most common treatment-emergentadverse reactions reported in clinical studies with adult epileptic patients, both in placebo and eslicarbazepine acetate groups were dizziness, somnolence, headache, and nausea. The majority of adverse reactions were reported in <3% of subjects in any treatment group.

Tabulated list of adverse reactions

The following convention has been used for the classification of adverse reactions very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and not known (frequency cannot be estimated from available data). Within each frequency category, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions associated with Zebinix obtained from adjunctive therapy in clinical studies and post-marketing surveillance

System Organ Class	**Very common**	**Common**	**Uncommon**		**Not known**
Blood and lymphatic system disorders			Anaemia		Thrombocytopenia, leukopenia
Immune system disorders			Hypersensitivity		
Endocrine disorders			Hypothyroidism		
Metabolism and nutrition disorders		Hyponatraemia, decreased appetite	Electrolyte imbalance, dehydration, hypochloraemia		
Psychiatric disorders		Insomnia	Psychotic disorder, apathy, depression, nervousness, agitation, irritability, attention deficit/ hyperactivity disorder, confusional state, mood swings, crying, psychomotor retardation		

Nervous system disorders	Dizziness, somnolence	Headache, disturbance in attention, tremor, ataxia, balance disorder	Coordination abnormal, memory impairment, amnesia, hypersomnia, sedation, aphasia, dysaesthesia, dystonia, lethargy, parosmia, cerebellar syndrome, convulsion, peripheral neuropathy, nystagmus, speech disorder, dysarthria, burning sensation, paraesthesia, migraine		
Eye disorders		Diplopia, vision blurred	Visual impairment, oscillopsia, binocular eye movement disorder, ocular hyperaemia		
Ear and labyrinth disorders		Vertigo	Hypoacusis, tinnitus		
Cardiac disorders			Palpitations, bradycardia		
Vascular disorders			Hypertension (including hypertensive crisis), hypotension, orthostatic hypotension, flushing, peripheral coldness		
Respiratory, thoracic and mediastinal disorders			Epistaxis, chest pain		

Gastrointestinal disorders		Nausea, vomiting, diarrhoea	Constipation, dyspepsia, gastritis, abdominal pain, dry mouth, abdominal discomfort, abdominal distension, gingivitis , melaena, toothache		Pancreatitis
Hepatobiliary disorders			Liver disorder		
Skin and subcutaneous tissue disorders		Rash	Alopecia, dry skin, hyperhidrosis, erythema, skin disorder, pruritus, dermatitis allergic		Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders			Myalgia, bone metabolism disorder, muscular weakness, pain in extremity		
Renal and urinary disorders			Urinary tract infection		
General disorders and administration site conditions		Fatigue, gait disturbance, asthenia	Malaise, chills, oedema peripheral		
Investigations			Blood pressure decreased, weight decreased, blood pressure increased, blood sodium decreased, blood chloride decreased, osteocalcin increased, haematocrit decreased, haemoglobin decreased, transaminases increased		

Injury, poisoning and procedural complications			Drug toxicity, fall, thermal burn		

Description of selected adverse reactions

Eye and nervous system disorders
In patients concomitantly treated with carbamazepine and eslicarbazepine acetate in placebo-controlled studies, the following adverse reactions were observed: diplopia (11.4% of subjects with concomitant carbamazepine, 2.4% of subjects without concomitant carbamazepine), abnormal coordination (6.7% with concomitant carbamazepine, 2.7% without concomitant carbamazepine), and dizziness (30.0% with concomitant carbamazepine, 11.5% without concomitant carbamazepine), see section 4.5.

PR interval
The use of eslicarbazepine acetate is associated with increase in the PR interval. Adverse reactions associated with PR interval prolongation (e.g. AV block, syncope, bradycardia) may occur.

Class related adverse reactions
Rare adverse reactions such as bone marrow depression, anaphylactic reactions, severe cutaneous reactions (e.g. Stevens-Johnson Syndrome), systemic lupus erythematosus or serious cardiac arrhythmias did not occur during the placebo-controlled studies of the epilepsy program with eslicarbazepine acetate. However, they have been reported with oxcarbazepine. Therefore, their occurrence after treatment with eslicarbazepine acetate cannot be excluded.

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with the structurally related antiepileptic drugs carbamazepine and oxcarbazepine. The mechanism by which bone metabolism is affected has not been identified.

Paediatric population

In placebo-controlled studies involving patients aged from 2 to 18 years with partial-onset seizures (238 patients treated with eslicarbazepine acetate and 189 with placebo), 35.7% of patients treated with eslicarbazepine acetate and 19% of patients treated with placebo experienced adverse reactions. The most common adverse reaction in the group treated with eslicarbazepine acetate were diplopia (5.0%), somnolence (8.0%) and vomiting (4.6%).

The adverse reaction profile of eslicarbazepine acetate is generally similar across age goups. In the age group from 6 to 11 years of age, the most common adverse reaction observed in more than two patients treated with eslicarbazepine acetate were diplopia (9.5%), somnolence (7.4%), diziness (6.3%), convulsion (6.3%) and nausea (3.2%); in the age group from 12 to 18 years were somnolence (7.4%), vomiting (4.2%), diplopia (3.2%) and fatigue (3.2%). The safety of Zebinix in children aged 6 years and below has not yet been established.

The safety profile of eslicarbazepine acetate was generally similar between adult and paediatric patients, except for agitation (common, 1.3%) and abdominal pain (common, 2.1%) which were more common in children than in adults. Dizziness; somnolence; vertigo; asthenia; gait disturbance; tremor; ataxia; balance disorder; vision blurred; diarrhoea and rash were less common in children than in adults. Hyponatraemia was only reported in adult population. Dermatitis allergic (uncommon, 0.8%) was reported only in the paediatric population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Central nervous symptoms such as vertigo, walking instability and hemi-paresis have been observed with accidental eslicarbazepine acetate overdose. There is no known specific antidote. Symptomatic and supportive treatment should be administered as appropriate. Eslicarbazepine acetate metabolites can effectively be cleared by haemodialysis, if necessary (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, carboxamide derivatives, ATC code: N03AF04

Mechanism of action

The precise mechanisms of action of eslicarbazepine acetate are unknown. However, in vitro electrophysiological studies indicate that both eslicarbazepine acetate and its metabolites stabilise the inactivated state of voltage-gated sodium channels, preventing their return to the activated state and thereby sustaining repetitive neuronal firing.

Pharmacodynamic effect

Eslicarbazepine acetate and its active metabolites prevented the development of seizures in nonclinical models predictive of anticonvulsant efficacy in man. In humans, the pharmacological activity of eslicarbazepine acetate is primarily exerted through the active metabolite eslicarbazepine.

Clinical efficacy and safety

Adult population
The efficacy and safety of eslicarbazepine acetate has been demonstrated in four phase III double-blind placebo-controlled studies in 1,703 randomized adult patients with partial epilepsy refractory to treatment with one to three concomitant antiepileptic medicinal products. Oxcarbazepine and felbamate were not allowed as concomitant medicinal products in these studies. Eslicarbazepine acetate was tested at doses of 400 mg (in -301 and -302 studies only), 800 mg and 1,200 mg, once daily. Eslicarbazepine acetate 800 mg once daily and 1,200 mg once daily were significantly more effective than placebo in reducing seizure frequency over a 12-week maintenance period. The percentage of subjects with ≥50% reduction (1581 analyzed) in seizure frequency in the phase III studies was 19.3% for placebo, 20.8% for eslicarbazepine acetate 400 mg, 30.5% for eslicarbazepine acetate 800 mg and 35.3% for eslicarbazepine acetate 1,200 mg daily.

Elderly population
The safety and efficacy of eslicarbazepine acetate as adjunctive therapy for partial seizures in elderly patients were evaluated in one non-controlled study, with a duration of 26 weeks, in 72 elderly (aged ≥ 65 years). The data shows that the incidence of adverse reactions in this population (65.3 %) is similar to the general population enrolled in the double-blind epilepsy studies (66.8%).The most frequent individual adverse reactions were dizziness (12.5% of subjects), somnolence (9.7%), fatigue, convulsion and hyponatraemia (8.3%, each), nasopharyngitis (6.9%) and upper respiratory tract infection (5.6%). A total of 50 of the 72 subjects starting the study completed the 26-week treatment period that corresponds to a retention rate of 69.4% (see section 4.2 for information on elderly use).

Paediatric population

The efficacy and safety of eslicarbazepine acetate as adjunctive therapy for partial-onset seizures in children was evaluated in one phase II study in children aged from 6 to 16 years (N=123) and one phase III study in children aged from 2 to 18 years (N=304). Both studies were double-blind and placebo controlled with a duration of maintenance of 8 weeks (study 208) and 12 weeks (study 305), respectively. Eslicarbazepine acetate was tested at doses of 20 and 30 mg/kg/day, up to a maximum of 1,200 mg/day. The target dose was 30 mg/kg/day in study 208 and 20 mg/kg/day in study 305. Doses could be adjusted based on tolerability and treatment response.

In the phase II study, evaluation of efficacy was a secondary objective. The least square mean reduction in standardised seizure frequency from baseline to maintenance period was significantly ($p<0.001$) higher with eslicarbazepine acetate (-34.8%) compared to placebo (-13.8%). Forty-two patients (50.6%) in the eslicarbazepine acetate group compared to 10 patients (25.0%) in the placebo group were responders (≥50% reduction of standardised seizure frequency), resulting in a significant difference ($p=0.009$).

In the phase III study, the least square mean reduction in standardised seizure frequency with eslicarbazepine acetate (-18.1% versus baseline) was different to placebo (-8.6% versus baseline) but not statistically significant ($p=0.2490$). Forty-one patients (30.6%) in the eslicarbazepine acetate group compared to 40 patients (31.0%) in the placebo group were responders (≥50% reduction of standardised seizure frequency), resulting in a non-significant difference ($p=0.9017$). *Post-hoc* subgroup analyses for the phase III study were conducted by age strata and above 6 years, as well as by dose. In children above 6 years, 36 patients (35.0%) in the eslicarbazepine acetate group compared to 29 patients (30.2%) in the placebo group were responders ($p=0.4759$) and the least square mean reduction in standardised seizure frequency was higher in the eslicarbazepine acetate group compared to placebo (-24.4% versus -10.5%); however, the difference of 13.9% was not statistically significant ($p=0.1040$). A total of 39% patients in study 305 were up titrated to the maximum possible dose (30 mg/kg/day). Amongst these, when excluding patients aged 6 years and younger, 14 (48.3%) and 11 (30.6%) of patients in the eslicarbazepine acetate and placebo group, respectively, were responders ($p=0.1514$). Although the robustness of these *post-hoc* subgroup analyses is limited, the data suggest an age and dose dependent increase in effect size.

The European Medicines Agency has deferred the obligation to submit the results of studies with Zebinix in one or more subsets of the paediatric population in the treatment of epilepsy with partial onset seizures (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Eslicarbazepine acetate is extensively converted to eslicarbazepine. Plasma levels of eslicarbazepine acetate usually remain below the limit of quantification, following oral administration. Eslicarbazepine C_{max} is attained at 2 to 3 hours post-dose (t_{max}). Bioavailability may be assumed as high because the amount of metabolites recovered in urine corresponded to more than 90% of an eslicarbazepine acetate dose.

Distribution

The binding of eslicarbazepine to plasma proteins is relatively low (<40%) and independent from concentration. *In vitro* studies have shown that plasma protein binding was not relevantly affected by the presence of warfarin, diazepam, digoxin, phenytoin and tolbutamide. The binding of warfarin, diazepam, digoxin, phenytoin and tolbutamide was not significantly affected by the presence of eslicarbazepine.

Biotransformation

Eslicarbazepine acetate is rapidly and extensively biotransformed to its major active metabolite eslicarbazepine by hydrolytic first-pass metabolism. The steady state plasma concentrations are attained after 4 to 5 days of once daily dosing, consistent with an effective half-life in the order of 20-24 hours. In studies in healthy subjects and epileptic adult patients, the apparent half-life of

eslicarbazepine was 10-20 hours and 13-20 hours, respectively. Minor metabolites in plasma are R-licarbazepine and oxcarbazepine, which were shown to be active, and the glucuronic acid conjugates of eslicarbazepine acetate, eslicarbazepine, R-licarbazepine and oxcarbazepine.

Eslicarbazepine acetate does not affect its own metabolism or clearance.

Eslicarbazepine is a weak inducer of CYP3A4 and has inhibiting properties with respect to CYP2C19 (as stated in section 4.5).

In studies with eslicarbazepine in fresh human hepatocytes a mild induction of UGT1A1 mediated glucuronidation was observed.

Elimination
Eslicarbazepine acetate metabolites are eliminated from the systemic circulation primarily by renal excretion, in the unchanged and glucuronide conjugate forms. In total, eslicarbazepine and its glucuronide correspond to more than 90% of total metabolites excreted in urine, approximately two thirds in the unchanged form and one third as glucuronide conjugate.

Linearity/non-linearity
The pharmacokinetics of eslicarbazepine acetate is linear and dose-proportional in the range 400-1,200 mg both in healthy subjects and patients.

Elderly (over 65 years of age)
The pharmacokinetic profile of eslicarbazepine acetate is unaffected in the elderly patients with creatinine clearance >60 ml/min (see section 4.2).

Renal impairment
Eslicarbazepine acetate metabolites are eliminated from the systemic circulation primarily by renal excretion. A study in adult patients with mild to severe renal impairment showed that clearance is dependent on renal function. During treatment with Zebinix dose adjustment is recommended in patients, adult and children above 6 years of age with creatinine clearance <60 ml/min (see section 4.2).
In children from 2 to 6 years of age, the use of eslicarbazepine acetate is not recommended. At this age the intrinsic activity of the elimination process has not yet reached maturation.

Haemodialysis removes eslicarbazepine acetate metabolites from plasma.

Hepatic impairment
The pharmacokinetics and metabolism of eslicarbazepine acetate were evaluated in healthy subjects and moderately liver-impaired patients after multiple oral doses. Moderate hepatic impairment did not affect the pharmacokinetics of eslicarbazepine acetate. No dose adjustment is recommended in patients with mild to moderate liver impairment (see section 4.2).
The pharmacokinetics of eslicarbazepine acetate has not been evaluated in patients with severe hepatic impairment.

