ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Exalief 400 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg of eslicarbazepine acetate.

For a 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

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

4.2 Posology and method of administration

Posology

Exalief 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 1200 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 Exalief in these patients.

Paediatric population
The safety and efficacy of Exalief in children below 18 years has not yet been established. No data are available.

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

- CL_{CR} >60 ml/min: no dose adjustment required
- CL_{CR} 30-60 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.
- CL_{CR} <30 ml/min: use is not recommended in patients with severe renal impairment due to insufficient data

Patients with hepatic impairment
No dose adjustment is needed in patients with mild to moderate hepatic impairment.
The pharmacokinetics of eslicarbazepine has not been evaluated in patients with severe hepatic impairment (see section 4.4 and 5.2) and use in these patients is therefore not recommended.

Method of administration

Exalief 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.

Known second or third degree atrioventricular (AV) block.

4.4 Special warnings and precautions for use

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

Exalief may decrease the effectiveness of hormonal contraceptives. Additional non-hormonal forms of contraception are recommended when using Exalief (see section 4.5 and 4.6).

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

Concomitant use of Exalief 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 Exalief (switch to monotherapy).

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

The influence of Exalief 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_{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, Exalief 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 Exalief. 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 Exalief 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 Exalief is being used just prior to or in combination with other medicines that require dose adjustment when co-administered with Exalief. 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 Exalief 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 Exalief 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 interindividual 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 ethinyloestradiol, respectively, most likely caused by an induction of CYP3A4. Therefore, women of childbearing potential must use adequate contraception during treatment with Exalief, and up to the end of the current menstruation cycle after the treatment has been discontinued (see section 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.

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.

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 Exalief 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.

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.

Breastfeeding
It is unknown whether eslicarbazepine acetate is excreted in human breast 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 Exalief.

Fertility
Eslicarbazepine acetate was evaluated in rats and mice for potential adverse effects 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

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.

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.

System Organ Class	Very common	Common	Uncommon	Rare
Blood and lymphatic system disorders			Anaemia	Thrombocytopenia, leukopenia
Immune system disorders			Hypersensitivity	
Endocrine disorders			Hypothyroidism	
Metabolism and nutrition disorders			Increased appetite, decreased appetite, hyponatraemia, electrolyte imbalance, cachexia, dehydration, obesity	
Psychiatric disorders			Insomnia, apathy, depression, nervousness, agitation, irritability, attention deficit/ hyperactivity disorder, confusional state, mood swings, crying, psychomotor retardation, stress, psychotic disorder	
Nervous system disorders	Dizziness*, somnolence	Headache, abnormal coordination *, disturbance in attention, tremor	Memory impairment, balance disorder, amnesia, hypersomnia, 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	
Eye disorders		Diplopia*, vision blurred	Vision disturbance, oscillopsia, binocular eye movement disorder, ocular hyperaemia, saccadic eye	

			movement, eye pain	
Ear and labyrinth disorders		Vertigo	Ear pain, hypoacusis, tinnitus	
Cardiac disorders			Palpitations, bradycardia, sinus bradycardia	
Vascular disorders			Hypertension, hypotension, orthostatic hypotension	
Respiratory, thoracic and mediastinal disorders			Dysphonia, epistaxis, chest pain	
Gastrointestinal disorders		Nausea, vomiting, diarrhoea	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	Pancreatitis
Hepatobiliary disorders			Liver disorder	
Skin and subcutaneous tissue disorders		Rash	Alopecia, dry skin, hyperhidrosis, erythema, nail disorder, skin disorder	
Musculoskeletal and connective tissue disorders			Myalgia, back pain, neck pain	
Renal and urinary disorders			Nocturia, urinary tract infection	
Reproductive system and breast disorders			Menstruation irregular	
General disorders and administration site conditions		Fatigue, gait disturbance	Asthenia, malaise, chills, oedema peripheral, adverse drug reaction, peripheral coldness	
Investigations			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, tri-iodothyronine (T3) free decreased, thyroxine (T4) free decreased	
Injury, poisoning			Drug toxicity, fall, joint	

and procedural complications			injury, poisoning, skin injury	

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

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.

