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. The score line is not intended for breaking the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zebinix is indicated as adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation.

4.2 Posology and method of administration

Posology

*Adul*ts
Zebinix must be added to existing anticonvulsant therapy. 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).

*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 with renal impairment and the dose should be adjusted according to creatinine clearance (CL\textsubscript{CR}) as follows:
- \( \text{CL}_{\text{CR}} > 60 \text{ ml/min} \): no dose adjustment required.
- \( \text{CL}_{\text{CR}} 30-60 \text{ ml/min} \): initial dose of 200 mg once daily or 400 mg every other day for 2 weeks followed by a once daily dose of 400 mg. However, based on individual response, the dose may be increased.
- \( \text{CL}_{\text{CR}} < 30 \text{ ml/min} \): 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*
The safety and efficacy of eslicarbazepine acetate in children and adolescents below 18 years has not yet been established.

Method of administration

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

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 anti-epileptic active substances in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for eslicarbazepine acetate. Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Nervous system 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.

Oral contraceptives
Eslicarbazepine acetate may decrease the effectiveness of hormonal contraceptives. Additional non-hormonal forms of contraception are recommended when using Zebinix (see sections 4.5 and 4.6).

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.
Concomitant use of eslicarbazepine acetate with oxcarbazepine is not recommended because this may cause overexposure to the active metabolites.
There is no experience regarding the withdrawal of concomitant use of anti-epileptic 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 compounds. If
patients of these acetate 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.

The prevalence of the HLA-B*1502 allele is negligible in e.g. European descent, African, Hispanic populations sampled, and in Japanese and Koreans (<1%).

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.
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 sections 4.4 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 anti-epileptic therapy should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of anti-epileptic 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 section 5.3). 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
Anti-epileptic 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 anti-epileptic 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
Eslicarbazepine acetate was evaluated in rats and mice for potential adverse reactions on fertility of the parental and F1 generation. In a fertility study in male and female rats, impairment of female fertility by eslicarbazepine acetate was shown. In a fertility study in mice, developmental effects were observed in embryos; however, effects could also result from lower corpora lutea count and thus show impairment of fertility. In the mouse, the overall incidence of major abnormalities and the incidence for major skeletal abnormalities were increased. No effects on F1 fertility parameters were observed in rats and mice.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. 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 patients with partial-onset seizures (1,282) patients treated with eslicarbazepine acetate and 560 treated with placebo), 50.7% of patients treated with eslicarbazepine acetate and 27.7% 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-emergent 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 treatment emergent adverse reactions were reported in <3% of subjects in any treatment group.

Tabulated list of adverse reactions

In the table below all adverse reactions, which were identified based on the review of the full Eslicarbazepine acetate safety database are presented by System Organ Class and frequency. The initial review was done by considering all treatment emergent adverse events in the double-blind epilepsy studies in the total Eslicarbazepine acetate group. The following were also considered: incidence rates higher than placebo, severity, seriousness and causality assessment of each individual case, consistency with Eslicarbazepine acetate pharmacology and data from open-label study phases and post-marketing safety data.

