SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Piolex 200 mg Tablet

Eslicarbazepine Zentiva 200mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of eslicarbazepine acetate.

3 PHARMACEUTICAL FORM

Tablet.

White to off-white tablets, oval and biconvex, 11.3 mm in length with I debossed on one side and a break score on both sides. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Piolex is indicated as:

- monotherapy in the treatment of partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy;
- adjunctive therapy in adults, adolescents and children aged above 6 years, with partial-onset seizures with or without secondary generalisation.

4.2 Posology and method of administration

Posology

Adults

Piolex may be taken as monotherapy or 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. Some patients on monotherapy regimen may benefit from a dose of 1600 mg once daily (see section 5.1).

Special populations

Elderly (over 65 years of age)

No dose adjustment is needed in the elderly population provided that the renal function is not disturbed. Due to very limited data on the 1,600 mg monotherapy regimen in the elderly, this dose is not recommended for this population.

Renal impairment

Caution should be exercised in the treatment of patients, adult and children above 6 years of age, with renal impairment and the dose should be adjusted according to creatinine clearance (CLCR) as follows:

- CLCR >60 ml/min: no dose adjustment required.
- CLCR 30-60 ml/min: initial dose of 200 mg (or 5 mg/kg in children above 6 years) once daily or 400 mg (or 10 mg/kg in children above 6 years) every other day for 2 weeks followed by a once daily dose of 400 mg (or 10 mg/kg in children above 6 years). However, based on individual response, the dose may be increased.
- 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

Children above 6 years of age.

The recommended starting dose is 10 mg/kg/day once daily. Dosage should be increased in weekly or biweekly increments of 10 mg/kg/day up to 30 mg/kg/day, based on individual response. The maximum dose is 1,200 mg once daily (see section 5.1).

Children with a body weight of ≥60 kg

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

Method of administration

Oral use.

Piolex may be taken with or without food.

Switching preparations

Since comparative bioavailability data for Piolex and for any other formulations e.g. suspensions and vice versa are not available, switching patients from one formulation to the other should be done with caution.

4.3 Contraindications

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

Second or third degree atrioventricular (AV) block.

4.4 Special warnings and precautions for use

Suicidal ideation
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic active substances in several indications. A meta-analysis of randomised placebo-controlled trials of antiepileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for eslicarbazepine acetate. Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.
Nervous system disorders
Eslicarbazepine acetate has been associated with some central nervous system adverse reactions, such as dizziness and somnolence, which could increase the occurrence of accidental injury.
Other warnings and precautions
If Piolex is to be discontinued it is recommended to withdraw it gradually to minimise the potential of increased seizure frequency.
Cutaneous reactions
Rash developed as an adverse reaction in 1.2% of total population treated with eslicarbazepine in clinical studies in epileptic patients. Urticaria and angioedema cases have been reported in patients taking eslicarbazepine. Angioedema in the context of hypersensitivity/anaphylactic reaction associated with laryngeal oedema can be fatal. If signs or symptoms of hypersensitivity develop, eslicarbazepine acetate must be discontinued immediately and alternative treatment should be initiated. Severe cutaneous adverse reactions (SCARS) including Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in post-marketing experience with eslicarbazepine acetate treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Piolex should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patients have developed such reactions, treatment with eslicarbazepine must not be restarted in these patients at any time.
HLA-B* 1502 allele - in Han Chinese, Thai and other Asian populations
HLA-B* 1502 in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing the severe cutaneous reactions known as Stevens Johnson syndrome (SJS) when treated with carbamazepine. The chemical structure of eslicarbazepine acetate is similar to that of carbamazepine, and it is possible that patients who are positive for HLA-B*1502 may also be at risk for SJS after treatment with eslicarbazepine acetate. The prevalence of HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations. Whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine or chemically-related active substances. If patients of these ethnic origins are tested positive for HLA- B*1502 allele, the use of eslicarbazepine acetate may be considered if the benefits are thought to exceed risks. Because of the prevalence of this allele in other Asian populations (e.g, above 15% in the Philippines and Malaysia), testing genetically at risk populations for the presence of HLA- B*1502 may be considered.
HLA-A*3101 allele- European descent and Japanese populations

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

Hyponatraemia

Hyponatraemia has been reported as an adverse reaction in 1.5% of patients treated with eslicarbazepine acetate. 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.

Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per tablet, essentially ‘sodium-free’.

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 Piolex 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 Piolex is being used just prior to or in combination with other medicinal products that require dose adjustment when co-administered with Piolex. Eslicarbazepine has inhibiting properties with respect to CYP2C19. Thus, interactions can arise when co-administering high doses of eslicarbazepine acetate with medicinal products that are mainly metabolised by CYP2C19 (e.g. Phenytoin).

Interactions with other antiepileptic medicinal products

Carbamazepine

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

Phenytoin

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

Lamotrigine

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

Topiramate

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

Valproate and levetiracetam

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

Oxcarbazepine

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

Other medicinal products

Oral contraceptives

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

Simvastatin
A study in healthy subjects showed an average decrease of 50% in systemic exposure to simvastatin when co-administered with eslicarbazepine acetate 800 mg once daily, most likely caused by an induction of CYP3A4. An increase of the simvastatin dose may be required when used concomitantly with eslicarbazepine acetate.
Rosuvastatin
There was an average decrease of 36-39% in systemic exposure in healthy subjects when co-administered with eslicarbazepine acetate 1,200 mg once daily. The mechanism for this reduction is unknown, but could be due to interference of transporter activity for rosuvastatin alone or in combination with induction of its metabolism. Since the relationship between exposure and drug activity is unclear, the monitoring of response to therapy (e.g., cholesterol levels) is recommended.
Warfarin
Co-administration of eslicarbazepine acetate 1,200 mg once daily with warfarin showed a small (23%), but statistically significant decrease in exposure to S-warfarin. There was no effect on the R-warfarin pharmacokinetics or on coagulation. However, due to inter-individual variability in the interaction, special attention on monitoring of INR should be performed the first weeks after initiation or ending concomitant treatment of warfarin and eslicarbazepine acetate.
Digoxin
A study in healthy subjects showed no effect of eslicarbazepine acetate 1,200 mg once daily on digoxin pharmacokinetics, suggesting that eslicarbazepine acetate has no effect on the transporter P- glycoprotein.
Monoamino Oxidase Inhibitors (MAOIs)
Based on a structural relationship of eslicarbazepine acetate to tricyclic antidepressants, an interaction between eslicarbazepine acetate and MAOIs is theoretically possible.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general

It has been shown that in the offspring of women with epilepsy using an antiepileptic treatment, 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. Specialist medical advice regarding the potential risk to a foetus caused by both seizures and antiepileptic treatment should be given to all women of child-bearing potential taking antiepileptic treatment, and especially to women planning pregnancy and women who are pregnant. Sudden discontinuation of antiepileptic drug (AED)therapy should be avoided as this may lead to seizures that could have serious consequences for the woman and the unborn child.

Monotherapy is preferred for treating epilepsy in pregnancy whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated AEDs.

Neurodevelopmental disorders in children of mothers with epilepsy using an antiepileptic treatment has been observed. There is no data available for eslicarbazepine acetate on this risk.

Women of childbearing potential/contraception

Women of childbearing potential should use effective contraception during treatment with eslicarbazepine acetate. 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. Women of childbearing potential should be counselled regarding the use of other effective contraceptive methods. At least one effective method of contraception (such as an intra-uterine device) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, involving the patient in the discussion, when choosing the contraception method.

Risk related to eslicarbazepine acetate

There is limited amount of data from the use of eslicarbazepine acetate in pregnant women. Studies in animals have shown reproductive toxicity (see Fertility, section 5.3). A risk in humans (including of major congenital malformations, neurodevelopmental disorders and other reproductive toxic effects) is unknown.

Eslicarbazepine acetate should not be used during pregnancy unless the benefit is judged to outweigh the risk following careful consideration of alternative suitable treatment options.

If women receiving eslicarbazepine acetate become pregnant or plan to become pregnant, the use of Piolex should be carefully re-evaluated. Minimum effective doses should be given, and monotherapy whenever possible should be preferred at least during the first three months of pregnancy. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity to antenatal screening.