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 Exalief cannot be excluded.

4.9 Overdose

Central nervous symptoms such as vertigo, walking instability and hemi-paresis have been observed with accidental Exalief 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 1200 mg, once daily. Eslicarbazepine acetate 800 mg once daily and 1200 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 1200 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 t_{max} is

attained at 2 to 3 h 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_{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 h. In studies in healthy subjects and epileptic adult patients, the apparent half-life of eslicarbazepine was 10-20 h and 13-20 h, 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.

Excretion
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 is linear and dose-proportional in the range 400-1200 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 Exalief 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 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

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Exalief 400 mg tablets are packaged in ALU/ALU or ALU/PVC blisters placed into cardboard boxes containing 7, 14 or 28 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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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/1/09/520/001-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21.04.2009

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Exalief 600 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 600 mg of eslicarbazepine acetate.

For a 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 halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Exalief 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 1200 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 Exalief in these patients.

Paediatric population
The safety and efficacy of Exalief below 18 years has not yet been established. No data are available.

Patients with renal impairment
Caution should be exercised in the treatment of patients with renal impairment and the dose should be adjusted according to creatinine clearance (CL_{CR}) as follows:
- CL_{CR} >60 ml/min: no dose adjustment required
- CL_{CR} 30-60 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.
- CL_{CR} <30 ml/min: use is not recommended in patients with severe renal impairment due to insufficient data

Patients with hepatic impairment
No dose adjustment is needed in patients with mild to moderate hepatic impairment.
The pharmacokinetics of eslicarbazepine has not been evaluated in patients with severe hepatic impairment (see section 4.4 and 5.2) and use in these patients is therefore not recommended.

Method of administration

Exalief 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.

Known second or third degree atrioventricular (AV) block.

4.4 Special warnings and precautions for use

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

Exalief may decrease the effectiveness of hormonal contraceptives. Additional non-hormonal forms of contraception are recommended when using Exalief (see section 4.5 and 4.6).

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

Concomitant use of Exalief 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 Exalief (switch to monotherapy).

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

The influence of Exalief 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_{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, Exalief 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 Exalief. 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 Exalief 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 Exalief is being used just prior to or in combination with other medicines that require dose adjustment when co-administered with Exalief. 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 Exalief 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 Exalief 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 interindividual 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 ethinyloestradiol, respectively, most likely caused by an induction of CYP3A4. Therefore, women of childbearing potential must use adequate contraception during treatment with Exalief, and up to the end of the current menstruation cycle after the treatment has been discontinued (see section 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.

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.

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 Exalief 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.

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.

Breastfeeding
It is unknown whether eslicarbazepine acetate is excreted in human breast 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 Exalief.

Fertility
Eslicarbazepine acetate was evaluated in rats and mice for potential adverse effects 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

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.

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.

System Organ Class	Very common	Common	Uncommon	Rare
Blood and lymphatic system disorders			Anaemia	Thrombocytopenia, leukopenia
Immune system disorders			Hypersensitivity	
Endocrine disorders			Hypothyroidism	
Metabolism and nutrition disorders			Increased appetite, decreased appetite, hyponatraemia, electrolyte imbalance, cachexia, dehydration, obesity	
Psychiatric disorders			Insomnia, apathy, depression, nervousness, agitation, irritability, attention deficit/ hyperactivity disorder, confusional state, mood swings, crying, psychomotor retardation, stress, psychotic disorder	
Nervous system disorders	Dizziness*, somnolence	Headache, abnormal coordination *, disturbance in attention, tremor	Memory impairment, balance disorder, amnesia, hypersomnia, 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	
Eye disorders		Diplopia*, vision blurred	Vision disturbance, oscillopsia, binocular eye movement disorder, ocular hyperaemia, saccadic eye	