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>Anaemia</td>
<td>Thrombocytopenia, leukopenia</td>
<td></td>
<td></td>
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<tr>
<td>Immune system disorders</td>
<td></td>
<td>Hypersensitivity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Endocrine disorders</td>
<td></td>
<td>Hypothyroidism</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>Hyponatraemia, decreased appetite</td>
<td>Electrolyte imbalance, dehydration, hypochloremia</td>
<td></td>
<td></td>
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<tr>
<td>Psychiatric disorders</td>
<td></td>
<td>Insomnia</td>
<td>Apathy, depression, nervousness, agitation, irritability, attention deficit/ hyperactivity disorder, confusional state, mood swings, crying, psychomotor retardation, psychotic disorder</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th><strong>Nervous system disorders</strong></th>
<th>Dizziness, somnolence</th>
<th>Headache, disturbance in attention, tremor, ataxia, balance disorder</th>
<th>Coordination abnormal, memory impairment, amnesia, hypersomnia, sedation, aphasia, dysaesthesia, dystonia, lethargy, parosmia, cerebellar syndrome, convulsion, peripheral neuropathy, nystagmus, speech disorder, dysarthria, burning sensation, paresthesia, migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye disorders</strong></td>
<td>Diplopia, vision blurred</td>
<td>Visual impairment, oscillopsia, binocular eye movement disorder, ocular hyperaemia</td>
<td></td>
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<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td>Vertigo</td>
<td>Hypoacusis, tinnitus</td>
<td></td>
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<tr>
<td><strong>Cardiac disorders</strong></td>
<td>Palpitations, bradycardia</td>
<td></td>
<td></td>
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<tr>
<td><strong>Vascular disorders</strong></td>
<td>Hypertension (including hypertensive crisis), hypotension, orthostatic hypotension, flushing, peripheral coldness</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>Epistaxis, chest pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>Symptoms</td>
<td>Conditions</td>
<td></td>
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<tr>
<td>----------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Nausea, vomiting, diarrhoea</td>
<td>Constipation, dyspepsia, gastritis, abdominal pain, dry mouth, abdominal discomfort, abdominal distension, gingivitis, melaena, toothache</td>
<td></td>
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<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td>Liver disorder</td>
<td></td>
<td></td>
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<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Rash</td>
<td>Alopecia, dry skin, hyperhidrosis, erythema, skin disorder, pruritus</td>
<td></td>
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<td></td>
<td></td>
<td>Drug reaction with eosinophilia and systemic symptoms (DRESS)</td>
<td></td>
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<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>Myalgia, bone metabolism disorder, muscular weakness, pain in extremity</td>
<td></td>
<td></td>
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<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td>Urinary tract infection</td>
<td></td>
<td></td>
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<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Fatigue, gait disturbance, asthenia</td>
<td>Malaise, chills, oedema peripheral</td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td>Blood pressure decreased, weight decreased, blood pressure increased, blood sodium decreased, blood chloride decreased, osteocalcin increased, haematocrit decreased, haemoglobin decreased, transaminases increased</td>
<td></td>
</tr>
<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
<td>Drug toxicity, fall, thermal burn</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.

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
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 anti-epileptic 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 \( \geq 50\% \) 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.

Paediatric population
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).

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 \( \geq 65 \) years). The data shows that the incidence of treatment emergent adverse events in this population (65.3\%) is similar to the general population enrolled in the double-blind epilepsy studies (66.8\%). The most frequent individual treatment emergent adverse events 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).

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 t\( _{\text{max}} \) is attained at 2 to 3 hours post-dose. 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. Peak plasma concentrations (C\( _{\text{max}} \)) of eslicarbazepine are attained at 2-3 hours post-dose and 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 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 with creatinine clearance <60 ml/min (see section 4.2). 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.

### 5.3 Preclinical safety data

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

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  
Â 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/1/09/514/021-023

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. 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 with partial-onset seizures with or without secondary generalisation.

4.2 **Posology and method of administration**

**Posology**

**Adults**

Zebinix must be added to existing anticonvulsant therapy. 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).

**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 with renal impairment and the dose should be adjusted according to creatinine clearance (CLCR) as follows:

- CLCR >60 ml/min: no dose adjustment required.
- CLCR 30-60 ml/min: initial dose of 200 mg once daily or 400 mg every other day for 2 weeks followed by a once daily dose of 400 mg. However, based on individual response, the dose may be increased.
- CLCR <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**

The safety and efficacy of eslicarbazepine acetate in children and adolescents below 18 years has not yet been established.
Method of administration
Oral use.
Zebinix may be taken with or without food.

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 anti-epileptic active substances in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for eslicarbazepine acetate. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Nervous system 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.

Oral contraceptives
Eslicarbazepine acetate may decrease the effectiveness of hormonal contraceptives. Additional non-hormonal forms of contraception are recommended when using Zebinix (see sections 4.5 and 4.6).

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.
Concomitant use of eslicarbazepine acetate with oxcarbazepine is not recommended because this may cause overexposure to the active metabolites. There is no experience regarding the withdrawal of concomitant use of anti-epileptic 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 compounds. If patients of these acetate 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. The prevalence of the HLA-B*1502 allele is negligible in e.g. European descent, African, Hispanic populations sampled, and in Japanese and Koreans (<1%).

**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.

**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 sections 4.4 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.

Monoamine 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**

Anti-epileptic 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 anti-epileptic 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**

Eslicarbazepine acetate was evaluated in rats and mice for potential adverse reactions on fertility of the parental and F1 generation. In a fertility study in male and female rats, impairment of female fertility by eslicarbazepine acetate was shown. In a fertility study in mice, developmental effects were observed in embryos; however, effects could also result from lower *corpora lutea* count and thus show impairment of fertility. In the mouse, the overall incidence of major abnormalities and the incidence for major skeletal abnormalities were increased. No effects on F1 fertility parameters were observed in rats and mice.