Gender
Studies in healthy subjects and patients showed that pharmacokinetics of eslicarbazepine acetate were not affected by gender.

Paediatric population

Similar to adults, eslicarbazepine acetate is extensively converted to eslicarbazepine. Plasma levels of eslicarbazepine acetate usually remain below the limit of quantification, following oral administration. Eslicarbazepine C_{max} is attained at 2 to 3 hours post-dose (t_{max}). Body weight was shown to have an effect on volume of distribution and clearance. Furthermore, a role of age independently of weight

with regards to clearance of eslicarbazepine acetate could not be excluded, in particular for the youngest age group (2-6 years).

Children aged 6 years and below
Population pharmacokinetics indicate that in the subgroup of children aged from 2 to 6 years, doses of 27.5 mg/kg/day and 40 mg/kg/day are required in order to achieve exposures that are equivalent to the therapeutic doses of 20 and 30 mg/kg/day in children above 6 years of age.

Children above 6 years of age
Population pharmacokinetics indicate that comparable eslicarbazepine exposure is observed between 20 and 30 mg/kg/day in children above 6 years old and adults with 800 and 1200 mg of eslicarbazepine acetate once-daily, respectively (see section 4.2).

5.3 Preclinical safety data

Adverse reactions observed in animal studies occurred at exposure levels appreciably lower than the clinical exposure levels to eslicarbazepine (the principal and pharmacologically active metabolite of eslicarbazepine acetate). Safety margins based on comparative exposure have thus not been established.

Evidence of nephrotoxicity was observed in repeated dose-toxicity studies in the rat, but was not seen in studies in mice or dogs, and is consistent with an exacerbation of spontaneous chronic progressive nephropathy in this species.

Liver centrilobular hypertrophy was seen in repeated-dose toxicity studies in mice and rats and an increased incidence of liver tumours was observed in the carcinogenicity study in mice; these findings are consistent with an induction of hepatic microsomal enzymes, an effect which has not been observed in patients receiving eslicarbazepine acetate.

Juvenile animals studies
In repeat-dose studies in juvenile dogs, the toxicity profile was comparable to that observed in adult animals. In the 10-month study decreases in bone mineral content, bone area and/or bone mineral density in lumbar vertebrae and/or femur were observed in high-dose female animals at exposure levels lower than the clinical exposure levels to eslicarbazepine in children.

Genotoxicity studies with eslicarbazepine acetate indicate no special hazards for humans.

Impairment of fertility was observed in female rats; decreases in implantations and live embryos seen in the mouse fertility study may also indicate effects on female fertility, however, corpora lutea counts were not evaluated. Eslicarbazepine acetate was not teratogenic in the rat or rabbit, but did induce skeletal abnormalities in the mouse. Ossification delays, reduced foetal weights, an increase in minor skeletal and visceral anomalies were observed at maternal toxic doses in embryotoxicity studies in mice, rats and rabbits. A delay in the sexual development of the F1 generation was observed in peri/postnatal studies in mice and rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K 29/32
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium / Aluminium or PVC/Aluminium blisters placed into cardboard boxes containing 20, 30, 60 or 90 tablets.

HDPE bottles with polypropylene child resistant closure, placed into cardboard boxes, containing 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BIAL - Portela & Cª, SA
À Av. da Siderurgia Nacional 4745-457 S. Mamede do Coronado - Portugal
tel: +351 22 986 61 00
fax: +351 22 986 61 99
e-mail: info@bial.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/514/012-020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21.04.2009

Date of latest renewal: 22.01.2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Zebinix 50 mg/ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral suspension contains 50 mg of eslicarbazepine acetate.

Excipients with known effect:

Each ml of oral suspension contains 2.0 mg of methyl parahydroxybenzoate (E218) and approximately 0.00001 mg of sulphites.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension.
Off-white to white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zebinix is indicated as adjunctive therapy in adults, adolescents and children aged above 6 years, with partial-onset seizures with or without secondary generalisation.

4.2 Posology and method of administration

Posology

Adults
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 (see section 5.1).

Special populations

Elderly (over 65 years of age)
No dose adjustment is needed in the elderly population provided that the renal function is not disturbed.

Renal impairment
Caution should be exercised in the treatment of patients, adult and children above 6 years of age, 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.
- CL_{CR} 30-60 ml/min: initial dose of 200 mg (or 5 mg/kg in children above 6 years) once daily or 400 mg (or 10 mg/kg in children above 6 years)every other day for 2 weeks followed by a once daily dose of 400 mg (or 10 mg/kg in children above 6 years). 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.
The pharmacokinetics of eslicarbazepine acetate has not been evaluated in patients with severe hepatic impairment (see sections 4.4 and 5.2) and use in these patients is, therefore, not recommended.

Paediatric population
Children above 6 years of age
The recommended starting dose is 10 mg/kg/day once daily. Dosage should be increased in weekly or bi-weekly increments of 10 mg/kg/day up to 30 mg/kg/day,based on individual response. The maximum dose is1,200 mg once daily (see section 5.1).

Children with a body weight of ≥60 kg
Children with a body weight of 60 kg or more should be given the same dose as for adults.
The safety and efficacy of eslicarbazepine acetate in children aged 6 years and below has not yet been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Oral use.
Zebinix may be taken with or without food.

Switching preparations
Since comparative bioavailability data for the tablet and the suspension formulation are not available, switching patients from one formulation to the other should be done with caution.

4.3 Contraindications

Hypersensitivity to the active substance, to other carboxamide derivatives (e.g. carbamazepine, oxcarbazepine) or to any of the excipients listed in section 6.1.

Second or third degree atrioventricular (AV) block.

4.4 Special warnings and precautions for use

Suicidal ideation

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic active substances in several indications. A meta-analysis of randomised placebo-controlled trials of antiepileptic 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 disorders

Eslicarbazepine acetate has been associated with some central nervous system adverse reactions, such as dizziness and somnolence, which could increase the occurrence of accidental injury.

Other warnings and precautions

If Zebinix is to be discontinued it is recommended to withdraw it gradually to minimise the potential of increased seizure frequency.
There is no experience regarding the withdrawal of concomitant use of antiepileptic medicinal products during treatment with Zebinix (i.e. switching to monotherapy).

Cutaneous reactions

Rash developed as an adverse reaction in 1.1% of total population treated with Zebinix in placebo-controlled add-on studies in epileptic patients. If signs or symptoms of hypersensitivity develop, eslicarbazepine acetate must be discontinued.

HLA-B* 1502 allele - in Han Chinese, Thai and other Asian populations

HLA-B* 1502 in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing the severe cutaneous reactions known as Stevens Johnson syndrome (SJS) when treated with carbamazepine. The chemical structure of eslicarbazepine acetate is similar to that of carbamazepine, and it is possible that patients who are positive for HLA-B*1502 may also be at risk for SJS after treatment with eslicarbazepine acetate. The prevalence of HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations. Whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine or chemically-related active substances. If patients of these ethnic origins are tested positive for HLA- B*1502 allele, the use of eslicarbazepine acetate may be considered if the benefits are thought to exceed risks.
Because of the prevalence of this allele in other Asian populations (e.g, above 15% in the Philippines and Malaysia), testing genetically at risk populations for the presence of HLA- B*1502 may be considered.

HLA-A*3101 allele- European descent and Japanese populations

There are some data that suggest HLA-A*3101 is associated with an increased risk of carbamazepine induced cutaneous adverse drug reactions including SJS, TEN, Drug rash with eosinophilia (DRESS), or less severe acute generalized exanthematous pustulosis (AGEP) and maculopapular rash in people of European descent and the Japanese.
The frequency of the HLA-A*3101 allele varies widely between ethnic populations. HLA-A*3101 allele has a prevalence of 2 to 5% in European populations and about 10% in Japanese population. The presence of HLA-A*3101 allele may increase the risk for carbamazepine induced cutaneous reactions (mostly less severe) from 5.0% in general population to 26.0% among subjects of European ancestry, whereas its absence may reduce the risk from 5.0% to 3.8%.
There are insufficient data supporting a recommendation for HLA-A*3101 screening before starting carbamazepine or chemically-related compounds treatment.
If patients of European descent or Japanese origin are known to be positive for HLA-A*3101 allele, the use of carbamazepine or chemically-related compounds may be considered if the benefits are thought to exceed risks.

Hyponatraemia

Hyponatraemia has been reported as an adverse reaction in 1.2% of patients treated with Zebinix. Hyponatraemia is asymptomatic in most cases, however, it may be accompanied by clinical symptoms like worsening of seizures, confusion, decreased consciousness. Frequency of hyponatraemia increased with increasing eslicarbazepine acetate 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, carbamazepine), serum sodium levels should be examined before and during treatment with eslicarbazepine acetate. Furthermore, serum sodium levels should be determined if clinical signs of hyponatraemia occur. Apart from this, sodium levels should be determined during routine laboratory examination. If clinically-relevant hyponatraemia develops, eslicarbazepine acetate should be discontinued.

PR interval

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.

Renal impairment

Caution should be exercised in the treatment of patients with renal impairment and the dose should be adjusted according to creatinine clearance (see section 4.2). In patients with CLCR <30 ml/min use is not recommended due to insufficient data.

Hepatic impairment

As clinical data are limited in patients with mild to moderate hepatic impairment and pharmacokinetic and clinical data are missing in patients with severe hepatic impairment, eslicarbazepine acetate should be used with caution in patients with mild to moderate hepatic impairment and is not recommended in patients with severe hepatic impairment.

Zebinix oral suspension contains methyl parahydroxybenzoate (E218) which may cause allergic reactions (possibly delayed) and sulphites which may rarely cause severe hypersensitivity reactions and bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Eslicarbazepine acetate is extensively converted to eslicarbazepine, which is mainly eliminated by glucuronidation. *In vitro* eslicarbazepine is a weak inducer of CYP3A4 and UDP-glucuronyl transferases. *In vivo* eslicarbazepine showed an inducing effect on the metabolism of medicinal products that are mainly eliminated by metabolism through CYP3A4 (e.g. Simvastatin). Thus, an increase in the dose of the medicinal products that are mainly metabolised through CYP3A4 may be required, when used concomitantly with eslicarbazepine acetate. Eslicarbazepine *in vivo* may have an inducing effect on the metabolism of medicinal products that are mainly eliminated by conjugation through the UDP-glucuronyl transferases. When initiating or discontinuing treatment with Zebinix 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 Zebinix is being used just prior to or in combination with other medicinal products that require dose adjustment when co-administered with Zebinix. Eslicarbazepine has inhibiting properties with respect to CYP2C19. Thus, interactions can arise when co-administering high doses of eslicarbazepine acetate with medicinal products that are mainly metabolised by CYP2C19 (e.g. Phenytoin).

Interactions with other antiepileptic medicinal products

Carbamazepine
In a study in healthy subjects, concomitant administration of eslicarbazepine acetate 800 mg once daily and carbamazepine 400 mg twice daily resulted in an average decrease of 32% in exposure to the active metabolite eslicarbazepine, most likely caused by an induction of glucuronidation. No change in exposure to carbamazepine or its metabolite carbamazepine-epoxide was noted. Based on individual response, the dose of eslicarbazepine acetate may need to be increased if used concomitantly with carbamazepine. Results from patient studies showed that concomitant treatment increased the risk of the following adverse reactions: diplopia, abnormal coordination and dizziness. The risk of increase of other specific adverse reactions caused by co-administration of carbamazepine and eslicarbazepine acetate cannot be excluded.

Phenytoin
In a study in healthy subjects, concomitant administration of eslicarbazepine acetate 1,200 mg once daily and phenytoin resulted in an average decrease of 31-33% in exposure to the active metabolite,

eslicarbazepine, most likely caused by an induction of glucuronidation, and an average increase of 31-35% in exposure to phenytoin, most likely caused by an inhibition of CYP2C19. Based on individual response, the dose of eslicarbazepine acetate may need to be increased and the dose of phenytoin may need to be decreased.

Lamotrigine
Glucuronidation is the major metabolic pathway for both eslicarbazepine and lamotrigine and, therefore, an interaction could be expected. A study in healthy subjects with eslicarbazepine acetate 1,200 mg once daily showed a minor average pharmacokinetic interaction (exposure of lamotrigine decreased 15%) between eslicarbazepine acetate and lamotrigine and consequently no dose adjustments are required. However, due to inter-individual variability, the effect may be clinically relevant in some individuals.

Topiramate
In a study in healthy subjects, concomitant administration of eslicarbazepine acetate 1,200 mg once daily and topiramate showed no significant change in exposure to eslicarbazepine but an 18% decrease in exposure to topiramate, most likely caused by a reduced bioavailability of topiramate. No dose adjustment is required.

Valproate and levetiracetam
A population pharmacokinetics analysis of phase III studies in epileptic adult patients indicated that concomitant administration with valproate or levetiracetam did not affect the exposure to eslicarbazepine but this has not been verified by conventional interaction studies.

Oxcarbazepine
Concomitant use of eslicarbazepine acetate with oxcarbazepine is not recommended because this may cause overexposure to the active metabolites.

Other medicinal products

Oral contraceptives
Administration of eslicarbazepine acetate 1,200 mg once daily to female subjects using a combined oral contraceptive showed an average decrease of 37% and 42% in systemic exposure to levonorgestrel and ethinylestradiol, respectively, most likely caused by an induction of CYP3A4. Therefore, women of childbearing potential must use adequate contraception during treatment with Zebinix, and up to the end of the current menstruation cycle after the treatment has been discontinued (see section 4.6).

Simvastatin
A study in healthy subjects showed an average decrease of 50% in systemic exposure to simvastatin when co-administered with eslicarbazepine acetate 800 mg once daily, most likely caused by an induction of CYP3A4. An increase of the simvastatin dose may be required when used concomitantly with eslicarbazepine acetate.

Rosuvastatin
There was an average decrease of 36-39% in systemic exposure in healthy subjects when co-administered with eslicarbazepine acetate 1,200 mg once daily. The mechanism for this reduction is unknown, but could be due to interference of transporter activity for rosuvastatin alone or in combination with induction of its metabolism. Since the relationship between exposure and drug activity is unclear, the monitoring of response to therapy (e.g., cholesterol levels) is recommended.