			movement, eye pain	
Ear and labyrinth disorders		Vertigo	Ear pain, hypoacusis, tinnitus	
Cardiac disorders			Palpitations, bradycardia, sinus bradycardia	
Vascular disorders			Hypertension, hypotension, orthostatic hypotension	
Respiratory, thoracic and mediastinal disorders			Dysphonia, epistaxis, chest pain	
Gastrointestinal disorders		Nausea, vomiting, diarrhoea	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	Pancreatitis
Hepatobiliary disorders			Liver disorder	
Skin and subcutaneous tissue disorders		Rash	Alopecia, dry skin, hyperhidrosis, erythema, nail disorder, skin disorder	
Musculoskeletal and connective tissue disorders			Myalgia, back pain, neck pain	
Renal and urinary disorders			Nocturia, urinary tract infection	
Reproductive system and breast disorders			Menstruation irregular	
General disorders and administration site conditions		Fatigue, gait disturbance	Asthenia, malaise, chills, oedema peripheral, adverse drug reaction, peripheral coldness	
Investigations			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, tri-iodothyronine (T3) free decreased, thyroxine (T4) free decreased	
Injury, poisoning			Drug toxicity, fall, joint	

and procedural complications			injury, poisoning, skin injury	

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

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.

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 Exalief cannot be excluded.

4.9 Overdose

Central nervous symptoms such as vertigo, walking instability and hemi-paresis have been observed with accidental Exalief 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 1200 mg, once daily. Eslicarbazepine acetate 800 mg once daily and 1200 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 1200 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 t_{max} is

attained at 2 to 3 h 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_{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 h. In studies in healthy subjects and epileptic adult patients, the apparent half-life of eslicarbazepine was 10-20 h and 13-20 h, 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.

Excretion
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 is linear and dose-proportional in the range 400-1200 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 Exalief 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 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

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

Exalief 600 mg tablets are packed in ALU/ALU or ALU/PVC blisters placed into cardboard boxes containing 30 or 60 tablets.

Exalief 600 mg tablets are packed in 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

No special requirements.

7. MARKETING AUTHORISATION HOLDER

BIAL - Portela & C^{a}, 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/1/09/520/007-011

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21.04.2009

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Exalief 800 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 800 mg of eslicarbazepine acetate.

For a 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 halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Exalief 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 1200 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 Exalief in these patients.

Paediatric population
The safety and efficacy of Exalief in children below 18 years has not yet been established. No data are available.

Patients with renal impairment
Caution should be exercised in the treatment of patients with renal impairment and the dose should be adjusted according to creatinine clearance (CL_{CR}) as follows:
- CL_{CR} >60 ml/min: no dose adjustment required
- CL_{CR} 30-60 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.
- CL_{CR} <30 ml/min: use is not recommended in patients with severe renal impairment due to insufficient data.

Patients with hepatic impairment
No dose adjustment is needed in patients with mild to moderate hepatic impairment.
The pharmacokinetics of eslicarbazepine has not been evaluated in patients with severe hepatic impairment (see section 4.4 and 5.2) and use in these patients is therefore not recommended.

Method of administration

Exalief 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.

Known second or third degree atrioventricular (AV) block.

4.4 Special warnings and precautions for use

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

Exalief may decrease the effectiveness of hormonal contraceptives. Additional non-hormonal forms of contraception are recommended when using Exalief (see section 4.5 and 4.6).

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

Concomitant use of Exalief 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 Exalief (switch to monotherapy).

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

The influence of Exalief 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_{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, Exalief 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 Exalief. 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 Exalief 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 Exalief is being used just prior to or in combination with other medicines that require dose adjustment when co-administered with Exalief. 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 Exalief 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 Exalief 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 interindividual 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 ethinyloestradiol, respectively, most likely caused by an induction of CYP3A4. Therefore, women of childbearing potential must use adequate contraception during treatment with Exalief, and up to the end of the current menstruation cycle after the treatment has been discontinued (see section 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.