Monitoring and prevention

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

In the newborn child

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

Summary of the safety profile

In clinical studies (adjunctive therapy treatment and monotherapy), 2,434 patients with partial-onset seizures were treated with eslicarbazepine acetate (1,983 adult patients and 451 paediatric patients) and 51% of those patients 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 eslicarbazepine acetate are mainly class-based, dose-dependent undesirable effects. The most common adverse reactions reported in placebo controlled adjunctive therapy studies with adult epileptic patients and in an active controlled monotherapy study comparing eslicarbazepine acetate with carbamazepine controlled release, were dizziness, somnolence, headache, and nausea. The majority of adverse reactions were reported in <3% of subjects in any treatment group.

Severe cutaneous adverse reactions (SCARS), including Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in post-marketing experience with eslicarbazepine acetate treatment (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions associated with eslicarbazepine acetate obtained from clinical studies and post-marketing surveillance are tabulated below.

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

Table 1: Treatment emergent adverse reactions associated with eslicarbazepine acetate obtained from clinical studies and post-marketing surveillance

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

				symptoms of lethargy, nausea, dizziness, decrease in serum (blood) osmolality, vomiting, headache, confusional state or other neurological signs and symptoms.
Psychiatric disorders		Insomnia	Psychotic disorder, apathy, depression, nervousness, agitation, irritability, attention deficit/hyperactivity disorder, confusional state, mood swings, crying, psychomotor retardation, anxiety	
Nervous system disorders	Dizziness, somnolence	Headache, disturbances in attention, tremor, ataxia, balance disorder	Coordination abnormal, memory impairment, amnesia, hypersomnia, sedation, aphasia, dysaesthesia dystonia, lethargy, parosmia, cerebellar syndrome, convulsion, peripheral neuropathy, nystagmus, speech disorder, dysarthria, burning sensation, paraesthesia, migraine	
Eye disorders		Diplopia, vision blurred	Visual impairment, oscillopsia, binocular eye movement disorder, ocular hyperaemia	
Ear and labyrinth disorders		Vertigo	Hypoacusis, tinnitus	
Cardiac disorders			Palpitations, bradycardia	
Vascular			Hypertension (including	

disorders			hypertensive crisis), hypotension, orthostatic hypotension, flushing, peripheral coldness	
Respiratory, thoracic and mediastinal disorders			Epistaxis, chest pain	
Gastrointestinal disorders		Nausea, vomiting, diarrhoea	Constipation, dyspepsia, gastritis, abdominal pain, dry mouth, abdominal discomfort, abdominal distension, gingivitis, melaena, toothache	Pancreatitis
Hepatobiliary disorders			Liver disorder	
Skin and subcutaneous tissue disorders		Rash	Alopecia, dry skin, hyperhidrosis, erythema, skin disorder, pruritus, dermatitis allergic	Toxic epidermal necrolysis, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), angioedema, urticaria
Musculoskeletal and connective tissue disorders			Myalgia, bone metabolism disorder, muscular weakness, pain in extremity	
Renal and urinary disorders			Urinary tract infection	
General disorders and administration site conditions		Fatigue, gait disturbance, asthenia	Malaise, chills, oedema peripheral	
Investigations		Weight increased	Blood pressure decreased, weight decreased, blood pressure increased, blood sodium	

			decreased, blood chloride decreased, osteocalcin increased, haematocrit decreased, haemoglobin decreased, hepatic enzymes increased	
Injury, poisoning and procedural complications			Drug toxicity, fall, thermal burn	

Description of selected adverse reactions

Eye and nervous system disorders

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

PR interval

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

Class related adverse reactions

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

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

Paediatric population

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

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

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

Long-term safety data in the paediatric population obtained from open label extensions of the phase III study was consistent with the known safety profile of the product with no new findings of concern.