Warfarin
Co-administration of eslicarbazepine acetate 1,200 mg once daily 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 the first weeks after initiation or ending concomitant treatment of warfarin and eslicarbazepine acetate.

Digoxin
A study in healthy subjects showed no effect of eslicarbazepine acetate 1,200 mg once daily on digoxin pharmacokinetics, suggesting that eslicarbazepine acetate has no effect on the transporter P-glycoprotein.

Monoamino Oxidase Inhibitors (MAOIs)
Based on a structural relationship of eslicarbazepine acetate to tricyclic antidepressants, an interaction between eslicarbazepine acetate and MAOIs is theoretically possible.

4.6 Fertility, pregnancy and lactation

Risk related to epilepsy and antiepileptic medicinal products in general
It has been shown that in the offspring of women with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic medicinal product therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practised whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of child-bearing potential. The need for antiepileptic therapy should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both mother and child.

Women of childbearing potential/contraception
Eslicarbazepine acetate adversely interacts with oral contraceptives. Therefore, an alternative, effective and safe method of contraception should be used during treatment and up to the end of the current menstrual cycle after treatment has been stopped.

Pregnancy
There are no data from the use of eslicarbazepine acetate in pregnant women. Studies in animals have shown reproductive toxicity (see Fertility). If women receiving eslicarbazepine acetate become pregnant or plan to become pregnant, the use of Zebinix should be carefully re-evaluated. Minimum effective doses should be given, and monotherapy whenever possible should be preferred at least during the first three months of pregnancy. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity to antenatal screening.

Monitoring and prevention
Antiepileptic medicinal products may contribute to folic acid deficiency, a possible contributory cause of foetal abnormality. Folic acid supplementation is recommended before and during pregnancy. As the efficacy of this supplementation is not proven, a specific antenatal diagnosis can be offered even for women with a supplementary treatment of folic acid.

In the newborn child
Bleeding disorders in the newborn caused by antiepileptic medicinal products 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.

Breast-feeding
It is unknown whether eslicarbazepine acetate is excreted in human milk. Animal studies have shown excretion of eslicarbazepine in breast milk. As a risk to the breast-fed child cannot be excluded breast-feeding should be discontinued during treatment with eslicarbazepine acetate.

Fertility

There are no data on the effects of eslicarbazepine acetate on human fertility. Studies in animals have shown impairment of fertility after treatment with eslicarbazepine acetate (see section 5.3).

4.7 Effects on ability to drive and use machines

Zebinix has minor to moderate influence on the ability to drive and use machines. Some patients might experience dizziness, somnolence or visual disorders, particularly on initiation of treatment. Therefore, patients should be advised that their physical and/or mental abilities needed for operating machinery or driving may be impaired and they are recommended not to do so until it has been established that their ability to perform such activities is not affected.

4.8 Undesirable effects

Summary of the safety profile
In placebo-controlled studies involving 1,842 adult and 427 paediatric patients with partial-onset seizures (1,520 patients treated with eslicarbazepine acetate and 749 treated with placebo), 48.9% of patients treated with eslicarbazepine acetate and 26% of patients treated with placebo experienced adverse reactions.

Adverse reactions were usually mild to moderate in intensity and occurred predominantly during the first weeks of treatment with eslicarbazepine acetate.

The risks that have been identified for Zebinix are mainly class-based, dose-dependent undesirable effects. The most common adverse reactions reported in clinical studies with adult epileptic patients, both in placebo and eslicarbazepine acetate groups were dizziness, somnolence, headache, and nausea. The majority of adverse reactions were reported in <3% of subjects in any treatment group.

Tabulated list of adverse reactions

The following convention has been used for the classification of adverse reactions very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and not known (frequency cannot be estimated from available data). Within each frequency category, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions associated with Zebinix obtained from adjunctive therapy in clinical studies and post-marketing surveillance

System Organ Class	Very common	Common	Uncommon	Not known
Blood and lymphatic system disorders			Anaemia	Thrombocytopenia, leukopenia
Immune system disorders			Hypersensitivity	
Endocrine disorders			Hypothyroidism	
Metabolism and nutrition disorders		Hyponatraemia, decreased appetite	Electrolyte imbalance, dehydration, hypochloraemia	

Psychiatric disorders		Insomnia	Psychotic disorder, apathy, depression, nervousness, agitation, irritability, attention deficit/ hyperactivity disorder, confusional state, mood swings, crying, psychomotor retardation	
Nervous system disorders	Dizziness, somnolence	Headache, disturbance in attention, tremor, ataxia, balance disorder	Coordination abnormal, memory impairment, amnesia, hypersomnia, sedation, aphasia, dysaesthesia, dystonia, lethargy, parosmia, cerebellar syndrome, convulsion, peripheral neuropathy, nystagmus, speech disorder, dysarthria, burning sensation, paraesthesia, migraine	
Eye disorders		Diplopia, vision blurred	Visual impairment, oscillopsia, binocular eye movement disorder, ocular hyperaemia	
Ear and labyrinth disorders		Vertigo	Hypoacusis, tinnitus	
Cardiac disorders			Palpitations, bradycardia	

Vascular disorders			Hypertension (including hypertensive crisis), hypotension, orthostatic hypotension, flushing, peripheral coldness	
Respiratory, thoracic and mediastinal disorders			Epistaxis, chest pain	
Gastrointestinal disorders		Nausea, vomiting, diarrhoea	Constipation, dyspepsia, gastritis, abdominal pain, dry mouth, abdominal discomfort, abdominal distension, gingivitis, melaena, toothache	Pancreatitis
Hepatobiliary disorders			Liver disorder	
Skin and subcutaneous tissue disorders		Rash	Alopecia, dry skin, hyperhidrosis, erythema, skin disorder, pruritus, dermatitis allergic	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders			Myalgia, bone metabolism disorder, muscular weakness, pain in extremity	
Renal and urinary disorders			Urinary tract infection	
General disorders and administration site conditions		Fatigue, gait disturbance, asthenia	Malaise, chills, oedema peripheral	

Investigations			Blood pressure decreased, weight decreased, blood pressure increased, blood sodium decreased, blood chloride decreased, osteocalcin increased, haematocrit decreased, haemoglobin decreased, transaminases increased	
Injury, poisoning and procedural complications			Drug toxicity, fall, thermal burn	

Description of selected adverse reactions

Eye and nervous system disorders
In patients concomitantly treated with carbamazepine and eslicarbazepine acetate in placebo-controlled studies, the following adverse reactions were observed: diplopia (11.4% of subjects with concomitant carbamazepine, 2.4% of subjects without concomitant carbamazepine), abnormal coordination (6.7% with concomitant carbamazepine, 2.7% without concomitant carbamazepine), and dizziness (30.0% with concomitant carbamazepine, 11.5% without concomitant carbamazepine), see section 4.5.

PR interval
The use of eslicarbazepine acetate is associated with increase in the PR interval. Adverse reactions associated with PR interval prolongation (e.g. AV block, syncope, bradycardia) may occur.

Class related adverse reactions
Rare adverse reactions such as bone marrow depression, anaphylactic reactions, severe cutaneous reactions (e.g. Stevens-Johnson Syndrome), systemic lupus erythematosus or serious cardiac arrhythmias did not occur during the placebo-controlled studies of the epilepsy program with eslicarbazepine acetate. However, they have been reported with oxcarbazepine. Therefore, their occurrence after treatment with eslicarbazepine acetate cannot be excluded.

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with the structurally related antiepileptic drugs carbamazepine and oxcarbazepine. The mechanism by which bone metabolism is affected has not been identified.

Paediatric population

In placebo-controlled studies involving patients aged from 2 to 18 years with partial-onset seizures (238 patients treated with eslicarbazepine acetate and 189 with placebo), 35.7% of patients treated with eslicarbazepine acetate and 19% of patients treated with placebo experienced adverse reactions. The most common adverse reaction in the group treated with eslicarbazepine acetate were diplopia (5.0%), somnolence (8.0%) and vomiting (4.6%).

The adverse reaction profile of eslicarbazepine acetate is generally similar across age goups. In the age group from 6 to 11 years of age, the most common adverse reaction observed in more than two patients treated with eslicarbazepine acetate were diplopia (9.5%), somnolence (7.4%), diziness (6.3%), convulsion (6.3%) and nausea (3.2%); in the age group from 12 to 18 years were somnolence (7.4%), vomiting (4.2%), diplopia (3.2%) and fatigue (3.2%). The safety of Zebinix in children aged 6 years and below has not yet been established.

The safety profile of eslicarbazepine acetate was generally similar between adult and paediatric patients, except for agitation (common, 1.3%) and abdominal pain (common, 2.1%) which were more common in children than in adults. Dizziness; somnolence; vertigo; asthenia; gait disturbance; tremor; ataxia; balance disorder; vision blurred; diarrhoea and rash were less common in children than in adults. Hyponatraemia was only reported in adult population. Dermatitis allergic (uncommon, 0.8%) was reported only in the paediatric population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Central nervous symptoms such as vertigo, walking instability and hemi-paresis have been observed with accidental eslicarbazepine acetate overdose. There is no known specific antidote. Symptomatic and supportive treatment should be administered as appropriate. Eslicarbazepine acetate metabolites can effectively be cleared by haemodialysis, if necessary (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, carboxamide derivatives, ATC code: N03AF04

Mechanism of action

The precise mechanisms of action of eslicarbazepine acetate are unknown. However, *in vitro* electrophysiological studies indicate that both eslicarbazepine acetate and its metabolites stabilise the inactivated state of voltage-gated sodium channels, preventing their return to the activated state and thereby sustaining repetitive neuronal firing.

Pharmacodynamic effect

Eslicarbazepine acetate and its active metabolites prevented the development of seizures in nonclinical models predictive of anticonvulsant efficacy in man. In humans, the pharmacological activity of eslicarbazepine acetate is primarily exerted through the active metabolite eslicarbazepine.

Clinical efficacy and safety

Adult population
The efficacy and safety of eslicarbazepine acetate has been demonstrated in four phase III double-blind placebo-controlled studies in 1,703 randomized adult patients with partial epilepsy refractory to treatment with one to three concomitant antiepileptic medicinal products. Oxcarbazepine and felbamate were not allowed as concomitant medicinal products in these studies. Eslicarbazepine acetate was tested at doses of 400 mg (in -301 and -302 studies only), 800 mg and 1,200 mg, once

daily. Eslicarbazepine acetate 800 mg once daily and 1,200 mg once daily were significantly more effective than placebo in reducing seizure frequency over a 12-week maintenance period. The percentage of subjects with ≥50% reduction (1581 analyzed) in seizure frequency in the phase III studies was 19.3% for placebo, 20.8% for eslicarbazepine acetate 400 mg, 30.5% for eslicarbazepine acetate 800 mg and 35.3% for eslicarbazepine acetate 1,200 mg daily.

Elderly population
The safety and efficacy of eslicarbazepine acetate as adjunctive therapy for partial seizures in elderly patients were evaluated in one non-controlled study, with a duration of 26 weeks, in 72 elderly (aged ≥ 65 years). The data shows that the incidence of adverse reactions in this population (65.3 %) is similar to the general population enrolled in the double-blind epilepsy studies (66.8%).The most frequent individual adverse reactions were dizziness (12.5% of subjects), somnolence (9.7%), fatigue, convulsion and hyponatraemia (8.3%, each), nasopharyngitis (6.9%) and upper respiratory tract infection (5.6%). A total of 50 of the 72 subjects starting the study completed the 26-week treatment period that corresponds to a retention rate of 69.4% (see section 4.2 for information on elderly use).

Paediatric population
The efficacy and safety of eslicarbazepine acetate as adjunctive therapy for partial-onset seizures in children was evaluated in one phase II study in children aged from 6 to 16 years (N=123) and one phase III study in children aged from 2 to 18 years (N=304). Both studies were double-blind and placebo controlled with a duration of maintenance of 8 weeks (study 208) and 12 weeks (study 305), respectively. Eslicarbazepine acetate was tested at doses of 20 and 30 mg/kg/day, up to a maximum of 1,200 mg/day. The target dose was 30 mg/kg/day in study 208 and 20 mg/kg/day in study 305. Doses could be adjusted based on tolerability and treatment response.

In the phase II study, evaluation of efficacy was a secondary objective, The least square mean reduction in standardised seizure frequency from baseline to maintenance period was significantly ($p<0.001$) higher with eslicarbazepine acetate (-34.8%) compared to placebo (-13.8%). Forty-two patients (50.6%) in the eslicarbazepine acetate group compared to 10 patients (25.0%) in the placebo group were responders (≥50% reduction of standardised seizure frequency), resulting in a significant difference ($p=0.009$).

In the phase III study, the least square mean reduction in standardised seizure frequency with eslicarbazepine acetate (-18.1% versus baseline) was different to placebo (-8.6% versus baseline) but not statistically significant ($p=0.2490$). Forty-one patients (30.6%) in the eslicarbazepine acetate group compared to 40 patients (31.0%) in the placebo group were responders (≥50% reduction of standardised seizure frequency), resulting in a non-significant difference ($p=0.9017$). *Post-hoc* subgroup analyses for the phase III study were conducted by age strata and above 6 years, as well as by dose. In children above 6 years, 36 patients (35.0%) in the eslicarbazepine acetate group compared to 29 patients (30.2%) in the placebo group were responders ($p=0.4759$) and the least square mean reduction in standardised seizure frequency was higher in the eslicarbazepine acetate group compared to placebo (-24.4% versus -10.5%); however, the difference of 13.9% was not statistically significant ($p=0.1040$). A total of 39% patients in study 305 were up titrated to the maximum possible dose (30 mg/kg/day). Amongst these, when excluding patients aged 6 years and younger, 14 (48.3%) and 11 (30.6%) of patients in the eslicarbazepine acetate and placebo group, respectively, were responders ($p=0.1514$). Although the robustness of these *post-hoc* subgroup analyses is limited, the data suggest an age and dose dependent increase in effect size.