**4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed. 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 patients with partial-onset seizures (1,282 patients treated with eslicarbazepine acetate and 560 treated with placebo), 50.7% of patients treated with eslicarbazepine acetate and 27.7% 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-emergent 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 treatment emergent adverse reactions were reported in <3% of subjects in any treatment group.
Tabulated list of adverse reactions

In the table below all adverse reactions, which were identified based on the review of the full Eslicarbazepine acetate safety database are presented by System Organ Class and frequency. The initial review was done by considering all treatment emergent adverse events in the double-blind epilepsy studies in the total Eslicarbazepine acetate group. The following were also considered: incidence rates higher than placebo, severity, seriousness and causality assessment of each individual case, consistency with Eslicarbazepine acetate pharmacology and data from open-label study phases and post-marketing safety data.

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, rare ≥1/10,000 to <1/1,000 and not known (frequency cannot be estimated from available data). Within each frequency category, adverse reactions are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>Anaemia</td>
<td></td>
<td>Thrombocytopenia, leukopenia</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td>Hypersensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td></td>
<td>Hypothyroidism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyponatraemia, decreased appetite</td>
<td>Electrolyte imbalance, dehydration, hypochloremia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>Apathy, depression, nervousness, agitation, irritability, attention deficit/ hyperactivity disorder, confusional state, mood swings, crying, psychomotor retardation, psychotic disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness, somnolence</td>
<td>Headache, disturbance in attention, tremor, ataxia, balance disorder</td>
<td>Coordination abnormal, memory impairment, amnesia, hypersomnia, sedation, aphasia, dysesthesia, dystonia, lethargy, parosmia, cerebellar syndrome, convulsion, peripheral neuropathy, nystagmus, speech disorder, dysarthria, burning sensation, paresthesia, migraine</td>
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<td>---------------------------------------------------------------</td>
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<tr>
<td>Eye disorders</td>
<td>Diplopia, vision blurred</td>
<td>Visual impairment, oscillopsia, binocular eye movement disorder, ocular hyperaemia</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo</td>
<td>Hypoacusis, tinnitus</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Palpitations, bradycardia</td>
<td></td>
<td></td>
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<tr>
<td>Vascular disorders</td>
<td></td>
<td>Hypertension (including hypertensive crisis), hypotension, orthostatic hypotension, flushing, peripheral coldness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td>Epistaxis, chest pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Nausea, vomiting, diarrhoea</td>
<td>Constipation, dyspepsia, gastritis, abdominal pain, dry mouth, abdominal discomfort, abdominal distension, gingivitis, melaena, toothache</td>
<td>Pancreatitis</td>
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<td></td>
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<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td>Liver disorder</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Rash</td>
<td>Alopecia, dry skin, hyperhidrosis, erythema, skin disorder, pruritus</td>
<td>Drug reaction with eosinophilia and systemic symptoms (DRESS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>Myalgia, bone metabolism disorder, muscular weakness, pain in extremity</td>
<td></td>
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<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td>Urinary tract infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Fatigue, gait disturbance, asthenia</td>
<td>Malaise, chills, oedema peripheral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Blood pressure decreased, weight decreased, blood pressure increased, blood sodium decreased, blood chloride decreased, osteocalcin increased, haematocrit decreased, haemoglobin decreased, transaminases increased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
<td>Drug toxicity, fall, thermal burn</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.

**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
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 anti-epileptic 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.

Paediatric population
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).

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 treatment emergent adverse events in this population (65.3 %) is similar to the general population enrolled in the double-blind epilepsy studies (66.8%). The most frequent individual treatment emergent adverse events 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).

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 t\textsubscript{max} is attained at 2 to 3 hours post-dose. 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. Peak plasma concentrations (C\textsubscript{max}) of eslicarbazepine are attained at 2-3 hours post-dose and 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 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 with creatinine clearance <60 ml/min (see section 4.2).
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.

**5.3 Preclinical safety data**
Adverse affects 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.
Genotoxicity studies with eslicarbazepine acetate indicate no special hazards for humans.