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 Yellow Card Scheme at: http://www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms observed after an overdose of eslicarbazepine acetate are primarily associated with central nervous symptoms (e.g. seizures of all types, status epilepticus) and cardiac disorders (e.g. cardiac arrhythmia). 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, precluding their return to the activated state and thereby preventing 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

Adult population

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

studies only), 800 mg and 1,200 mg, once daily. Eslicarbazepine acetate 800 mg once daily and 1,200 mg once daily were significantly more effective than placebo in reducing seizure frequency over a 12-week maintenance period. The percentage of subjects with ≥50% reduction (1581 analysed) 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.
The efficacy of eslicarbazepine acetate as monotherapy has been demonstrated in a double-blind, active controlled (carbamazepine controlled release) study, involving 815 randomized adult patients with newly diagnosed partial-onset seizures. Eslicarbazepine acetate was tested at once-daily doses of 800 mg, 1,200 mg and 1,600 mg. The doses of the active comparator, carbamazepine controlled release, were 200 mg, 400 mg and 600 mg, twice-daily. All subjects were randomized to the lowest dose level and only if a seizure occurred subjects were to be escalated to the next dose level. From the 815 randomized patients, 401 patients were treated with eslicarbazepine acetate once-daily [271 patients (67.6%) remained at dose of 800 mg, 70 patients (17.5%) remained at dose of 1,200 mg and 60 patients (15.0%) were treated with 1,600 mg]. In the primary efficacy analysis, in which drop-outs were considered as non-responders, 71.1% subjects were classified as seizure free in the eslicarbazepine acetate group and 75.6% in the carbamazepine controlled release group during the 26 week evaluation period (average risk difference -4.28%, 95% confidence interval: [-10, 30; 1,74]. The treatment effect observed during the 26-week evaluation period was maintained over 1 year of treatment with 64.7 % eslicarbazepine acetate subjects and 70.3 % carbamazepine controlled release subjects classified as seizure free (average risk difference -5.46%, 95% confidence interval: [-11.88; 0.97]. In the analysis of treatment failure (seizure risk) based on time to event analysis (Kaplan-Meier analysis and Cox regression), the Kaplan-Meier estimates of seizure risk at the end of the evaluation period was 0.06 with carbamazepine and 0.12 with eslicarbazepine acetate and by the end of 1 year with an additional increased risk to 0.11 with carbamazepine and 0.19 with eslicarbazepine acetate (p=0.0002).

At 1 year, the probability for subjects to withdraw due to either adverse reactions or lack of efficacy was 0.26 for eslicarbazepine acetate and 0.21 for carbamazepine controlled release.
The efficacy of eslicarbazepine acetate as conversion to monotherapy was evaluated in 2 double-blind, randomized controlled studies in 365 adult patients with partial-onset seizures. Eslicarbazepine acetate was tested at doses of 1,200 mg and 1,600 mg once-daily. Seizure-free rates during the entire 10 week monotherapy period were 7.6% (1,600 mg) and 8.3 % (1,200 mg) in one study and 10.0% (1,600 mg) and 7.4 % (1,200 mg) in the other study, respectively.

Elderly population
The safety and efficacy of eslicarbazepine acetate as adjunctive therapy for partial seizures in elderly patients were evaluated in one non-controlled study, with a duration of 26 weeks, in 72 elderly (aged ≥ 65 years). The data shows that the incidence of adverse reactions in this population (65.3%) is similar to the general population enrolled in the double-blind epilepsy studies (66.8%).The most frequent individual adverse reactions were dizziness (12.5% of subjects), somnolence (9.7%), fatigue, convulsion and hyponatraemia (8.3%, each), nasopharyngitis (6.9%) and upper respiratory tract infection (5.6%). A total of 50 of the 72 subjects starting the study completed the 26-week treatment period that corresponds to a retention rate of 69.4% (see section 4.2 for information on elderly use). There is limited data on monotherapy regimen available in the elderly population. Only a few subjects (N=27) aged above 65 years were treated with eslicarbazepine acetate in monotherapy study.
Paediatric population
The efficacy and safety of eslicarbazepine acetate as adjunctive therapy for partial-onset seizures in children was evaluated in one phase II study in children aged from 6 to 16 years (N=123) and one phase III study in children aged from 2 to 18 years (N=304). Both studies were double-blind and placebo controlled with a duration of maintenance of 8 weeks (study 208) and 12 weeks (study 305), respectively. Study 208 included 2 additional

subsequent long-term, open-label extensions (1 year in part II and 2 years in part III) and Study 305 included 4 subsequent long-term, open-label extension periods (1 year in Parts II, III and IV and 2 years in Part V). Eslicarbazepine acetate was tested at doses of 20 and 30 mg/kg/day, up to a maximum of 1,200 mg/day. The target dose was 30 mg/kg/day in study 208 and 20 mg/kg/day in study 305. Doses could be adjusted based on tolerability and treatment response.