The European Medicines Agency has deferred the obligation to submit the results of studies with Zebinix in one or more subsets of the paediatric population in the treatment of epilepsy with partial onset seizures (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Eslicarbazepine acetate is extensively converted to eslicarbazepine. Plasma levels of eslicarbazepine acetate usually remain below the limit of quantification, following oral administration. Eslicarbazepine C_{max} is attained at 2 to 3 hours post-dose (t_{max}). Bioavailability may be assumed as high because the amount of metabolites recovered in urine corresponded to more than 90% of an eslicarbazepine acetate dose.

Distribution
The binding of eslicarbazepine to plasma proteins is relatively low (<40%) and independent from concentration. *In vitro* studies have shown that plasma protein binding was not relevantly affected by the presence of warfarin, diazepam, digoxin, phenytoin and tolbutamide. The binding of warfarin, diazepam, digoxin, phenytoin and tolbutamide was not significantly affected by the presence of eslicarbazepine.

Biotransformation
Eslicarbazepine acetate is rapidly and extensively biotransformed to its major active metabolite eslicarbazepine by hydrolytic first-pass metabolism. The steady state plasma concentrations are attained after 4 to 5 days of once daily dosing, consistent with an effective half-life in the order of 20-24 hours. In studies in healthy subjects and epileptic adult patients, the apparent half-life of eslicarbazepine was 10-20 hours and 13-20 hours, respectively. Minor metabolites in plasma are R-licarbazepine and oxcarbazepine, which were shown to be active, and the glucuronic acid conjugates of eslicarbazepine acetate, eslicarbazepine, R-licarbazepine and oxcarbazepine.

Eslicarbazepine acetate does not affect its own metabolism or clearance.

Eslicarbazepine is a weak inducer of CYP3A4 and has inhibiting properties with respect to CYP2C19 (as stated in section 4.5).

In studies with eslicarbazepine in fresh human hepatocytes a mild induction of UGT1A1 mediated glucuronidation was observed.

Elimination
Eslicarbazepine acetate metabolites are eliminated from the systemic circulation primarily by renal excretion, in the unchanged and glucuronide conjugate forms. In total, eslicarbazepine and its glucuronide correspond to more than 90% of total metabolites excreted in urine, approximately two thirds in the unchanged form and one third as glucuronide conjugate.

Linearity/non-linearity
The pharmacokinetics of eslicarbazepine acetate is linear and dose-proportional in the range 400-1,200 mg both in healthy subjects and patients.

Elderly (over 65 years of age)
The pharmacokinetic profile of eslicarbazepine acetate is unaffected in the elderly patients with creatinine clearance >60 ml/min (see section 4.2).

Renal impairment
Eslicarbazepine acetate metabolites are eliminated from the systemic circulation primarily by renal excretion. A study in adult patients with mild to severe renal impairment showed that clearance is dependent on renal function. During treatment with Zebinix dose adjustment is recommended in patients,adult and children above 6 years of age with creatinine clearance <60 ml/min (see section 4.2).
In children from 2 to 6 years of age, the use of eslicarbazepine acetate is not recommended. At this age the intrinsic activity of the elimination process has not yet reached maturation.

Haemodialysis removes eslicarbazepine acetate metabolites from plasma.

Hepatic impairment

The pharmacokinetics and metabolism of eslicarbazepine acetate were evaluated in healthy subjects and moderately liver-impaired patients after multiple oral doses. Moderate hepatic impairment did not affect the pharmacokinetics of eslicarbazepine acetate. No dose adjustment is recommended in patients with mild to moderate liver impairment (see section 4.2).
The pharmacokinetics of eslicarbazepine acetate has not been evaluated in patients with severe hepatic impairment.

Gender
Studies in healthy subjects and patients showed that pharmacokinetics of eslicarbazepine acetate were not affected by gender.

Paediatric population

Similar to adults, eslicarbazepine acetate is extensively converted to eslicarbazepine. Plasma levels of eslicarbazepine acetate usually remain below the limit of quantification, following oral administration. Eslicarbazepine C_{max} is attained at 2 to 3 hours post-dose (t_{max}). Body weight was shown to have an effect on volume of distribution and clearance. Furthermore, a role of age independently of weight with regards to clearance of eslicarbazepine acetate could not be excluded, in particular for the youngest age group (2-6 years).

Children aged 6 years and below
Population pharmacokinetics indicate that in the subgroup of children aged from 2 to 6 years, doses of 27.5 mg/kg/day and 40 mg/kg/day are required in order to achieve exposures that are equivalent to the therapeutic doses of 20 and 30 mg/kg/day in children above 6 years of age.

Children above 6 years of age
Population pharmacokinetics indicate that comparable eslicarbazepine exposure is observed between 20 and 30 mg/kg/day in children above 6 years old and adults with 800 and 1200 mg of eslicarbazepine acetate once-daily, respectively (see section 4.2).

5.3 Preclinical safety data

Adverse reactions observed in animal studies occurred at exposure levels appreciably lower than the clinical exposure levels to eslicarbazepine (the principal and pharmacologically active metabolite of eslicarbazepine acetate). Safety margins based on comparative exposure have thus not been established.

Evidence of nephrotoxicity was observed in repeated dose-toxicity studies in the rat, but was not seen in studies in mice or dogs, and is consistent with an exacerbation of spontaneous chronic progressive nephropathy in this species.

Liver centrilobular hypertrophy was seen in repeated-dose toxicity studies in mice and rats and an increased incidence of liver tumours was observed in the carcinogenicity study in mice; these findings are consistent with an induction of hepatic microsomal enzymes, an effect which has not been observed in patients receiving eslicarbazepine acetate.

Juvenile animals studies
In repeat-dose studies in juvenile dogs, the toxicity profile was comparable to that observed in adult animals.
In the 10-month study decreases in bone mineral content, bone area and/or bone mineral density in lumbar vertebrae and/or femur were observed in high-dose female animals at exposure levels lower than the clinical exposure levels to eslicarbazepine in children.

Genotoxicity studies with eslicarbazepine acetate indicate no special hazards for humans.

Impairment of fertility was observed in female rats; decreases in implantations and live embryos seen in the mouse fertility study may also indicate effects on female fertility, however, corpora lutea counts were not evaluated. Eslicarbazepine acetate was not teratogenic in the rat or rabbit, but did induce skeletal abnormalities in the mouse. Ossification delays, reduced foetal weights, an increase in minor skeletal and visceral anomalies were observed at maternal toxic doses in embryotoxicity studies in mice, rats and rabbits. A delay in the sexual development of the F1 generation was observed in peri/postnatal studies in mice and rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Xanthan gum (E415)
Macrogol-100 stearate
Methyl parahydroxybenzoate (E218)
Saccharin sodium (E954)
Flavour Tutti-Frutti artificial (contains maltodextrin, propylene glycol, natural and artificial flavouring, and gum acacia (E414)
Masking flavour (contains propylene glycol, water and natural and artificial flavouring)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After first opening: 3 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Amber glass bottles with HDPE child resistant closures containing 200 ml oral suspension, inside a cardboard box. Each cardboard box contains a 10 ml polypropylene graduated syringe with 0.2 ml graduations, and a copolymer push-in bottle adapter.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BIAL - Portela & Cª, SA
À Av. da Siderurgia Nacional
4745-457 S. Mamede do Coronado - Portugal
tel: +351 22 986 61 00
fax: +351 22 986 61 99
e-mail: info@bial.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/514/024

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21.04.2009

Date of latest renewal: 22.01.2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS O R RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

BIAL -Portela & Cª, S.A.
À Av. da Siderurgia Nacional
4745-457 S. Mamede do Coronado
Portugal

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Box of 20 or 60 tablets

1. NAME OF THE MEDICINAL PRODUCT

Zebinix 200 mg tablets
Eslicarbazepine acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg of eslicarbazepine acetate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 tablets
60 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BIAL-Portela & Cª, S.A.
À Av. da Siderurgia Nacional
4745-457 S. Mamede do Coronado
Portugal

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/514/021 20 tablets - PVC/ALU blister
EU/1/09/514/022 60 tablets - PVC/ALU blister

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zebinix 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.
(only for outer packaging)

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
(only for outer packaging)

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

PVC/ALU blister

1. NAME OF THE MEDICINAL PRODUCT

Zebinix 200 mg tablets
Eslicarbazepine acetate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BIAL

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND ON THE IMMEDIATE PACKAGING

HPDE bottles carton and HPDE bottles of 60 tablets

1. NAME OF THE MEDICINAL PRODUCT

Zebinix 200 mg tablets
Eslicarbazepine acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg of eslicarbazepine acetate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BIAL-Portela & Cª, S.A.
À Av. da Siderurgia Nacional
4745-457 S. Mamede do Coronado
Portugal

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/514/023

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zebinix 200 mg

(outer pack only)

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.
(only for outer packaging)

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
(only for outer packaging)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Box of 7, 14 or 28 tablets

1. NAME OF THE MEDICINAL PRODUCT

Zebinix 400 mg tablets
Eslicarbazepine acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 400 mg of eslicarbazepine acetate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

7 tablets
14 tablets
28 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BIAL-Portela & Cª, S.A.
À Av. da Siderurgia Nacional
4745-457 S. Mamede do Coronado
Portugal

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/514/001 7 tablets - ALU/ALU blister
EU/1/09/514/002 14 tablets - ALU/ALU blister
EU/1/09/514/003 28 tablets - ALU/ALU blister
EU/1/09/514/004 7 tablets - PVC/ALU blister
EU/1/09/514/005 14 tablets - PVC/ALU blister
EU/1/09/514/006 28 tablets - PVC/ALU blister

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zebinix 400 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.
(only for outer packaging)

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
(only for outer packaging)

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

ALU/ALU blister
PVC/ALU blister

1. NAME OF THE MEDICINAL PRODUCT

Zebinix 400 mg tablets
Eslicarbazepine acetate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BIAL

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Box of 30 or 60 tablets

1. NAME OF THE MEDICINAL PRODUCT

Zebinix 600 mg tablets
Eslicarbazepine acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 600 mg of eslicarbazepine acetate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
60 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BIAL-Portela & Cª, S.A.
À Av. da Siderurgia Nacional
4745-457 S. Mamede do Coronado
Portugal

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/514/007 30 tablets - ALU/ALU blister
EU/1/09/514/008 60 tablets - ALU/ALU blister
EU/1/09/514/009 30 tablets - PVC/ALU blister
EU/1/09/514/010 60 tablets - PVC/ALU blister

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zebinix 600 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.
(only for outer packaging)

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
(only for outer packaging)

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

ALU/ALU blister
PVC/ALU blister

1. NAME OF THE MEDICINAL PRODUCT

Zebinix 600 mg tablets
Eslicarbazepine acetate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BIAL

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND ON THE IMMEDIATE PACKAGING

HPDE bottles carton and HPDE bottles of 90 tablets

1. NAME OF THE MEDICINAL PRODUCT

Zebinix 600 mg tablets
Eslicarbazepine acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 600 mg of eslicarbazepine acetate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BIAL-Portela & Cª, S.A.
À Av. da Siderurgia Nacional
4745-457 S. Mamede do Coronado
Portugal

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/514/011

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zebinix 600 mg

(outer pack only)

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.
(only for outer packaging)

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
(only for outer packaging)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Box of 20, 30, 60 or 90 tablets

1. NAME OF THE MEDICINAL PRODUCT

Zebinix 800 mg tablets
Eslicarbazepine acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 800 mg of eslicarbazepine acetate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 tablets
30 tablets
60 tablets
90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BIAL-Portela & Cª, S.A.
À Av. da Siderurgia Nacional
4745-457 S. Mamede do Coronado
Portugal

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/514/012 20 tablets - ALU/ALU blister
EU/1/09/514/013 30 tablets - ALU/ALU blister
EU/1/09/514/014 60 tablets - ALU/ALU blister
EU/1/09/514/015 90 tablets - ALU/ALU blister
EU/1/09/514/016 20 tablets - PVC/ALU blister
EU/1/09/514/017 30 tablets - PVC/ALU blister
EU/1/09/514/018 60 tablets - PVC/ALU blister
EU/1/09/514/019 90 tablets - PVC/ALU blister

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zebinix 800 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.
(only for outer packaging)

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
(only for outer packaging)

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

ALU/ALU blister
PVC/ALU blister

1. NAME OF THE MEDICINAL PRODUCT

Zebinix 800 mg tablets
Eslicarbazepine acetate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BIAL

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND ON THE IMMEDIATE PACKAGING

HPDE bottles carton and HPDE bottles of 90 tablets

1. NAME OF THE MEDICINAL PRODUCT

Zebinix 800 mg tablets
Eslicarbazepine acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet constains 800 mg of eslicarbazepine acetate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BIAL-Portela & C[a], S.A.
À Av. da Siderurgia Nacional
4745-457 S. Mamede do Coronado
Portugal

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/514/020

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zebinix 800 mg

(outer pack only)

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.
(only for outer packaging)

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
(only for outer packaging)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Outer carton / bottle

1. NAME OF THE MEDICINAL PRODUCT

Zebinix 50 mg/ml oral suspension
Eslicarbazepine acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral suspension contains 50 mg of eslicarbazepine acetate

3. LIST OF EXCIPIENTS

Contains methyl parahydroxybenzoate (E218) and sulphites
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

oral suspension

200 ml bottle
oral syringe (10 ml) (outer pack only)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use
Shake well before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After first opening, oral suspension may be used for up to 3 months
Open date: ---/---/---

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BIAL-Portela & Cª, S.A.
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4745-457 S. Mamede do Coronado
Portugal

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/514/024

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zebinix 50 mg/ml

(outer pack only)

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.
(only for outer packaging)

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
(only for outer packaging)

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Zebinix 200 mg tablets
Eslicarbazepine acetate

Read all of this leaflet carefully before you or your child start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zebinix is and what it is used for

Zebinix contains the active substance eslicarbazepine acetate.
Zebinix belongs to a group of medicines called antiepileptics used to treat epilepsy, a condition where someone has repeated seizures or fits.

Zebinix is used in adult, adolescents and children patients above 6 years of age, who are already taking other antiepileptic medicines and are still experiencing seizures that affect one part of the brain (partial seizure). These seizures may or may not be followed by a seizure affecting all of the brain (secondary generalisation).

Zebinix has been given to you by your doctor to reduce your number of seizures.