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 AUTHORITY

BIAL - Portela & Cª, SA
Â 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 AUTHORITY NUMBER(S)

EU/1/09/514/001-006

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORITY

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. The tablet can be divided into equal doses.

4. **CLINICAL PARTICULARS**

4.1 Therapeutic indications

Zebinix is indicated as adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation.

4.2 Posology and method of administration

**Posology**

**Adults**

Zebinix must be added to existing anticonvulsant therapy. 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).

**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 with renal impairment and the dose should be adjusted according to creatinine clearance (CL\text{CR}) as follows:

- CL\text{CR} >60 ml/min: no dose adjustment required.
- CL\text{CR} 30-60 ml/min: initial dose of 200 mg once daily or 400 mg every other day for 2 weeks followed by a once daily dose of 400 mg. However, based on individual response, the dose may be increased.
- CL\text{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**

The safety and efficacy of eslicarbazepine acetate in children and adolescents below 18 years has not yet been established.
Method of administration
Oral use.
Zebinix may be taken with or without food.

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 anti-epileptic active substances in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for eslicarbazepine acetate. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Nervous system 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.

Oral contraceptives
Eslicarbazepine acetate may decrease the effectiveness of hormonal contraceptives. Additional non-hormonal forms of contraception are recommended when using Zebinix (see sections 4.5 and 4.6).

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. Concomitant use of eslicarbazepine acetate with oxcarbazepine is not recommended because this may cause overexposure to the active metabolites. There is no experience regarding the withdrawal of concomitant use of anti-epileptic 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 compounds. If patients of these acetate 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.

The prevalence of the HLA-B*1502 allele is negligible in e.g. European descent, African, Hispanic populations sampled, and in Japanese and Koreans (<1%).

**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**

Prolongation 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.

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 sections 4.4 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 anti-epileptic 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 anti-epileptic therapy should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of anti-epileptic 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**
Eslicarbazepine acetate was evaluated in rats and mice for potential adverse reactions on fertility of the parental and F1 generation. In a fertility study in male and female rats, impairment of female fertility by eslicarbazepine acetate was shown. In a fertility study in mice, developmental effects were observed in embryos; however, effects could also result from lower corpora lutea count and thus show impairment of fertility. In the mouse, the overall incidence of major abnormalities and the incidence for major skeletal abnormalities were increased. No effects on F1 fertility parameters were observed in rats and mice.

**4.7 Effects on ability to drive and use machines**
No studies on the effects on the ability to drive and use machines have been performed. 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 patients with partial-onset seizures (1,282 patients treated with eslicarbazepine acetate and 560 treated with placebo), 50.7% of patients treated with eslicarbazepine acetate and 27.7% 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-emergent 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 treatment emergent adverse reactions were reported in <3% of subjects in any treatment group.
Tabulated list of adverse reactions

In the table below all adverse reactions, which were identified based on the review of the full Eslicarbazepine acetate safety database are presented by System Organ Class and frequency. The initial review was done by considering all treatment emergent adverse events in the double-blind epilepsy studies in the total Eslicarbazepine acetate group. The following were also considered: incidence rates higher than placebo, severity, seriousness and causality assessment of each individual case, consistency with Eslicarbazepine acetate pharmacology and data from open-label study phases and post-marketing safety data.