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.

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 Exalief 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.

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.

Breastfeeding
It is unknown whether eslicarbazepine acetate is excreted in human breast 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 Exalief.

Fertility
Eslicarbazepine acetate was evaluated in rats and mice for potential adverse effects 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

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.

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.

System Organ Class	Very common	Common	Uncommon	Rare
Blood and lymphatic system disorders			Anaemia	Thrombocytopenia, leukopenia
Immune system disorders			Hypersensitivity	
Endocrine disorders			Hypothyroidism	
Metabolism and nutrition disorders			Increased appetite, decreased appetite, hyponatraemia, electrolyte imbalance, cachexia, dehydration, obesity	
Psychiatric disorders			Insomnia, apathy, depression, nervousness, agitation, irritability, attention deficit/ hyperactivity disorder, confusional state, mood swings, crying, psychomotor retardation, stress, psychotic disorder	
Nervous system disorders	Dizziness*, somnolence	Headache, abnormal coordination *, disturbance in attention, tremor	Memory impairment, balance disorder, amnesia, hypersomnia, 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	
Eye disorders		Diplopia*, vision blurred	Vision disturbance, oscillopsia, binocular eye movement disorder, ocular hyperaemia, saccadic eye	

			movement, eye pain	
Ear and labyrinth disorders		Vertigo	Ear pain, hypoacusis, tinnitus	
Cardiac disorders			Palpitations, bradycardia, sinus bradycardia	
Vascular disorders			Hypertension, hypotension, orthostatic hypotension	
Respiratory, thoracic and mediastinal disorders			Dysphonia, epistaxis, chest pain	
Gastrointestinal disorders		Nausea, vomiting, diarrhoea	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	Pancreatitis
Hepatobiliary disorders			Liver disorder	
Skin and subcutaneous tissue disorders		Rash	Alopecia, dry skin, hyperhidrosis, erythema, nail disorder, skin disorder	
Musculoskeletal and connective tissue disorders			Myalgia, back pain, neck pain	
Renal and urinary disorders			Nocturia, urinary tract infection	
Reproductive system and breast disorders			Menstruation irregular	
General disorders and administration site conditions		Fatigue, gait disturbance	Asthenia, malaise, chills, oedema peripheral, adverse drug reaction, peripheral coldness	
Investigations			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, tri-iodothyronine (T3) free decreased, thyroxine (T4) free decreased	
Injury, poisoning			Drug toxicity, fall, joint	

and procedural complications			injury, poisoning, skin injury	

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

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.

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 Exalief cannot be excluded.

4.9 Overdose

Central nervous symptoms such as vertigo, walking instability and hemi-paresis have been observed with accidental Exalief 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 1200 mg, once daily. Eslicarbazepine acetate 800 mg once daily and 1200 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 1200 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 t_{max} is

attained at 2 to 3 h 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_{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 h. In studies in healthy subjects and epileptic adult patients, the apparent half-life of eslicarbazepine was 10-20 h and 13-20 h, 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.

Excretion
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 is linear and dose-proportional in the range 400-1200 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 Exalief 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 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

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

Exalief 800 mg tablets are packed in ALU/ALU or ALU/PVC blisters placed into cardboard boxes containing 20, 30, 60 or 90 tablets.

Exalief 800 mg tablets are packed in 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

No special requirements.

7. MARKETING AUTHORISATION HOLDER

BIAL - Portela & C^{a}, 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/1/09/520/012-020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21.04.2009

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER 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 OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 4.0 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Box of 7, 14 or 28 tablets

1. NAME OF THE MEDICINAL PRODUCT

Exalief 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

Oral use.

Read the package leaflet before use.