2. What you need to know before you take Zebinix

Do not take Zebinix:
- if you are allergic to eslicarbazepine acetate, to other carboxamide derivatives (e.g. carbamazepine or oxcarbazepine, medicines used to treat epilepsy) or to any of the other ingredients of this medicine (listed in section 6);
- if you suffer from a certain type of heart rhythm disorder (second or third degree atrioventricular (AV) block).

Warnings and precautions

A small number of people being treated with antiepileptics have had thoughts of harming or killing themselves. If at any time you have these thoughts, when taking Zebinix, contact your doctor immediately.

Talk to your doctor or pharmacist before taking Zebinix.

Contact your doctor immediately:

- if you have rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. These could be signs of an allergic reaction.
- if you suffer from confusion, worsening of seizures or decreased consciousness which can be signs of low blood salt levels.

Please tell your doctor:
- if you have kidney problems. Your doctor may need to adjust the dose. Zebinix is not recommended in patients with severe renal disease.
- if you have liver problems. Zebinix is not recommended in patients with severe liver problems.
- if you are taking any medicine which can cause an abnormality on the ECG (electrocardiogram) called increased PR interval. If you are not sure if the medicines you are taking could have this effect, discuss with your doctor.
- if you suffer from a heart disease such as heart failure or heart attack, or have any heart rhytm disorder.
- if you suffer from seizures that begin with a widespread electric discharge that involves both sides of the brain.

Zebinix may make you feel dizzy and/or drowsy, particularly at the beginning of treatment. Take special care when taking Zebinix to avoid accidental injury, such as fall.

In patients of Han Chinese or Thai origin the risk of serious skin reactions associated with carbamazepine or chemically-related compounds may be predicted by testing a blood sample of these patients. Your doctor should be able to advise if a blood test is necessary before taking Zebinix.

Children
Zebinix is not to be given to children aged 6 years and below.

Other medicines and Zebinix

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is just in case any of them interfere with how Zebinix works or how Zebinix interferes with their effect.
Tell your doctor if you are taking:
- phenytoin (a medicine used to treat epilepsy) since your dose may need to be adjusted;
- carbamazepine (a medicine used to treat epilepsy) since your dose may have to be adjusted and the following side effects of Zebinix may occur in higher frequency: seeing double, abnormal coordination and dizziness;
- hormonal contraceptives (such as the contraceptive pill) since Zebinix may make these less effective;
- simvastatin (a medicine used to lower cholesterol levels) since your dose may have to be adjusted;
- rosuvastatin, a medicine used to lower cholesterol level;
- the blood thinner - warfarin;
- tricyclic antidepressants e.g. amitriptyline;
- Do not take oxcarbazepine (a medicine used to treat epilepsy) with Zebinix, as it is not known whether it is safe to take these medicines together.

See ‘Pregnancy and breast-feeding’ section for advice about contraception.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

There are no data from the use of eslicarbazepine acetate in pregnant women. Research has shown an increased risk of birth defects in children of women taking antiepileptic medicines. On the other hand effective antiepileptic therapy must not be interrupted since the worsening of the disease is harmful to both the mother and the unborn child.

Do not breast-feed while you are taking Zebinix. It is not known whether it passes into breast milk.

Zebinix may make hormonal contraceptives such as the contraceptive pill less effective. Therefore, it is recommended that you use other forms of safe and effective contraception, when taking Zebinix up to the end of the current menstrual cycle after stopping treatment.

Driving and using machines
Zebinix may make you feel dizzy, drowsy and affect your vision, particularly at the beginning of treatment. If this happens to you, do not drive or use any tools or machines.

3. How to take Zebinix

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Adults

Dose when you start treatment
400 mg once daily for one or two weeks, before increasing to the maintenance dose. Your doctor will decide whether you will be given this dose for one or two weeks.

Maintenance dose
The usual maintenance dose is 800 mg once daily.
Depending on how you respond to Zebinix, your dose may be increased to 1,200 mg once daily.

Patients with kidney problems
If you have kidney problems you will usually be given a lower dose of Zebinix. Your doctor will work out the correct dose for you. Zebinix is not recommended if you have severe kidney problems.

Children above 6 years of age

Dose when you start treatment
The starting dose is 10 mg per kg body weight taken once a day for one or two weeks, before increasing to the maintenance dose.

Maintenance dose
Depending on the response to Zebinix, the dose may be increased by 10 mg per kg body weight, at intervals of one or two weeks, up to 30 mg per kg body weight. The maximum dose is 1,200 mg once daily.

Children with ≥60 kg
Children with 60 kg or more body weight should take the same dose as adults.

Other form of this medicine, like oral suspension, maybe more suitable for children. Ask your doctor or pharmacist.

Method and route of administration
Zebinix is for oral use. Swallow the tablet with a glass of water.
Zebinix tablets may be taken with or without food.

If you take more Zebinix than you should
If you accidently take more Zebinix than you should, you may feel or walk unsteady or have muscular weakness on one side of the body. Tell a doctor or go to a hospital accident and emergency department immediately. Take the medicine pack with you. This is so the doctor knows what you have taken.

If you forget to take Zebinix
If you forget to take a tablet, take it as soon as you remember and carry on as usual. Do not take a double dose to make up for a forgotten dose.

If you stop taking Zebinix
Do not stop taking your tablets suddenly. If you do, you are at risk of having more seizures. Your doctor will decide how long you should take Zebinix. Should your doctor decide to stop your treatment with Zebinix your dose will usually be reduced gradually. It is important that your treatment is completed as advised by your doctor or your symptoms may get worse.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects can be very serious. If they happen to you stop taking Zebinix and tell a doctor or go to a hospital immediately, as you may need urgent medical treatment**:**
- rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. These could be signs of an allergic reaction.

Very common (may affect more than 1 in 10 people) side effects are:
- Feeling dizzy or sleepy.

Common (may affect up to 1 in 10 people) side effects are:
- Feeling unsteady or having a sensation of spinning or floating;
- Feeling sick or vomiting;
- Headache;
- Diarrhoea;
- Seeing double or blurred vision;
- Difficulty in concentration;
- Feeling low in energy or tired;
- Shaking;
- Skin rash;
- Blood tests showing that you have low levels of sodium in your blood;
- Decrease of appetite;
- Difficulty in sleeping;
- Difficulty in coordinating movements (ataxia).

Uncommon (may affect up to 1 in 100 people) side effects are:
- Clumsiness;
- Allergy;
- Constipation;
- Seizures;
- Underactive thyroid gland. Symptoms include decreased level of thyroid hormone levels (seen in blood tests), cold intolerance, large tongue, thin and brittle fingernails or hair and low body temperature;
- Liver problems;
- High blood pressure or severe increase in blood pressure;
- Low blood pressure or a fall in blood pressure on standing up;
- Blood tests showing that you have low levels of salts (including chloride) in your blood or a reduction in red blood cells;
- Dehydration;
- Eye movement changes, fuzzy vision or red eye;

- Having falls;
- Thermal burn;
- Poor memory or forgetfulness;
- Crying, feeling depressed, nervous or confused, lack of interest or emotion;
- Inability to speak or write or understand spoken or written language;
- Agitation;
- Attention deficit/ hyperactivity disorder;
- Irritability;
- Mood changes or hallucinations;
- Difficulty in speaking;
- Nosebleed;
- Chest pain;
- Tingling and/or feeling numb in any part of your body;
- Migraine;
- Burning sensation;
- Abnormal sense of touch;
- Disturbances in the sense of smell;
- Ringing in the ears;
- Hearing difficulty;
- Swelling in your legs and arms;
- Heart burn, stomach upset, abdominal pain, abdominal bloating and discomfort or dry mouth;
- Charcoal (dark) stool;
- Inflamed gums or toothache;
- Sweating or having dry skin;
- Itching;
- Skin changes (e.g. red skin);
- Hair loss;
- Urinary tract infection;
- Feeling generally weak, unwell or having chills;
- Weight loss;
- Muscle pain, pain in limbs, muscular weakness;
- Bone metabolism disorder;
- Increased bone proteins;
- Flushing, cold limbs;
- Slower or irregular heart beat;
- Feeling extremely sleepy;
- Sedation;
- Neurological movement disorder where your muscles contract causing twisting and repetitive movements or abnormal postures. Symptoms include tremors, pain, cramping;
- Medicine toxicity.

Not known (frequency cannot be estimated from available data) side effects are:
- Reduction in blood platelets which increases risk of bleeding or bruising;
- Severe pain in the back and stomach (caused by inflamation of the pancreas);
- Reduction in white blood cells which makes infections more likely.
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): signs and symptoms may include skin rash, fever, fatigue, swelling of lymph glands, increase of eosinophils (type of white blood cells) and abnormalities in liver, kidney or lung function; DRESS may develop weeks after treatment initiation.

The use of Zebinix is associated with an abnormality in ECG (electrocardiogram) called increase in PR interval. Side effects associated with this ECG abnormality (e.g. fainting and slowing of heart beat) may occur.

There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures with structurally related antiepileptics medicines like carbamazepine and oxcarbazepine. Check with your doctor or pharmacist, if you are on long-term antiepileptic treatment, have a history of osteoporosis, or take steroids.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zebinix

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the blister, bottle and the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zebinix contains
- The active substance is eslicarbazepine acetate. Each tablet contains 200 mg of eslicarbazepine acetate.
- The other ingredients are povidone K29/32, croscarmellose sodium and magnesium stearate.

What Zebinix looks like and contents of the pack
Zebinix 200 mg tablets are white and oblong. The tablets have ‘ESL 200’engraved on one side and are scored on the other side, with a length of 11 mm. The tablet can be divided into equal doses.

The tablets are packaged in blisters in cardboard boxes containing 20 or 60 tablets, and in HDPE bottles with child resistant closure in cardboard boxes containing 60 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
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This leaflet was last revised in MM/YYYY

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the user

Zebinix 400 mg tablets
Eslicarbazepine acetate

Read all of this leaflet carefully before you or your child start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zebinix is and what it is used for

Zebinix contains the active substance eslicarbazepine acetate.
Zebinix belongs to a group of medicines called antiepileptics used to treat epilepsy, a condition where someone has repeated seizures or fits.

Zebinix is used in adult, adolescents and children patients above 6 years of age, who are already taking other antiepileptic medicines and are still experiencing seizures that affect one part of the brain (partial seizure). These seizures may or may not be followed by a seizure affecting all of the brain (secondary generalisation).

Zebinix has been given to you by your doctor to reduce your number of seizures.

2. What you need to know before you take Zebinix

Do not take Zebinix:
- if you are allergic to eslicarbazepine acetate, to other carboxamide derivatives (e.g. carbamazepine or oxcarbazepine, medicines used to treat epilepsy) or to any of the other ingredients of this medicine (listed in section 6);
- if you suffer from a certain type of heart rhythm disorder (second or third degree atrioventricular (AV) block).

Warnings and precautions

A small number of people being treated with antiepileptics have had thoughts of harming or killing themselves. If at any time you have these thoughts, when taking Zebinix, contact your doctor immediately.

Talk to your doctor or pharmacist before taking Zebinix.

Contact your doctor immediately:

- if you have rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. These could be signs of an allergic reaction.
- if you suffer from confusion, worsening of seizures or decreased consciousness which can be signs of low blood salt levels.

Please tell your doctor:
- if you have kidney problems. Your doctor may need to adjust the dose. Zebinix is not recommended in patients with severe renal disease.
- if you have liver problems. Zebinix is not recommended in patients with severe liver problems.
- if you are taking any medicine which can cause an abnormality on the ECG (electrocardiogram) called increased PR interval. If you are not sure if the medicines you are taking could have this effect, discuss with your doctor.
- if you suffer from a heart disease such as heart failure or heart attack, or have any heart rhytm disorder.
- if you suffer from seizures that begin with a widespread electric discharge that involves both sides of the brain.

Zebinix may make you feel dizzy and/or drowsy, particularly at the beginning of treatment. Take special care when taking Zebinix to avoid accidental injury, such as fall.

In patients of Han Chinese or Thai origin the risk of serious skin reactions associated with carbamazepine or chemically-related compounds may be predicted by testing a blood sample of these patients. Your doctor should be able to advise if a blood test is necessary before taking Zebinix.

Children
Zebinix is not to be given to children aged 6 years and below.

Other medicines and Zebinix

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is just in case any of them interfere with how Zebinix works or how Zebinix interferes with their effect.
Tell your doctor if you are taking:
- phenytoin (a medicine used to treat epilepsy) since your dose may need to be adjusted;
- carbamazepine (a medicine used to treat epilepsy) since your dose may have to be adjusted and the following side effects of Zebinix may occur in higher frequency: seeing double, abnormal coordination and dizziness;
- hormonal contraceptives (such as the contraceptive pill) since Zebinix may make these less effective;
- simvastatin (a medicine used to lower cholesterol levels) since your dose may have to be adjusted;
- rosuvastatin, a medicine used to lower cholesterol level;
- the blood thinner - warfarin;
- tricyclic antidepressants e.g. amitriptyline;
- Do not take oxcarbazepine (a medicine used to treat epilepsy) with Zebinix, as it is not known whether it is safe to take these medicines together.

See ‘Pregnancy and breast-feeding’ section for advice about contraception.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

There are no data from the use of eslicarbazepine acetate in pregnant women. Research has shown an increased risk of birth defects in children of women taking antiepileptic medicines. On the other hand effective antiepileptic therapy must not be interrupted since the worsening of the disease is harmful to both the mother and the unborn child.

Do not breast-feed while you are taking Zebinix. It is not known whether it passes into breast milk.

Zebinix may make hormonal contraceptives such as the contraceptive pill less effective. Therefore it is recommended that you use other forms of safe and effective contraception, when taking Zebinix up to the end of the current menstrual cycle after stopping treatment.

Driving and using machines
Zebinix may make you feel dizzy, drowsy and affect your vision, particularly at the beginning of treatment. If this happens to you, do not drive or use any tools or machines.

3. How to take Zebinix

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Adults

Dose when you start treatment
400 mg once daily for one or two weeks, before increasing to the maintenance dose. Your doctor will decide whether you will be given this dose for one or two weeks.

Maintenance dose
The usual maintenance dose is 800 mg once daily.
Depending on how you respond to Zebinix, your dose may be increased to 1,200 mg once daily.