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

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

In the subsequent 1-year open-label extension (Part II) of the phase III study (ITT set N=225) the total responder rate was 46.7% (steadily increasing from 44.9% (weeks 1-4) to 57.5% (weeks > 40)). The total median standardised seizure frequency was 6.1 (decreasing from 7.0 (weeks 1-4) to 4.0 (weeks >40), resulting in a median relative change compared to the baseline period of -46.7%). The median relative change was larger in the previous placebo group (-51.4%) than in the previous ESL group (-40.4%). The proportion of patients with exacerbation (increase of ≥25%) compared to the baseline period was 14.2%.

In the subsequent 3 open-label extensions (ITT set N=148), the overall responder rate was 26.6% when compared to baseline Parts III–V (i.e. the last 4 weeks in part II). The total median standardised seizure frequency was 2.4 (resulting in a median relative change from Baseline Part III–V of -22.9%). The overall median relative decrease in Part I was greater in patients treated with ESL (-25.8%) than in patients treated with placebo (-16.4%). The overall proportion of patients with exacerbation (increase of ≥25%) compared to Baseline Parts III–V was 25.7%.

Of the 183 patients who completed parts I and II of the study, 152 patients were enrolled into part III. Of these, 65 patients had received ESL and 87 patients had received placebo during the double-blind part of the study. 14 patients (9.2%) completed open-label treatment with ESL through Part V. The most common reason for withdrawal during any part of the study was sponsor request (30 patients in part III [19.7% of the patients who entered part III], 9 in part IV [9.6% of the patients who entered part IV], and 43 in part V [64.2% of the patients who entered Part V]).

Taking into consideration the limitations of open label uncontrolled data, the long-term response to eslicarbazepine acetate in the open-label parts of the study was overall maintained.

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

5.2 Pharmacokinetic properties

Absorption
Eslicarbazepine acetate is extensively converted to eslicarbazepine. Plasma levels of eslicarbazepine acetate usually remain below the limit of quantification, following oral administration. Eslicarbazepine Cmax is attained at 2 to 3 hours post-dose (tmax). Bioavailability may be assumed as high because the amount of metabolites recovered in urine corresponded to more than 90% of an eslicarbazepine acetate dose.
Distribution
The binding of eslicarbazepine to plasma proteins is relatively low (<40%) and independent from concentration. In vitro studies have shown that plasma protein binding was not relevantly affected by the presence of warfarin, diazepam, digoxin, phenytoin and tolbutamide. The binding of warfarin, diazepam, digoxin, phenytoin and tolbutamide was not significantly affected by the presence of eslicarbazepine.
Biotransformation
Eslicarbazepine acetate is rapidly and extensively biotransformed to its major active metabolite eslicarbazepine by hydrolytic first-pass metabolism. The steady state plasma concentrations are attained after 4 to 5 days of once daily dosing, consistent with an effective half-life in the order of 20-24 hours. In studies in healthy subjects and epileptic adult patients, the apparent half-life of eslicarbazepine was 10-20 hours and 13-20 hours, respectively. Minor metabolites in plasma are R- licarbazepine and oxcarbazepine, which were shown to be active, and the glucuronic acid conjugates of eslicarbazepine acetate, eslicarbazepine, R-licarbazepine and oxcarbazepine.
Eslicarbazepine acetate does not affect its own metabolism or clearance.
Eslicarbazepine is a weak inducer of CYP3A4 and has inhibiting properties with respect to CYP2C19 (as stated in section 4.5).
In studies with eslicarbazepine in fresh human hepatocytes a mild induction of UGT1A1 mediated
glucuronidation was observed.
Elimination
Eslicarbazepine acetate metabolites are eliminated from the systemic circulation primarily by renal excretion, in the unchanged and glucuronide conjugate forms. In total, eslicarbazepine and its glucuronide correspond to more than 90% of total metabolites excreted in urine, approximately two thirds in the unchanged form and one third as glucuronide conjugate.
Linearity/non-linearity
The pharmacokinetics of eslicarbazepine acetate is linear and dose-proportional in the range 400-1,200 mg both in healthy subjects and patients.
Elderly (over 65 years of age)
The pharmacokinetic profile of eslicarbazepine acetate is unaffected in the elderly patients with creatinine clearance >60 ml/min (see section 4.2).
Renal impairment
Eslicarbazepine acetate metabolites are eliminated from the systemic circulation primarily by renal excretion. A study in adult patients with mild to severe renal impairment showed that clearance is dependent on renal function. During treatment with Piolex dose adjustment is recommended in patients, adult and children above 6 years of age with creatinine clearance <60 ml/min (see section 4.2). In children from 2 to 6 years of age, the use of eslicarbazepine