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

Keep out of the reach and sight 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/1/09/520/001 7 tablets - ALU/ALU blister
EU/1/09/520/002 14 tablets - ALU/ALU blister
EU/1/09/520/003 28 tablets - ALU/ALU blister
EU/1/09/520/004 7 tablets - PVC/ALU blister
EU/1/09/520/005 14 tablets - PVC/ALU blister
EU/1/09/520/006 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

Exalief 400 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

ALU/ALU blister
PVC/ALU blister

1. NAME OF THE MEDICINAL PRODUCT

Exalief 400 mg tablets
Eslicarbazepine acetate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BIAL

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Box of 30 or 60 tablets

1. NAME OF THE MEDICINAL PRODUCT

Exalief 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

Oral use.

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BIAL-Portela & C^{a}, S.A.

À Av. da Siderurgia Nacional
4745-457 S. Mamede do Coronado
Portugal

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/520/007 30 tablets - ALU/ALU blister
EU/1/09/520/008 60 tablets - ALU/ALU blister
EU/1/09/520/009 30 tablets - PVC/ALU blister
EU/1/09/520/010 60 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

Exalief 600 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

ALU/ALU blister
PVC/ALU blister

1. NAME OF THE MEDICINAL PRODUCT

Exalief 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

Exalief 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

Oral use.

Read the package leaflet before use.

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

Keep out of the reach and sight 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/1/09/520/011

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exalief 600 mg

(outer pack only)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Box of 20, 30, 60 or 90 tablets

1. NAME OF THE MEDICINAL PRODUCT

Exalief 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

Oral use.

Read the package leaflet before use.

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

Keep out of the reach and sight 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/1/09/520/012 20 tablets - ALU/ALU blister
EU/1/09/520/013 30 tablets - ALU/ALU blister
EU/1/09/520/014 60 tablets - ALU/ALU blister
EU/1/09/520/015 90 tablets - ALU/ALU blister
EU/1/09/520/016 20 tablets - PVC/ALU blister
EU/1/09/520/017 30 tablets - PVC/ALU blister
EU/1/09/520/018 60 tablets - PVC/ALU blister
EU/1/09/520/019 90 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

Exalief 800 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

ALU/ALU blister
PVC/ALU blister

1. NAME OF THE MEDICINAL PRODUCT

Exalief 800 mg tablets
Eslicarbazepine acetate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BIAL

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

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

HPDE bottles carton and HPDE bottles of 90 tablets

1. NAME OF THE MEDICINAL PRODUCT

Exalief 800 mg tablets
Eslicarbazepine acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet constains 800 mg of eslicarbazepine acetate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

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

Keep out of the reach and sight 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/1/09/520/020

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exalief 800 mg

(outer pack only)

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Exalief 400 mg tablets

Eslicarbazepine acetate

Read all of this leaflet carefully before you start taking this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT EXALIEF IS AND WHAT IT IS USED FOR

Exalief belongs to a group of medicines called anti-epileptics used to treat epilepsy, a condition where someone has repeated seizures or fits.

Exalief 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).

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

2. BEFORE YOU TAKE EXALIEF

Do not take Exalief if:
- you are allergic (hypersensitive) to the active substance (eslicarbazepine acetate), to other carboxamide derivatives (e.g. carbamazepine or oxcarbazepine, medicines used to treat epilepsy) or to any of the other ingredients
- you suffer from a certain type of heart rhythm disorder (second or third degree atrioventricular (AV) block)

Take special care with Exalief
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.
- 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. Exalief is not recommended in patients with severe renal disease.
- you have liver problems. Exalief is not recommended in patients with severe liver problems.

- 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.
- you suffer from a heart disease such as heart failure or heart attack.
- you suffer from seizures that begin with a widespread electric discharge that involves both sides of the brain

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

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 Exalief, contact your doctor immediately.

Children
Exalief is not to be given to children and adolescents.