Patients with kidney problems
If you have kidney problems you will usually be given a lower dose of Zebinix. Your doctor will work out the correct dose for you. Zebinix is not recommended if you have severe kidney problems.

Children above 6 years of age

Dose when you start treatment
The starting dose is 10 mg per kg body weight taken once a day for one or two weeks, before increasing to the maintenance dose.

Maintenance dose
Depending on the response to Zebinix, the dose may be increased by 10 mg per kg body weight, at intervals of one or two weeks, up to 30 mg per kg body weight. The maximum is 1,200 mg once daily.

Children with ≥60 kg
Children with 60 kg or more body weight should take the same dose as adults.

Other form of this medicine, like oral suspension, maybe more suitable for children. Ask your doctor or pharmacist.

Method and route of administration
Zebinix is for oral use. Swallow the tablet with a glass of water.
Zebinix tablets may be taken with or without food.

The score line is only there to help you break the tablet if you have difficulty swallowing it whole.

If you take more Zebinix than you should
If you accidently take more Zebinix than you should, you may feel or walk unsteady or have muscular weakness on one side of the body. Tell a doctor or go to a hospital accident and emergency department immediately. Take the medicine pack with you. This is so the doctor knows what you have taken.

If you forget to take Zebinix
If you forget to take a tablet, take it as soon as you remember and carry on as usual. Do not take a double dose to make up for a forgotten dose.

If you stop taking Zebinix
Do not stop taking your tablets suddenly. If you do, you are at risk of having more seizures. Your doctor will decide how long you should take Zebinix. Should your doctor decide to stop your treatment with Zebinix your dose will usually be reduced gradually. It is important that your treatment is completed as advised by your doctor or your symptoms may get worse.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects can be very serious. If they happen to you stop taking Zebinix and tell a doctor or go to a hospital immediately, as you may need urgent medical treatment**:**
- Rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. These could be signs of an allergic reaction.

Very common (may affect more than 1 in 10 people) side effects are:
- Feeling dizzy or sleepy.

Common (may affect up to 1 in 10 people) side effects are:
- Feeling unsteady or having a sensation of spinning or floating;
- Feeling sick or vomiting;
- Headache;
- Diarrhoea;
- Seeing double or blurred vision;
- Difficulty in concentration;
- Feeling low in energy or tired;
- Shaking;
- Skin rash;
- Blood tests showing that you have low levels of sodium in your blood;
- Decrease of appetite;
- Difficulty in sleeping;
- Difficulty in coordinating movements (ataxia).

Uncommon (may affect up to 1 in 100 people) side effects are:
- Clumsiness;
- Allergy;
- Constipation;
- Seizures;
- Underactive thyroid gland. Symptoms include decreased level of thyroid hormone levels (seen in blood tests), cold intolerance, large tongue, thin and brittle fingernails or hair and low body temperature;
- Liver problems;
- High blood pressure or severe increase in blood pressure;
- Low blood pressure or a fall in blood pressure on standing up;
- Blood tests showing that you have low levels of salts (including chloride) in your blood or a reduction in red blood cells;
- Dehydration;

- Eye movement changes, fuzzy vision or red eye;
- Having falls;
- Thermal burn;
- Poor memory or forgetfulness;
- Crying, feeling depressed, nervous or confused, lack of interest or emotion;
- Inability to speak or write or understand spoken or written language;
- Agitation;
- Attention deficit/ hyperactivity disorder;
- Irritability;
- Mood changes or hallucinations;
- Difficulty in speaking;
- Nosebleed;
- Chest pain;
- Tingling and/or feeling numb in any part of your body;
- Migraine;
- Burning sensation;
- Abnormal sense of touch;
- Disturbances in the sense of smell;
- Ringing in the ears;
- Hearing difficulty;
- Swelling in your legs and arms;
- Heart burn, stomach upset, abdominal pain, abdominal bloating and discomfort or dry mouth;
- Charcoal (dark) stool;
- Inflamed gums or toothache;
- Sweating or having dry skin;
- Itching;
- Skin changes (e.g. red skin);
- Hair loss;
- Urinary tract infection;
- Feeling generally weak, unwell or having chills;
- Weight loss;
- Muscle pain, pain in limbs, muscular weakness;
- Bone metabolism disorder;
- Increased bone proteins;
- Flushing, cold limbs;
- Slower or irregular heart beat;
- Feeling extremely sleepy;
- Sedation;
- Neurological movement disorder where your muscles contract causing twisting and repetitive movements or abnormal postures. Symptoms include tremors, pain, cramping;
- Medicine toxicity.

Not known (frequency cannot be estimated from available data) side effects are:
- Reduction in blood platelets which increases risk of bleeding or bruising;
- Severe pain in the back and stomach (caused by inflamation of the pancreas);
- Reduction in white blood cells which makes infections more likely.
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): signs and symptoms may include skin rash, fever, fatigue, swelling of lymph glands, increase of eosinophils (type of white blood cells) and abnormalities in liver, kidney or lung function; DRESS may develop weeks after treatment initiation.

The use of Zebinix is associated with an abnormality in ECG (electrocardiogram) called increase in PR interval. Side effects associated with this ECG abnormality (e.g. fainting and slowing of heart beat) may occur.

There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures with structurally related antiepileptics medicines like carbamazepine and oxcarbazepine. Check with your doctor or pharmacist, if you are on long-term antiepileptic treatment, have a history of osteoporosis, or take steroids.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zebinix

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the blister and the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zebinix contains
- The active substance is eslicarbazepine acetate. Each tablet contains 400 mg of eslicarbazepine acetate.
- The other ingredients are povidone K29/32, croscarmellose sodium and magnesium stearate.

What Zebinix looks like and contents of the pack
Zebinix 400 mg tablets are white, circular and biconvex. The tablets have 'ESL 400'engraved on one side and are scored on the other side, with a diameter of 11 mm.

The tablets are packaged in blisters in cardboard boxes containing 7, 14 or 28 tablets.
Not all pack sizes may be marketed.

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Package leaflet: Information for the user

Zebinix 600 mg tablets
Eslicarbazepine acetate

Read all of this leaflet carefully before you or your child start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
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- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1 What Zebinix is and what it is used for

Zebinix contains the active substance eslicarbazepine acetate.
Zebinix belongs to a group of medicines called antiepileptics used to treat epilepsy, a condition where someone has repeated seizures or fits.

Zebinix is used in adult, adolescents and children patients above 6 years of age, who are already taking other antiepileptic medicines and are still experiencing seizures that affect one part of the brain (partial seizure). These seizures may or may not be followed by a seizure affecting all of the brain (secondary generalisation).

Zebinix has been given to you by your doctor to reduce your number of seizures.

2 What you need to know before you take Zebinix

Do not take Zebinix:
- if you are allergic to eslicarbazepine acetate, to other carboxamide derivatives (e.g. carbamazepine or oxcarbazepine, medicines used to treat epilepsy) or to any of the other ingredients of this medicine (listed in section 6);
- if you suffer from a certain type of heart rhythm disorder (second or third degree atrioventricular (AV) block).

Warnings and precautions

A small number of people being treated with antiepileptics have had thoughts of harming or killing themselves. If at any time you have these thoughts, when taking Zebinix, contact your doctor immediately.

Talk to your doctor or pharmacist before taking Zebinix.

Contact your doctor immediately:

- if you have rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. These could be signs of an allergic reaction.
- if you suffer from confusion, worsening of seizures or decreased consciousness which can be signs of low blood salt levels.

Please tell your doctor:
- if you have kidney problems. Your doctor may need to adjust the dose. Zebinix is not recommended in patients with severe renal disease.
- if you have liver problems. Zebinix is not recommended in patients with severe liver problems.
- if you are taking any medicine which can cause an abnormality on the ECG (electrocardiogram) called increased PR interval. If you are not sure if the medicines you are taking could have this effect, discuss with your doctor.
- if you suffer from a heart disease such as heart failure or heart attack, or have any heart rhytm disorder.
- if you suffer from seizures that begin with a widespread electric discharge that involves both sides of the brain.

Zebinix may make you feel dizzy and/or drowsy, particularly at the beginning of treatment. Take special care when taking Zebinix to avoid accidental injury, such as fall.

In patients of Han Chinese or Thai origin the risk of serious skin reactions associated with carbamazepine or chemically-related compounds may be predicted by testing a blood sample of these patients. Your doctor should be able to advise if a blood test is necessary before taking Zebinix.

Children
Zebinix is not to be given to children aged 6 years and below.

Other medicines and Zebinix
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is just in case any of them interfere with how Zebinix works or how Zebinix interferes with their effect.
Tell your doctor if you are taking:
- phenytoin (a medicine used to treat epilepsy) since your dose may need to be adjusted;
- carbamazepine (a medicine used to treat epilepsy) since your dose may have to be adjusted and the following side effects of Zebinix may occur in higher frequency: seeing double, abnormal coordination and dizziness;
- hormonal contraceptives (such as the contraceptive pill) since Zebinix may make these less effective;
- simvastatin (a medicine used to lower cholesterol levels) since your dose may have to be adjusted;
- rosuvastatin, a medicine used to lower cholesterol level;
- the blood thinner - warfarin;
- tricyclic antidepressants e.g. amitriptyline;
- Do not take oxcarbazepine (a medicine used to treat epilepsy) with Zebinix, as it is not known whether it is safe to take these medicines together.

See ‘Pregnancy and breast-feeding’ section for advice about contraception.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

There are no data from the use of eslicarbazepine acetate in pregnant women. Research has shown an increased risk of birth defects in children of women taking antiepileptic medicines. On the other hand effective antiepileptic therapy must not be interrupted since the worsening of the disease is harmful to both the mother and the unborn child.

Do not breast-feed while you are taking Zebinix. It is not known whether it passes into breast milk.

Zebinix may make hormonal contraceptives such as the contraceptive pill less effective. Therefore it is recommended that you use other forms of safe and effective contraception, when taking Zebinix up to the end of the current menstrual cycle after stopping treatment.

Driving and using machines
Zebinix may make you feel dizzy, drowsy and affect your vision, particularly at the beginning of treatment. If this happens to you, do not drive or use any tools or machines.

3 How to take Zebinix

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Adults

Dose when you start treatment
400 mg once daily for one or two weeks, before increasing to the maintenance dose. Your doctor will decide whether you will be given this dose for one or two weeks.

Maintenance dose
The usual maintenance dose is 800 mg once daily.
Depending on how you respond to Zebinix, your dose may be increased to 1,200 mg once daily.

Patients with kidney problems
If you have kidney problems you will usually be given a lower dose of Zebinix. Your doctor will work out the correct dose for you. Zebinix is not recommended if you have severe kidney problems.

Children above 6 years of age

Dose when you start treatment
The starting dose is 10 mg per kg body weight taken once a day for one or two weeks, before increasing to the maintenance dose.

Maintenance dose
Depending on the response to Zebinix, the dose may be increased by 10 mg per kg body weight, at intervals of one or two weeks, up to 30 mg per kg body weight. The maximum dose is 1,200 mg once daily.

Children with ≥60 kg
Children with 60 kg or more body weight should take the same dose as adults.

Other form of this medicine, like oral suspension, maybe more suitable for children. Ask your doctor or pharmacist.
Method and route of administration
Zebinix is for oral use. Swallow the tablet with a glass of water.
Zebinix tablets may be taken with or without food.

The tablet can be divided into equal doses.

If you take more Zebinix than you should
If you accidently take more Zebinix than you should, you may feel or walk unsteady or have muscular weakness on one side of the body. Tell a doctor or go to a hospital accident and emergency department immediately. Take the medicine pack with you. This is so the doctor knows what you have taken.

If you forget to take Zebinix
If you forget to take a tablet, take it as soon as you remember and carry on as usual. Do not take a double dose to make up for a forgotten dose.

If you stop taking Zebinix
Do not stop taking your tablets suddenly. If you do, you are at risk of having more seizures. Your doctor will decide how long you should take Zebinix. Should your doctor decide to stop your treatment with Zebinix your dose will usually be reduced gradually. It is important that your treatment is completed as advised by your doctor or your symptoms may get worse.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects can be very serious. If they happen to you stop taking Zebinix and tell a doctor or go to a hospital immediately, as you may need urgent medical treatment**:**
- Rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. These could be signs of an allergic reaction.

Very common (may affect more than 1 in 10 people) side effects are:
- Feeling dizzy or sleepy.

Common (may affect up to 1 in 10 people) side effects are:
- Feeling unsteady or having a sensation of spinning or floating;
- Feeling sick or vomiting;
- Headache;
- Diarrhoea;
- Seeing double or blurred vision;
- Difficulty in concentration;
- Feeling low in energy or tired;
- Shaking;
- Skin rash;
- Blood tests showing that you have low levels of sodium in your blood;
- Decrease of appetite;
- Difficulty in sleeping;
- Difficulty in coordinating movements (ataxia).

Uncommon (may affect up to 1 in 100 people) side effects are:
- Clumsiness;
- Allergy;
- Constipation;
- Seizures;
- Underactive thyroid gland. Symptoms include decreased level of thyroid hormone levels (seen in blood tests), cold intolerance, large tongue, thin and brittle fingernails or hair and low body temperature;
- Liver problems;
- High blood pressure or severe increase in blood pressure;
- Low blood pressure or a fall in blood pressure on standing up;
- Blood tests showing that you have low levels of salts (including chloride) in your blood or a reduction in red blood cells;
- Dehydration;
- Eye movement changes, fuzzy vision or red eye;

- Having falls;
- Thermal burn;
- Poor memory or forgetfulness;
- Crying, feeling depressed, nervous or confused, lack of interest or emotion;
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- Attention deficit/ hyperactivity disorder;
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- Mood changes or hallucinations;
- Difficulty in speaking;
- Nosebleed;
- Chest pain;
- Tingling and/or feeling numb in any part of your body;
- Migraine;
- Burning sensation;
- Abnormal sense of touch;
- Disturbances in the sense of smell;
- Ringing in the ears;
- Hearing difficulty;
- Swelling in your legs and arms;
- Heart burn, stomach upset, abdominal pain, abdominal bloating and discomfort or dry mouth;
- Charcoal (dark) stool;
- Inflamed gums or toothache;
- Sweating or having dry skin;
- Itching;
- Skin changes (e.g. red skin);
- Hair loss;
- Urinary tract infection;
- Feeling generally weak, unwell or having chills;
- Weight loss;
- Muscle pain, pain in limbs, muscular weakness;
- Bone metabolism disorder;
- Increased bone proteins;
- Flushing, cold limbs;
- Slower or irregular heart beat;
- Feeling extremely sleepy;
- Sedation;
- Neurological movement disorder where your muscles contract causing twisting and repetitive movements or abnormal postures. Symptoms include tremors, pain, cramping;
- Medicine toxicity.