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>Anaemia</td>
<td>Thrombocytopenia, leukopenia</td>
<td></td>
<td></td>
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<tr>
<td>Immune system disorders</td>
<td></td>
<td>Hypersensitivity</td>
<td></td>
<td></td>
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<tr>
<td>Endocrine disorders</td>
<td></td>
<td>Hypothyroidism</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>Hyponatraemia, decreased appetite</td>
<td>Electrolyte imbalance, dehydration, hypochloremia</td>
<td></td>
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<tr>
<td>Psychiatric disorders</td>
<td></td>
<td>Insomnia</td>
<td>Apathy, depression, nervousness, agitation, irritability, attention deficit/ hyperactivity disorder, confusional state, mood swings, crying, psychomotor retardation, psychotic disorder</td>
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<td></td>
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<tr>
<td>Nervous system disorders</td>
<td>Dizziness, somnolence</td>
<td>Headache, disturbance in attention, tremor, ataxia, balance disorder</td>
<td>Coordination abnormal, memory impairment, amnesia, hypersomnia, sedation, aphasia, dysaesthesia, dystonia, lethargy, parosmia, cerebellar syndrome, convulsion, peripheral neuropathy, nystagmus, speech disorder, dysarthria, burning sensation, paresthesia, migraine</td>
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<tr>
<td>Eye disorders</td>
<td>Diplopia, vision blurred</td>
<td>Visual impairment, oscillopsia, binocular eye movement disorder, ocular hyperaemia</td>
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<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo</td>
<td>Hypoacusis, tinnitus</td>
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<tr>
<td>Cardiac disorders</td>
<td>Palpitations, bradycardia</td>
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<td>Vascular disorders</td>
<td>Hypertension (including hypertensive crisis), hypotension, orthostatic hypotension, flushing, peripheral coldness</td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Epistaxis, chest pain</td>
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<tr>
<td>Condition Type</td>
<td>Symptom Examples</td>
<td>Other Conditions</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, vomiting, diarrhoea</td>
<td>Constipation, dyspepsia, gastritis, abdominal pain, dry mouth, abdominal discomfort, abdominal distension, gingivitis, melaena, toothache</td>
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<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td>Liver disorder</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>Alopecia, dry skin, hyperhidrosis, erythema, skin disorder, pruritus</td>
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<td>Drug reaction with eosinophilia and systemic symptoms (DRESS)</td>
<td></td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Myalgia, bone metabolism disorder, muscular weakness, pain in extremity</td>
<td></td>
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<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td>Urinary tract infection</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue, gait disturbance, asthenia</td>
<td>Malaise, chills, oedema peripheral</td>
<td></td>
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</tr>
<tr>
<td>Investigations</td>
<td>Blood pressure decreased, weight decreased, blood pressure increased, blood sodium decreased, blood chloride decreased, osteocalcin increased, haematocrit decreased, haemoglobin decreased, transaminases increased</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td>Drug toxicity, fall, thermal burn</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
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.

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
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 anti-epileptic 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.

Paediatric population

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).

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 treatment emergent adverse events in this population (65.3 %) is similar to the general population enrolled in the double-blind epilepsy studies (66.8%). The most frequent individual treatment emergent adverse events 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).

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 t\text{max} is attained at 2 to 3 hours post-dose. 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. Peak plasma concentrations (C\text{max}) of eslicarbazepine are attained at 2-3 hours post-dose and 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 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 with creatinine clearance <60 ml/min (see section 4.2). 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.

### 5.3 Preclinical safety data

Adverse affects 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.

Genotoxicity studies with eslicarbazepine acetate indicate no special hazards for humans.
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 & Cº, SA  
Â 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. The tablet can be divided into equal doses.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Zebinix is indicated as adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation.

4.2 **Posology and method of administration**

**Posology**

**Adults**
Zebinix must be added to existing anticonvulsant therapy. 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).

**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 with renal impairment and the dose should be adjusted according to creatinine clearance (CL\textsubscript{CR}) as follows:
- CL\textsubscript{CR} >60 ml/min: no dose adjustment required.
- CL\textsubscript{CR} 30-60 ml/min: initial dose of 200 mg once daily or 400 mg every other day for 2 weeks followed by a once daily dose of 400 mg. However, based on individual response, the dose may be increased.
- CL\textsubscript{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
The safety and efficacy of eslicarbazepine acetate in children and adolescents below 18 years has not yet been established.

Method of administration
Oral use.
Zebinix may be taken with or without food.

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 anti-epileptic active substances in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for eslicarbazepine acetate. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Nervous system 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.

Oral contraceptives
Eslicarbazepine acetate may decrease the effectiveness of hormonal contraceptives. Additional non-hormonal forms of contraception are recommended when using Zebinix (see sections 4.5 and 4.6).

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.
Concomitant use of eslicarbazepine acetate with oxcarbazepine is not recommended because this may cause overexposure to the active metabolites.
There is no experience regarding the withdrawal of concomitant use of anti-epileptic 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 compounds. If
patients of these acetate 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.

The prevalence of the HLA-B*1502 allele is negligible in e.g. European descent, African, Hispanic populations sampled, and in Japanese and Koreans (<1%).

**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-glucuronol 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.