acetate is not recommended. At this age the intrinsic activity of the elimination process has not yet reached maturation.
Haemodialysis removes eslicarbazepine acetate metabolites from plasma.
Hepatic impairment
The pharmacokinetics and metabolism of eslicarbazepine acetate were evaluated in healthy subjects and moderately liver-impaired patients after multiple oral doses. Moderate hepatic impairment did not affect the pharmacokinetics of eslicarbazepine acetate. No dose adjustment is recommended in patients with mild to moderate liver impairment (see section 4.2). The pharmacokinetics of eslicarbazepine acetate has not been evaluated in patients with severe hepatic impairment.
Gender
Studies in healthy subjects and patients showed that pharmacokinetics of eslicarbazepine acetate were not affected by gender.
Paediatric population
Similar to adults, eslicarbazepine acetate is extensively converted to eslicarbazepine. Plasma levels of eslicarbazepine acetate usually remain below the limit of quantification, following oral administration. Eslicarbazepine Cmax is attained at 2 to 3 hours post-dose (tmax). Body weight was shown to have an effect on volume of distribution and clearance. Furthermore, a role of age independently of weight with regards to clearance of eslicarbazepine acetate could not be excluded, in particular for the youngest age group (2-6 years).
Children aged 6 years and below
Population pharmacokinetics indicate that in the subgroup of children aged from 2 to 6 years, doses of 27.5 mg/kg/day and 40 mg/kg/day are required in order to achieve exposures that are equivalent to the therapeutic doses of 20 and 30 mg/kg/day in children above 6 years of age.
Children above 6 years of age
Population pharmacokinetics indicate that comparable eslicarbazepine exposure is observed between 20 and 30 mg/kg/day in children above 6 years old and adults with 800 and 1,200 mg of eslicarbazepine acetate once-daily, respectively (see section 4.2).

5.3 Preclinical safety data

Adverse reactions observed in animal studies occurred at exposure levels appreciably lower than the clinical exposure levels to eslicarbazepine (the principal and pharmacologically active metabolite of eslicarbazepine acetate). Safety margins based on comparative exposure have thus not been established.
Evidence of nephrotoxicity was observed in repeated dose-toxicity studies in the rat, but was not seen in studies in mice or dogs, and is consistent with an exacerbation of spontaneous chronic progressive nephropathy in this species.
Liver centrilobular hypertrophy was seen in repeated-dose toxicity studies in mice and rats and an increased incidence of liver tumours was observed in the carcinogenicity study in mice; these findings are consistent with an induction of hepatic microsomal enzymes, an effect which has not been observed in patients receiving eslicarbazepine acetate.
Juvenile animal studies
In repeat-dose studies in juvenile dogs, the toxicity profile was comparable to that observed in adult animals. In the 10-month study decreases in bone mineral content, bone area and/or bone mineral density in lumbar vertebrae and/or femur were observed in high-dose female animals at exposure levels lower than the clinical exposure levels to eslicarbazepine in children.
Genotoxicity studies with eslicarbazepine acetate indicate no special hazards for humans.
Impairment of fertility was observed in female rats; decreases in implantations and live embryos seen in the mouse fertility study may also indicate effects on female fertility,

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone (K29/32)

Croscarmellose sodium

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister packs:2 years.

Bottles: 18 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Transparent PVC/aluminium blisters packed in cardboard boxes containing 10 tablets per blister. Pack sizes: 20 and 60 tablets.

HDPE bottles with child resistant LDPE or PP closure. Pack size: 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

Zentiva Pharma UK Limited

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London EC4A 1JP

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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