Not known (frequency cannot be estimated from available data) side effects are:
- Reduction in blood platelets which increases risk of bleeding or bruising;
- Severe pain in the back and stomach (caused by inflamation of the pancreas);
- Reduction in white blood cells which makes infections more likely.
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): signs and symptoms may include skin rash, fever, fatigue, swelling of lymph glands, increase of eosinophils (type of white blood cells) and abnormalities in liver, kidney or lung function; DRESS may develop weeks after treatment initiation.

The use of Zebinix is associated with an abnormality in ECG (electrocardiogram) called increase in PR interval. Side effects associated with this ECG abnormality (e.g. fainting and slowing of heart beat) may occur.

There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures with structurally related antiepileptics medicines like carbamazepine and oxcarbazepine. Check with your doctor or pharmacist, if you are on long-term antiepileptic treatment, have a history of osteoporosis, or take steroids.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zebinix

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the blister and the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zebinix contains
- The active substance is eslicarbazepine acetate. Each tablet contains 600 mg of eslicarbazepine acetate.
- The other ingredients are povidone K29/32, croscarmellose sodium and magnesium stearate.

What Zebinix looks like and contents of the pack
Zebinix 600 mg tablets are white and oblong. The tablets have 'ESL 600'engraved on one side and are scored on the other side, with a length of 17.3 mm. The tablet can be divided into equal doses.

The tablets are packaged in blisters in cardboard boxes containing 30 or 60 tablets, and in HDPE bottles with child resistant closure in cardboard boxes containing 90 tablets.
Not all pack sizes may be marketed.

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This leaflet was last revised in MM/YYYY

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the user

Zebinix 800 mg tablets
Eslicarbazepine acetate

Read all of this leaflet carefully before you or your child start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zebinix is and what it is used for

Zebinix contains the active substance eslicarbazepine acetate.
Zebinix belongs to a group of medicines called antiepileptics used to treat epilepsy, a condition where someone has repeated seizures or fits.

Zebinix is used in adult, adolescents and children patients above 6 years of age, who are already taking other antiepileptic medicines and are still experiencing seizures that affect one part of the brain (partial seizure). These seizures may or may not be followed by a seizure affecting all of the brain (secondary generalisation).

Zebinix has been given to you by your doctor to reduce your number of seizures.

2. What you need to know before you take Zebinix

Do not take Zebinix:
- if you are allergic to eslicarbazepine acetate, to other carboxamide derivatives (e.g. carbamazepine or oxcarbazepine, medicines used to treat epilepsy) or to any of the other ingredients of this medicine (listed in section 6);
- if you suffer from a certain type of heart rhythm disorder (second or third degree atrioventricular (AV) block).

Warnings and precautions

A small number of people being treated with antiepileptics have had thoughts of harming or killing themselves. If at any time you have these thoughts, when taking Zebinix, contact your doctor immediately.

Talk to your doctor or pharmacist before taking Zebinix.

Contact your doctor immediately:

- if you have rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. These could be signs of an allergic reaction.
- if you suffer from confusion, worsening of seizures or decreased consciousness which can be signs of low blood salt levels.

Please tell your doctor:
- if you have kidney problems. Your doctor may need to adjust the dose. Zebinix is not recommended in patients with severe renal disease.
- if you have liver problems. Zebinix is not recommended in patients with severe liver problems.
- if you are taking any medicine which can cause an abnormality on the ECG (electrocardiogram) called increased PR interval. If you are not sure if the medicines you are taking could have this effect, discuss with your doctor.
- if you suffer from a heart disease such as heart failure or heart attack, or have any heart rhytm disorder.
- if you suffer from seizures that begin with a widespread electric discharge that involves both sides of the brain.

Zebinix may make you feel dizzy and/or drowsy, particularly at the beginning of treatment. Take special care when taking Zebinix to avoid accidental injury, such as fall.

In patients of Han Chinese or Thai origin the risk of serious skin reactions associated with carbamazepine or chemically-related compounds may be predicted by testing a blood sample of these patients. Your doctor should be able to advise if a blood test is necessary before taking Zebinix.

Children
Zebinix is not to be given to children aged 6 years and below.

Other medicines and Zebinix

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is just in case any of them interfere with how Zebinix works or how Zebinix interferes with their effect.
Tell your doctor if you are taking:
- phenytoin (a medicine used to treat epilepsy) since your dose may need to be adjusted;
- carbamazepine (a medicine used to treat epilepsy) since your dose may have to be adjusted and the following side effects of Zebinix may occur in higher frequency: seeing double, abnormal coordination and dizziness;
- hormonal contraceptives (such as the contraceptive pill) since Zebinix may make these less effective;
- simvastatin (a medicine used to lower cholesterol levels) since your dose may have to be adjusted;
- rosuvastatin, a medicine used to lower cholesterol level;
- the blood thinner - warfarin;
- tricyclic antidepressants e.g. amitriptyline;
- Do not take oxcarbazepine (a medicine used to treat epilepsy) with Zebinix, as it is not known whether it is safe to take these medicines together.

See ‘Pregnancy and breast-feeding’ section for advice about contraception.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

There are no data from the use of eslicarbazepine acetate in pregnant women. Research has shown an increased risk of birth defects in children of women taking antiepileptic medicines. On the other hand effective antiepileptic therapy must not be interrupted since the worsening of the disease is harmful to both the mother and the unborn child.

Do not breast-feed while you are taking Zebinix. It is not known whether it passes into breast milk.

Zebinix may make hormonal contraceptives such as the contraceptive pill less effective. Therefore it is recommended that you use other forms of safe and effective contraception, when taking Zebinix up to the end of the current menstrual cycle after stopping treatment.

Driving and using machines
Zebinix may make you feel dizzy, drowsy and affect your vision, particularly at the beginning of treatment. If this happens to you, do not drive or use any tools or machines.

3. How to take Zebinix

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Adults

Dose when you start treatment
400 mg once daily for one or two weeks, before increasing to the maintenance dose. Your doctor will decide whether you will be given this dose for one or two weeks.

Maintenance dose
The usual maintenance dose is 800 mg once daily.
Depending on how you respond to Zebinix, your dose may be increased to 1,200 mg once daily.

Patients with kidney problems
If you have kidney problems you will usually be given a lower dose of Zebinix. Your doctor will work out the correct dose for you. Zebinix is not recommended if you have severe kidney problems.

Children above 6 years of age

Dose when you start treatment
The starting dose is 10 mg per kg body weight taken once a day for one or two weeks, before increasing to the maintenance dose.

Maintenance dose
Depending on the response to Zebinix, the dose may be increased by 10 mg per kg body weight, at intervals of one one or two weeks, up to 30 mg per kg body weight. The maximum dose is 1,200 mg once daily.

Children ≥60 kg
Children with 60 kg or more body weight should take the same dose as adults.

Other form of this medicine, like oral suspension, maybe more suitable for children. Ask your doctor or pharmacist.

Method and route of administration
Zebinix is for oral use. Swallow the tablet with a glass of water.
Zebinix tablets may be taken with or without food.

The tablet can be divided into equal doses.

If you take more Zebinix than you should

If you accidently take more Zebinix than you should, you may feel or walk unsteady or have muscular weakness on one side of the body. Tell a doctor or go to a hospital accident and emergency department immediately. Take the medicine pack with you. This is so the doctor knows what you have taken.

If you forget to take Zebinix
If you forget to take a tablet, take it as soon as you remember and carry on as usual. Do not take a double dose to make up for a forgotten dose.

If you stop taking Zebinix
Do not stop taking your tablets suddenly. If you do, you are at risk of having more seizures. Your doctor will decide how long you should take Zebinix. Should your doctor decide to stop your treatment with Zebinix your dose will usually be reduced gradually. It is important that your treatment is completed as advised by your doctor or your symptoms may get worse.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects can be very serious. If they happen to you stop taking Zebinix and tell a doctor or go to a hospital immediately, as you may need urgent medical treatment**:**

- rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. These could be signs of an allergic reaction.

Very common (may affect more than 1 in 10 people) side effects are:

- Feeling dizzy or sleepy.

Common (may affect up to 1 in 10 people) side effects are:

- Feeling unsteady or having a sensation of spinning or floating;
- Feeling sick or vomiting;
- Headache;
- Diarrhoea;
- Seeing double or blurred vision;
- Difficulty in concentration;
- Feeling low in energy or tired;
- Shaking;
- Skin rash;
- Blood tests showing that you have low levels of sodium in your blood;
- Decrease of appetite;
- Difficulty in sleeping;
- Difficulty in coordinating movements (ataxia).

Uncommon (may affect up to 1 in 100 people) side effects are:

- Clumsiness;
- Allergy;
- Constipation;
- Seizures;
- Underactive thyroid gland. Symptoms include decreased level of thyroid hormone levels (seen in blood tests), cold intolerance, large tongue, thin and brittle fingernails or hair and low body temperature;
- Liver problems;
- High blood pressure or severe increase in blood pressure;
- Low blood pressure or a fall in blood pressure on standing up;

- Blood tests showing that you have low levels of salts (including chloride) in your blood or a reduction in red blood cells;
- Dehydration;
- Eye movement changes, fuzzy vision or red eye;
- Having falls;
- Thermal burn;
- Poor memory or forgetfulness;
- Crying, feeling depressed, nervous or confused, lack of interest or emotion;
- Inability to speak or write or understand spoken or written language;
- Agitation;
- Attention deficit/ hyperactivity disorder;
- Irritability;
- Mood changes or hallucinations;
- Difficulty in speaking;
- Nosebleed;
- Chest pain;
- Tingling and/or feeling numb in any part of your body;
- Migraine;
- Burning sensation;
- Abnormal sense of touch;
- Disturbances in the sense of smell;
- Ringing in the ears;
- Hearing difficulty;
- Swelling in your legs and arms;
- Heart burn, stomach upset, abdominal pain, abdominal bloating and discomfort or dry mouth;
- Charcoal (dark) stool;
- Inflamed gums or toothache;
- Sweating or having dry skin;
- Itching;
- Skin changes (e.g. red skin);
- Hair loss;
- Urinary tract infection;
- Feeling generally weak, unwell or having chills;
- Weight loss;
- Muscle pain, pain in limbs, muscular weakness;
- Bone metabolism disorder;
- Increased bone proteins;
- Flushing, cold limbs;
- Slower or irregular heart beat;
- Feeling extremely sleepy;
- Sedation;
- Neurological movement disorder where your muscles contract causing twisting and repetitive movements or abnormal postures. Symptoms include tremors, pain, cramping;
- Medicine toxicity.

Not known (frequency cannot be estimated from available data) side effects are:
- Reduction in blood platelets which increases risk of bleeding or bruising;
- Severe pain in the back and stomach (caused by inflamation of the pancreas);
- Reduction in white blood cells which makes infections more likely.
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): signs and symptoms may include skin rash, fever, fatigue, swelling of lymph glands, increase of eosinophils (type of white blood cells) and abnormalities in liver, kidney or lung function; DRESS may develop weeks after treatment initiation.

The use of Zebinix is associated with an abnormality in ECG (electrocardiogram) called increase in PR interval. Side effects associated with this ECG abnormality (e.g. fainting and slowing of heart beat) may occur.

There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures with structurally related antiepileptics medicines like carbamazepine and oxcarbazepine. Check with your doctor or pharmacist, if you are on long-term antiepileptic treatment, have a history of osteoporosis, or take steroids.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zebinix

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the blister and the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zebinix contains
- The active substance is eslicarbazepine acetate. Each tablet contains 800 mg of eslicarbazepine acetate.
- The other ingredients are povidone K29/32, croscarmellose sodium and magnesium stearate.

What Zebinix looks like and contents of the pack
Zebinix 800 mg tablets are white and oblong. The tablets have ‘ESL 800’engraved on one side and are scored on the other side, with a length of 19 mm. The tablet can be divided into equal doses.

The tablets are packaged in blisters in cardboard boxes containing 20, 30, 60 or 90 tablets, and in HDPE bottles with child resistant closure in cardboard boxes containing 90 tablets.
Not all pack sizes may be marketed.

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This leaflet was last revised in MM/YYYY

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the user

Zebinix 50 mg/ml oral suspension
Eslicarbazepine acetate

Read all of this leaflet carefully before you or your child start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zebinix is and what it is used for

Zebinix contains the active substance eslicarbazepine acetate.
Zebinix belongs to a group of medicines called antiepileptics used to treat epilepsy, a condition where someone has repeated seizures or fits.

Zebinix is used in adult, adolescents and children patients above 6 years of age, who are already taking other antiepileptic medicines and are still experiencing seizures that affect one part of the brain (partial seizure). These seizures may or may not be followed by a seizure affecting all of the brain (secondary generalisation).

Zebinix has been given to you by your doctor to reduce your number of seizures.

2. What you need to know before you take Zebinix

Do not take Zebinix:
- if you are allergic to eslicarbazepine acetate, to other carboxamide derivatives (e.g. carbamazepine or oxcarbazepine, medicines used to treat epilepsy) or to any of the other ingredients of this medicine (listed in section 6);
- if you suffer from a certain type of heart rhythm disorder (second or third degree atrioventricular (AV) block).

Warnings and precautions

A small number of people being treated with antiepileptics have had thoughts of harming or killing themselves. If at any time you have these thoughts, when taking Zebinix, contact your doctor immediately.

Talk to your doctor or pharmacist before taking Zebinix.

Contact your doctor immediately:

- if you have rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. These could be signs of an allergic reaction.
- if you suffer from confusion, worsening of seizures or decreased consciousness which can be signs of low blood salt levels.