**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 sections 4.4 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
Anti-epileptic 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 anti-epileptic 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
Eslicarbazepine acetate was evaluated in rats and mice for potential adverse reactions on fertility of the parental and F1 generation. In a fertility study in male and female rats, impairment of female fertility by eslicarbazepine acetate was shown. In a fertility study in mice, developmental effects were observed in embryos; however, effects could also result from lower corpora lutea count and thus show impairment of fertility. In the mouse, the overall incidence of major abnormalities and the incidence for major skeletal abnormalities were increased. No effects on F1 fertility parameters were observed in rats and mice.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. 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 patients with partial-onset seizures (1,282 patients treated with eslicarbazepine acetate and 560 treated with placebo), 50.7% of patients treated with eslicarbazepine acetate and 27.7% 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-emergent 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 treatment emergent adverse reactions were reported in <3% of subjects in any treatment group.
Tabulated list of adverse reactions

In the table below all adverse reactions, which were identified based on the review of the full Eslicarbazepine acetate safety database are presented by System Organ Class and frequency. The initial review was done by considering all treatment emergent adverse events in the double-blind epilepsy studies in the total Eslicarbazepine acetate group. The following were also considered: incidence rates higher than placebo, severity, seriousness and causality assessment of each individual case, consistency with Eslicarbazepine acetate pharmacology and data from open-label study phases and post-marketing safety data.

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, rare ≥1/10,000 to <1/1,000 and not known (frequency cannot be estimated from available data). Within each frequency category, adverse reactions are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
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<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>Anaemia</td>
<td></td>
<td>Thrombocytopenia, leukopenia</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td>Hypersensitivity</td>
<td></td>
<td></td>
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<tr>
<td>Endocrine disorders</td>
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<td>Hypothyroidism</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyponatraemia, decreased appetite</td>
<td>Electrolyte imbalance, dehydration, hypochloremia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>Apathy, depression, nervousness, agitation, irritability, attention deficit/ hyperactivity disorder, confusional state, mood swings, crying, psychomotor retardation, psychotic disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness, somnolence</td>
<td>Headache, disturbance in attention, tremor, ataxia, balance disorder</td>
<td>Coordination abnormal, memory impairment, amnesia, hypersomnina, sedation, aphasia, dysaesthesia, dystonia, lethargy, parosmia, cerebellar syndrome, convulsion, peripheral neuropathy, nystagmus, speech disorder, dysarthria, burning sensation, paresthesia, migrane</td>
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<td>------------------------------------------------------------------</td>
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<tr>
<td>Eye disorders</td>
<td>Diplopia, vision blurred</td>
<td>Visual impairment, oscillopsia, binocular eye movement disorder, ocular hyperaemia</td>
<td></td>
<td></td>
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<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo</td>
<td>Hypoacusis, tinnitus</td>
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<tr>
<td>Cardiac disorders</td>
<td>Palpitations, bradycardia</td>
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<tr>
<td>Vascular disorders</td>
<td>Hypertension (including hypertensive crisis), hypotension, orthostatic hypotension, flushing, peripheral coldness</td>
<td></td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Epistaxis, chest pain</td>
<td></td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, vomiting, diarrhoca</td>
<td>Constipation, dyspepsia, gastritis, abdominal pain, dry mouth, abdominal discomfort, abdominal distension, gingivitis, melaena, toothache</td>
<td>Pancreatitis</td>
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<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td>Liver disorder</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>Alopecia, dry skin, hyperhidrosis, erythema, skin disorder, pruritus</td>
<td>Drug reaction with eosinophilia and systemic symptoms (DRESS)</td>
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<td>Musculoskeletal and connective tissue disorders</td>
<td>Myalgia, bone metabolism disorder, muscular weakness, pain in extremity</td>
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<td>Renal and urinary disorders</td>
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<td>Urinary tract infection</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue, gait disturbance, asthenia</td>
<td>Malaise, chills, oedema peripheral</td>
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<tr>
<td>Investigations</td>
<td>Blood pressure decreased, weight decreased, blood pressure increased, blood sodium decreased, blood chloride decreased, osteocalcin increased, haematocrit decreased, haemoglobin decreased, transaminases increased</td>
<td>Drug toxicity, fall, thermal burn</td>
<td></td>
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<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
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</tbody>
</table>
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.

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
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 anti-epileptic 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 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.

Paediatric population

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).

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 treatment emergent adverse events in this population (65.3 %) is similar to the general population enrolled in the double-blind epilepsy studies (66.8%). The most frequent individual treatment emergent adverse events 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).

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 tmax is attained at 2 to 3 hours post-dose. 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. Peak plasma concentrations (Cmax) of eslicarbazepine are attained at 2-3 hours post-dose and 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 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 with creatinine clearance <60 ml/min (see section 4.2).

