ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
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)**

Caution should be exercised in the treatment of elderly patients as there is limited safety information on the use of eslicarbazepine acetate in these patients.

**Renal impairment**

Caution should be exercised in the treatment of patients with renal impairment and the dose should be adjusted according to creatinine clearance (CL\text{CR}) as follows:

- \( \text{CL}\text{CR} \geq 60 \text{ ml/min} \): no dose adjustment required.
- \( \text{CL}\text{CR} 30-60 \text{ ml/min} \): initial dose of 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 below 18 years has not yet been established. No data are available.
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.

Known second or third degree atrioventricular (AV) block.

4.4 Special warnings and precautions for use

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.

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).

As with other anti-epileptic medicinal products, 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).

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.

No cases of serious cutaneous reactions have been reported with eslicarbazepine acetate. Presence of HLA-B*1502 allele in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS) when treated with carbamazepine. Therefore, whenever possible, subjects of Han Chinese and Thai origin should be screened for this allele before starting treatment with carbamazepine or chemically-related compounds. The presence of HLA-B*1502 allele in other ethnicities is negligible. The allele HLA-B*1502 is not associated to SJS in the Caucasian population.

Hyponatraemia has been reported as an adverse reaction in less than 1% 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), 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.

The influence of eslicarbazepine acetate on primary generalised seizures has not been studied. Use is therefore not recommended in these patients.

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

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.

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.

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. 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.

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 (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). 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 1,192 adult patients with partial-onset seizures (856 patients treated with eslicarbazepine acetate and 336 treated with placebo), 45.3% of patients treated with eslicarbazepine acetate and 24.4% 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 side effects. The most common treatment-emergent adverse events 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 events were reported in <3% of subjects in any treatment group.

Tabulated list of adverse reactions

In the table below all adverse reactions, which occurred at an incidence greater than placebo and numerically present in more than 1 patient are listed by System Organ Class and frequency: 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. 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>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>Anaemia</td>
<td></td>
<td>Thrombocytopenia, leukopenia</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>
<td></td>
<td>Hypothyroidism</td>
<td></td>
<td></td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>Increased appetite, decreased appetite, hyponatraemia, electrolyte imbalance, cachexia, dehydration, obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td>Insomnia, apathy, depression, nervousness, agitation, irritability, attention deficit/ hyperactivity disorder, confusional state, mood swings, crying, psychomotor retardation, stress, psychotic disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system</td>
<td>Dizziness, Headache,</td>
<td></td>
<td>Memory impairment,</td>
<td></td>
</tr>
<tr>
<td>disorders</td>
<td>somnolence</td>
<td>abnormal coordination, disturbance in attention, tremor</td>
<td>balance disorder, amnesia, hypersonnia, sedation, aphasia, dysaesthesia, dystonia, lethargy, parosmia, autonomic nervous system imbalance, cerebellar ataxia, cerebellar syndrome, grand mal convulsion, neuropathy peripheral, sleep phase rhythm disturbance, nystagmus, speech disorder, dysarthria, hypoaesthesia, ageusia, burning sensation</td>
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<td>---</td>
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<tr>
<td>Eye disorders</td>
<td>Diplopia, vision blurred</td>
<td>Vision disturbance, oscillopsia, binocular eye movement disorder, ocular hyperaemia, saccadic eye movement, eye pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo</td>
<td>Ear pain, hypoacusis, tinnitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Palpitations, bradycardia, sinus bradycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td>Hypertension, hypotension, orthostatic hypotension</td>
<td></td>
<td></td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td>Dysphonia, epistaxis, chest pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, vomiting, diarrhoea</td>
<td>Dyspepsia, gastritis, abdominal pain, dry mouth, abdominal discomfort, abdominal distension, duodenitis, epigastric discomfort, gingival hyperplasia, gingivitis, irritable bowel syndrome, melaena, odynophagia, stomach discomfort, stomatitis, toothache</td>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td>Liver disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>Alopecia, dry skin, hyperhidrosis, erythema, nail disorder, skin disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td>Myalgia, back pain, neck pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td>Nocturia, urinary tract infection</td>
<td></td>
<td></td>
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<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td>Menstruation irregular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders</td>
<td>Fatigue, gait</td>
<td>Asthenia, malaise, chills,</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Investigations

<table>
<thead>
<tr>
<th>and administration site conditions</th>
<th>disturbance</th>
<th>oedema peripheral, adverse drug reaction, peripheral coldness</th>
</tr>
</thead>
</table>

| Injury, poisoning and procedural complications | Blood pressure decreased, weight decreased, blood pressure diastolic decreased, blood pressure increased, blood pressure systolic decreased, blood sodium decreased, haematocrit decreased, haemoglobin decreased, heart rate increased, transaminases increased, triglycerides increased, triiodothyronine (T3) free decreased, thyroxine (T4) free decreased |

| Description of selected adverse reactions |

#### Eye and nervous system disorders

In patients concomitantly treated with carbamazepine and eslicarbazepine acetate in placebo-controlled studies, diplopia, abnormal coordination and dizziness were reported more frequently.

#### 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. No second or higher degree AV block was seen in eslicarbazepine acetate-treated patients.

#### Class related adverse events

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.

### 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 three phase III double-blind placebo-controlled studies in 1,049 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, 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 a 50% reduction in seizure frequency over all phase III studies was 19% for placebo, 21% for eslicarbazepine acetate 400 mg, 34% for eslicarbazepine acetate 800 mg and 36% for eslicarbazepine acetate 1,200 mg daily.

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 acetate *t*<sub>max</sub> 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*<sub>max</sub>) 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.
In studies with eslicarbazepine in fresh human hepatocytes a mild activation 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.
Environmental Risk Assessment (ERA)
Eslicarbazepine acetate poses a risk to the environment, especially to sediment organisms (for instructions on disposal see section 6.6).

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

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/514/012-020
9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 21.04.2009

10. **DATE OF REVISION OF THE TEXT**