Please tell your doctor:
- if you have kidney problems. Your doctor may need to adjust the dose. Zebinix is not recommended in patients with severe renal disease.
- if you have liver problems. Zebinix is not recommended in patients with severe liver problems.
- if you are taking any medicine which can cause an abnormality on the ECG (electrocardiogram) called increased PR interval. If you are not sure if the medicines you are taking could have this effect, discuss with your doctor.
- if you suffer from a heart disease such as heart failure or heart attack, or have any heart rhytm disorder.
- if you suffer from seizures that begin with a widespread electric discharge that involves both sides of the brain.

Zebinix may make you feel dizzy and/or drowsy, particularly at the beginning of treatment. Take special care when taking Zebinix to avoid accidental injury, such as fall.

In patients of Han Chinese or Thai origin the risk of serious skin reactions associated with carbamazepine or chemically-related compounds may be predicted by testing a blood sample of these patients. Your doctor should be able to advise if a blood test is necessary before taking Zebinix.

Children
Zebinix is not to be given to children aged 6 years and below.

Other medicines and Zebinix

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is just in case any of them interfere with how Zebinix works or how Zebinix interferes with their effect.
Tell your doctor if you are taking:
- phenytoin (a medicine used to treat epilepsy) since your dose may need to be adjusted;
- carbamazepine (a medicine used to treat epilepsy) since your dose may have to be adjusted and the following side effects of Zebinix may occur in higher frequency: seeing double, abnormal coordination and dizziness;
- hormonal contraceptives (such as the contraceptive pill) since Zebinix may make these less effective;
- simvastatin (a medicine used to lower cholesterol levels) since your dose may have to be adjusted;
- rosuvastatin, a medicine used to lower cholesterol level;
- the blood thinner - warfarin;
- tricyclic antidepressants e.g. amitriptyline;
- Do not take oxcarbazepine (a medicine used to treat epilepsy) with Zebinix, as it is not known whether it is safe to take these medicines together.

See ‘Pregnancy and breast-feeding’ section for advice about contraception.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

There are no data from the use of eslicarbazepine acetate in pregnant women. Research has shown an increased risk of birth defects in children of women taking antiepileptic medicines. On the other hand effective antiepileptic therapy must not be interrupted since the worsening of the disease is harmful to both the mother and the unborn child.

Do not breast-feed while you are taking Zebinix. It is not known whether it passes into breast milk.

Zebinix may make hormonal contraceptives such as the contraceptive pill less effective. Therefore, it is recommended that you use other forms of safe and effective contraception, when taking Zebinix up to the end of the current menstrual cycle after stopping treatment.

Driving and using machines
Zebinix may make you feel dizzy, drowsy and affect your vision, particularly at the beginning of treatment. If this happens to you, do not drive or use any tools or machines.

Zebinix contains methyl parahydroxybenzoate (E218) and sulphites
Zebinix oral suspension contains methyl parahydroxybenzoate (E218) which may cause allergic reactions (possibly delayed) and sulphites which may rarely cause severe hypersensitivity reactions and bronchospasm.

3. How to take Zebinix

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Adults

Dose when you start treatment
400 mg once daily for one or two weeks, before increasing to the maintenance dose. Your doctor will decide whether you will be given this dose for one or two weeks.

Maintenance dose
The usual maintenance dose is 800 mg once daily.
Depending on how you respond to Zebinix, your dose may be increased to 1,200 mg once daily.

Patients with kidney problems
If you have kidney problems you will usually be given a lower dose of Zebinix. Your doctor will work out the correct dose for you. Zebinix is not recommended if you have severe kidney problems.

Children above 6 years of age

Dose when you start treatment
The starting dose is 10 mg per kg body weight taken once a day for one or two weeks, before increasing to the maintenance dose.

Maintenance dose
Depending on the response to Zebinix, the dose may be increased by 10 mg per kg body weight, at intervals of one or two weeks, up to 30 mg per kg body weight. The maximum dose is 1,200 mg once daily.

Children with ≥60 kg
Children with 60 kg or more body weight should take the same dose as adults.

Other form of this medicine, like oral suspension, maybe more suitable for children. Ask your doctor or pharmacist.

Method and route of administration
Zebinix is for oral use.
Zebinix oral suspension may be taken with or without food.

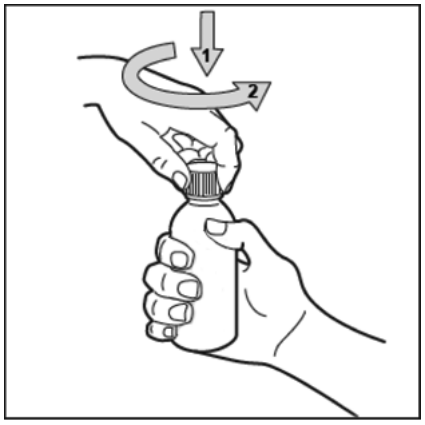
Shake well before use.

Always use the oral syringe provided to take your medicine.

Instructions for use:

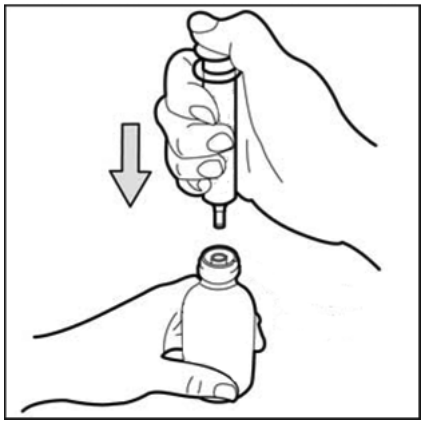
Step 1. Remove the bottle, the oral syringe and the bottle adapter from the box

Step 2. Shake the bottle for at least 10 seconds and remove the child resistant closure by pushing it down and turning it counter-clockwise (to the left).

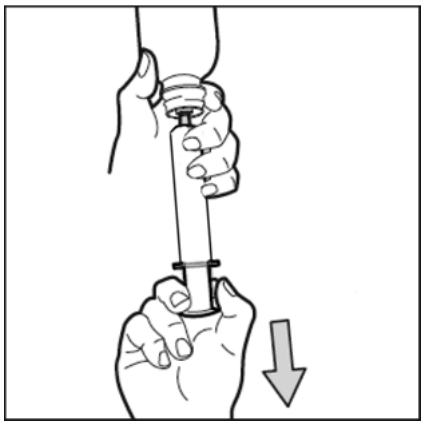


Step 3. Insert the bottle adapter in the bottle neck opening. You may need to apply some pressure to insert it securely. Once inserted, the bottle adapter must not be removed from the bottle. The bottle can be closed with the closure with the bottle adapter still in place.

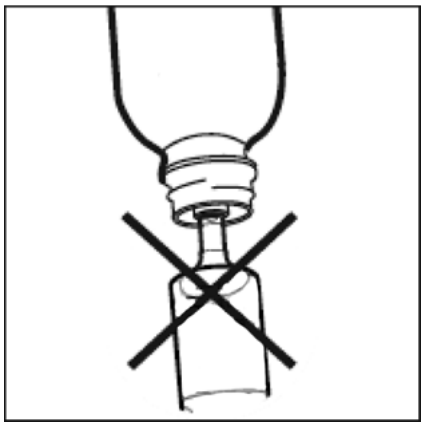
Step 4. To ease the process you should mark the desired volume in the syringe by moving the plunger. Insert the tip of the oral syringe into the bottle adapter opening, keeping the bottle upright. Push the plunger all the way down. This will create pressure inside the bottle that will help the dosing of the suspension, forcing it to leave from the bottle to the oral syringe.



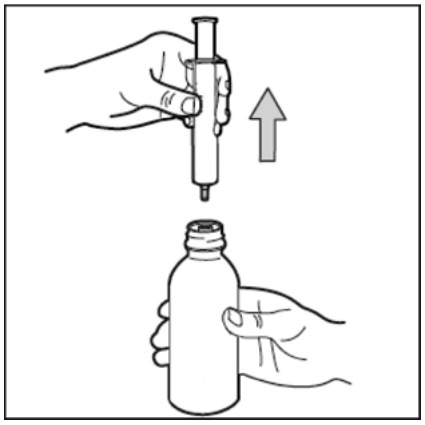
Step 5: Hold the oral syringe in place and turn the bottle upside down.
Gently pull the plunger of the oral syringe to the desired volume.



Step 6: If you see any air bubbles in the oral syringe, push the plunger upwards just far enough to completely push out any large air bubbles. Gently pull the plunger back downwards to the dose prescribed by your doctor.



Step 7. Turn the bottle upright and remove the entire oral syringe from the bottle. Be careful, do not push the plunger down when removing the oral syringe from the bottle.



Step 8. Replace the closure on the bottle by turning it clock-wise (to the right).

Step 9. Place the oral syringe into the mouth against the inside of the cheek. Press the plugger down slowly to release Zebinix into the mouth.

Step 10: Rinse the empty oral syringe after each use into a glass of clean water. Repeat this cleaning process 3 times.
Store the bottle and the oral syringe together in the carton until next use.

If you take more Zebinix than you should
If you accidently take more Zebinix than you should, you may feel or walk unsteady or have muscular weakness on one side of the body. Tell a doctor or go to a hospital accident and emergency department immediately. Take the medicine pack with you. This is so the doctor knows what you have taken.

If you forget to take Zebinix
If you forget to take a dose, take it as soon as you remember and carry on as usual. Do not take a double dose to make up for a forgotten dose.

If you stop taking Zebinix
Do not stop taking your oral suspension suddenly. If you do, you are at risk of having more seizures. Your doctor will decide how long you should take Zebinix. Should your doctor decide to stop your treatment with Zebinix your dose will usually be reduced gradually. It is important that your treatment is completed as advised by your doctor or your symptoms may get worse.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects can be very serious. If they happen to you stop taking Zebinix and tell a doctor or go to a hospital immediately, as you may need urgent medical treatment**:**

- rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. These could be signs of an allergic reaction.

Very common (may affect more than 1 in 10 people) side effects are:

- Feeling dizzy or sleepy.

Common (may affect up to 1 in 10 people) side effects are:

- Feeling unsteady or having a sensation of spinning or floating;
- Feeling sick or vomiting;
- Headache;
- Diarrhoea;
- Seeing double or blurred vision;
- Difficulty in concentration;
- Feeling low in energy or tired;
- Shaking;
- Skin rash;
- Blood tests showing that you have low levels of sodium in your blood;
- Decrease of appetite;
- Difficulty in sleeping;
- Difficulty in coordinating movements (ataxia).

Uncommon (may affect up to 1 in 100 people) side effects are:

- Clumsiness;
- Allergy;
- Constipation;
- Seizures;
- Underactive thyroid gland. Symptoms include decreased level of thyroid hormone levels (seen in blood tests), cold intolerance, large tongue, thin and brittle fingernails or hair and low body temperature;
- Liver problems;
- High blood pressure or severe increase in blood pressure;
- Low blood pressure or a fall in blood pressure on standing up;
- Blood tests showing that you have low levels of salts (including chloride) in your blood or a reduction in red blood cells;
- Dehydration;
- Eye movement changes, fuzzy vision or red eye;
- Having falls;
- Thermal burn;
- Poor memory or forgetfulness;
- Crying, feeling depressed, nervous or confused, lack of interest or emotion;
- Inability to speak or write or understand spoken or written language;
- Agitation;
- Attention deficit/ hyperactivity disorder;
- Irritability;
- Mood changes or hallucinations;
- Difficulty in speaking;
- Nosebleed;
- Chest pain;
- Tingling and/or feeling numb in any part of your body;
- Migraine;
- Burning sensation;

- Abnormal sense of touch;
- Disturbances in the sense of smell;
- Ringing in the ears;
- Hearing difficulty;
- Swelling in your legs and arms;
- Heart burn, stomach upset, abdominal pain, abdominal bloating and discomfort or dry mouth;
- Charcoal (dark) stool;
- Inflamed gums or toothache;
- Sweating or having dry skin;
- Itching;
- Skin changes (e.g. red skin);
- Hair loss;
- Urinary tract infection;
- Feeling generally weak, unwell or having chills;
- Weight loss;
- Muscle pain, pain in limbs, muscular weakness;
- Bone metabolism disorder;
- Increased bone proteins;
- Flushing, cold limbs;
- Slower or irregular heart beat;
- Feeling extremely sleepy;
- Sedation;
- Neurological movement disorder where your muscles contract causing twisting and repetitive movements or abnormal postures. Symptoms include tremors, pain, cramping;
- Medicine toxicity.

Not known (frequency cannot be estimated from available data) side effects are:
- Reduction in blood platelets which increases risk of bleeding or bruising;
- Severe pain in the back and stomach (caused by inflamation of the pancreas);
- Reduction in white blood cells which makes infections more likely.
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): signs and symptoms may include skin rash, fever, fatigue, swelling of lymph glands, increase of eosinophils (type of white blood cells) and abnormalities in liver, kidney or lung function; DRESS may develop weeks after treatment initiation.

The use of Zebinix is associated with an abnormality in ECG (electrocardiogram) called increase in PR interval. Side effects associated with this ECG abnormality (e.g. fainting and slowing of heart beat) may occur.

There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures with structurally related antiepileptics medicines like carbamazepine and oxcarbazepine. Check with your doctor or pharmacist, if you are on long-term antiepileptic treatment, have a history of osteoporosis, or take steroids.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zebinix

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the bottle and the carton after EXP. The expiry date refers to the last day of that month.

Once you have opened the bottle, you must not use it longer than 3 months

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zebinix contains

- The active substance is eslicarbazepine acetate. Each ml of oral suspension contains 50 mg of eslicarbazepine acetate.
  The other ingredients are xanthan gum (E415), macrogol-100 stearate, methyl parahydroxybenzoate (E218), saccharin sodium (E954), flavour tutti-frutti artificial (contains maltodextrin, propylene glycol, natural and artificial flavouring, and gum acacia (E414), masking flavour (contains propylene glycol, water and natural and artificial flavouring) and purified water.

What Zebinix looks like and contents of the pack
Zebinix 50 mg/ml is an off-white to white oral suspension.

The oral suspension is packaged in amber glass bottles with HDPE child resistant closures containing 200 ml oral suspension, inside a cardboard box. Each cardboard box contains a 10 ml polypropylene graduated syringe with 0.2 ml graduations, and a copolymer push-in bottle adapter.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.