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.

### 5.3 Preclinical safety data

Adverse affects 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.

Genotoxicity studies with eslicarbazepine acetate indicate no special hazards for humans.
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 & C°, 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 AUTHORIZATION

Date of first authorisation: 21.04.2009
Date of latest renewal: 22.01.2014

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR 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 marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

  If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.
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
<table>
<thead>
<tr>
<th>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</th>
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<tbody>
<tr>
<td>BIAL-Portela &amp; Cº, S.A.</td>
</tr>
<tr>
<td>À Av. da Siderurgia Nacional</td>
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<tr>
<td>4745-457 S. Mamede do Coronado</td>
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<td>Portugal</td>
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<th>12. MARKETING AUTHORISATION NUMBER(S)</th>
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<tr>
<td>EU/1/09/514/021  20 tablets - PVC/ALU blister</td>
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<tr>
<td>EU/1/09/514/022  60 tablets - PVC/ALU blister</td>
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<th>13. BATCH NUMBER</th>
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<td>Lot</td>
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<tr>
<th>14. GENERAL CLASSIFICATION FOR SUPPLY</th>
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<tbody>
<tr>
<td>Medicinal product subject to medical prescription.</td>
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<tr>
<th>15. INSTRUCTIONS ON USE</th>
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<tr>
<th>16. INFORMATION IN BRAILLE</th>
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<tr>
<td>zebinix 200 mg</td>
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</table>
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**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

zebinix 200 mg

*(outer pack only)*
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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zebinix 400 mg
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<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS</th>
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<td>ALU/ALU blister</td>
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<td>PVC/ALU blister</td>
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<td>Eslicarbazepine acetate</td>
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<th>3. EXPIRY DATE</th>
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<th>4. BATCH NUMBER</th>
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<th>5. OTHER</th>
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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)

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<td>30 tablets - ALU/ALU blister</td>
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13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zebinix 600 mg
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
<table>
<thead>
<tr>
<th>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</th>
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<tbody>
<tr>
<td>BIAL-Portela &amp; Cª, S.A.</td>
</tr>
<tr>
<td>À Av. da Siderurgia Nacional</td>
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<tr>
<td>4745-457 S. Mamede do Coronado</td>
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<td>Portugal</td>
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<th>12. MARKETING AUTHORISATION NUMBER(S)</th>
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<tr>
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<tr>
<th>13. BATCH NUMBER</th>
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<tr>
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<tbody>
<tr>
<td>Medicinal product subject to medical prescription.</td>
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<tr>
<th>15. INSTRUCTIONS ON USE</th>
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<tr>
<th>16. INFORMATION IN BRAILLE</th>
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<tbody>
<tr>
<td>zebinix 600 mg</td>
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<tr>
<td><em>(outer pack only)</em></td>
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</table>
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

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

12. MARKETING AUTHORISATION NUMBER(S)

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<td>ALU/ALU blister</td>
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14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zebinix 800 mg
**MINIMUM PARTICULARS TO APPEAR ON BLISTERS**

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<tr>
<td>PVC/ALU blister</td>
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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**
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**

   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**

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(outer pack only)
B. PACKAGE LEAFLET
Read all of this leaflet carefully before you 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
2. What you need to know before you take Zebinix
3. How to take Zebinix
4. Possible side effects
5. How to store Zebinix
6. Contents of the pack and other information

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 anti-epileptics used to treat epilepsy, a condition where someone has repeated seizures or fits.

Zebinix is used in adult patients who are already taking other anti-epileptic 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 anti-epileptics 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 rhythm 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 and adolescents
Zebinix is not to be given to children and adolescents.

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 anti-epileptic medicines. On the other hand effective anti-epileptic 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
There are two dosing regimes for 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.

Elderly (over 65 years of age)
If you are elderly your doctor will decide the suitable dose for you.

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.

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 accidentally take more Zebinix than you should, 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;
- Hypersensitivity;
- 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;
- Pruritus;
- 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;
- Osteocalcin increased;
- 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;
- Drug toxicity.

**Rare** (may affect up to 1 in 1,000 people) side effects are:
- Reduction in blood platelets which increases risk of bleeding or bruising;
- Severe pain in the back and stomach (caused by inflammation of the pancreas);
- Reduction in white blood cells which makes infections more likely.

**Not known** (frequency cannot be estimated from available data) side effects are:
- 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 anti-epileptic drugs like carbamazepine and oxcarbazepine. Check with your doctor or pharmacist, if you are on long-term antiepileptic medication, 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. The score line is not intended for breaking the tablet.

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**

BIAL - Portela & Cª, S.A., 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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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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:

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.
Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
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2. What you need to know before you take Zebinix
3. How to take Zebinix
4. Possible side effects
5. How to store Zebinix
6. Contents of the pack and other information

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 anti-epileptics used to treat epilepsy, a condition where someone has repeated seizures or fits.

Zebinix is used in adult patients who are already taking other anti-epileptic 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 anti-epileptics have had thoughts of harming or killing themselves. If at any time you have these thoughts, when taking Zebinix, contact your doctor immediately.

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- if you have rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. These could be signs of an allergic reaction.
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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.
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Zebinix is not to be given to children and adolescents.

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 anti-epileptic medicines. On the other hand effective anti-epileptic 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**
There are two dosing regimes for 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.

**Elderly (over 65 years of age)**
If you are elderly your doctor will decide the suitable dose for you.

**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.

**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, 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;
- Hypersensitivity;
- 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;
• Pruritus;
• 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;
• Osteocalcin increased;
• 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;
• Drug toxicity.

Rare (may affect up to 1 in 1,000 people) side effects are:
• Reduction in blood platelets which increases risk of bleeding or bruising;
• Severe pain in the back and stomach (caused by inflammation of the pancreas);
• Reduction in white blood cells which makes infections more likely.

Not known (frequency cannot be estimated from available data) side effects are:
• 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 anti-epileptics drugs like carbamazepine and oxcarbazepine. Check with your doctor or pharmacist, if you are on long-term antiepileptic medication, 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.

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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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.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.
Read all of this leaflet carefully before you 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
2. What you need to know before you take Zebinix
3. How to take Zebinix
4. Possible side effects
5. How to store Zebinix
6. Contents of the pack and other information

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 anti-epileptics used to treat epilepsy, a condition where someone has repeated seizures or fits.

Zebinix is used in adult patients who are already taking other anti-epileptic 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 anti-epileptics 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 rhythm 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 and adolescents
Zebinix is not to be given to children and adolescents.

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 anti-epileptic medicines. On the other hand effective anti-epileptic 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**
There are two dosing regimes for 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.

**Elderly (over 65 years of age)**
If you are elderly your doctor will decide the suitable dose for you.

**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.

**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 accidentally take more Zebinix than you should, 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;
- Hypersensitivity;
- 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;
• Pruritus;
• 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;
• Osteocalcin increased;
• 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;
• Drug toxicity.

**Rare** (may affect up to 1 in 1,000 people) side effects are:
• Reduction in blood platelets which increases risk of bleeding or bruising;
• Severe pain in the back and stomach (caused by inflammation of the pancreas);
• Reduction in white blood cells which makes infections more likely.

**Not known** (frequency cannot be estimated from available data) side effects are:
• 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 anti-epileptics drugs like carbamazepine and oxcarbazepine. Check with your doctor or pharmacist, if you are on long-term antiepileptic medication, 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. 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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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.
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 anti-epileptics used to treat epilepsy, a condition where someone has repeated seizures or fits.

Zebinix is used in adult patients who are already taking other anti-epileptic 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 anti-epileptics 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 rhythm 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 and adolescents**
Zebinix is not to be given to children and adolescents.

**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 anti-epileptic medicines. On the other hand effective anti-epileptic 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**
There are two dosing regimes for 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.

**Elderly (over 65 years of age)**
If you are elderly your doctor will decide the suitable dose for you.

**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.

**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, 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;
- Hypersensitivity;
- 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;
- Pruritus;
- 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;
- Osteocalcin increased;
- 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;
- Drug toxicity.

**Rare** (may affect up to 1 in 1,000 people) side effects are:
- Reduction in blood platelets which increases risk of bleeding or bruising;
- Severe pain in the back and stomach (caused by inflammation of the pancreas);
- Reduction in white blood cells which makes infections more likely.

**Not known** (frequency cannot be estimated from available data) side effects are:
- 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 anti-epileptics drugs like carbamazepine and oxcarbazepine. Check with your doctor or pharmacist, if you are on long-term antiepileptic medication, 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. 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.

**Marketing Authorisation Holder and Manufacturer**

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