Taking other medicines
- Tell your doctor if you are taking phenytoin (a medicine used to treat epilepsy) since your dose may need to be adjusted.
- Tell your doctor if you are taking carbamazepine (a medicine used to treat epilepsy) since your dose may have to be adjusted and the following side effects of Exalief may occur in higher frequency: seeing double, abnormal coordination and dizziness.
- Tell your doctor if you are taking simvastatin (a medicine used to lower cholesterol levels) since your dose may have to be adjusted.
- Tell your doctor if you are taking the blood thinner - warfarin.
- Tell your doctor if you are taking tricyclic antidepressants e.g. amitriptyline.
- Tell your doctor if you are taking hormonal/oral contraceptives. Exalief 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 Exalief up to the end of the current menstrual cycle after stopping treatment.
- Do not take oxcarbazepine (a medicine used to treat epilepsy) with Exalief, as it is not known whether it is safe to take these medicines together.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is just in case any of them interfere with how Exalief works or how Exalief interferes with their effect.

Taking Exalief with food and drink
Exalief tablets may be taken with or without food.

Pregnancy and breast-feeding
Tell your doctor immediately if you are pregnant or planning to become pregnant. You must only take Exalief during pregnancy if your doctor tells you.

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 Exalief. It is not known whether it passes into breast milk.

See **'**Taking other medicines' section for advice about contraception.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Exalief 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 EXALIEF

Always take Exalief exactly as your doctor has told you. You should 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 dose 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 Exalief, your dose may be increased to 1200 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 Exalief. Your doctor will work out the correct dose for you. Exalief is not recommended if you have severe kidney problems.

Patients with liver problems
The dose is the same as for adults. However, Exalief is not recommended if you have severe liver problems. Please talk to your doctor if you are unsure about the dose you should be taking.

Method and route of administration
Swallow the tablet with a glass of water.

If you take more Exalief than you should
If you accidently take more Exalief 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 Exalief
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 the one you have missed.

If you stop taking Exalief
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 Exalief for. Should your doctor decide to stop your treatment with Exalief 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 product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

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

The following side effects can be very serious. If they happen to you stop taking Exalief 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

The frequency of possible side effects listed below is defined as using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)

Very common side effects are:

- Feeling dizzy or sleepy

Common 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
- Clumsiness
- Skin rash
- Numbness and tingling in hands and feet

Uncommon side effects are:

- Hypersensitivity
- Worsening of seizures
- Underactive thyroid gland. Symptoms include cold intolerance, large tongue, thin and brittle fingernails or hair and low body temperature.
- Increased levels of circulating fats in your blood
- Difficulty in sleeping
- Liver problems
- High or low blood pressure or a fall in blood pressure on standing up
- Blood tests showing that you have low levels of salts or sodium in your blood or a reduction in red blood cells
- Dehydration
- Eye movement changes, fuzzy vision, red eye or eye pain
- Having falls
- 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
- Agitated
- Irritability
- Mood changes or hallucinations
- Difficulty in speaking
- Nosebleed
- Chest pain
- Weight loss and general ill health (Cachexia)
- Feeling numb in any part of your body
- Burning sensation

- Disturbances in the sense of smell and/or tasting
- Ear pain or ringing in the ears
- Swelling in your legs and arms
- Heart burn, stomach upset, abdominal pain, abdominal bloating and discomfort or dry mouth
- Blood in faeces
- Inflamed gums, mouth inflammation or toothache
- Painful swallowing
- Sweating or having dry skin
- Nail or skin changes (e.g. red skin)
- Hair loss
- Having irregular periods
- Increased urine production during night time
- Urinary tract infection
- Feeling generally unwell or having chills
- Increased or decreased appetite
- Weight loss or extreme weight gain
- Muscle pain
- Back pain or neck pain
- Cold limbs
- Faster, slower or irregular heart beat
- Feeling sleepy
- Neurological movement disorder where your muscles contract causing twisting and repetitive movements or abnormal postures. Symptoms include tremors, pain, cramping.
- Irritable Bowel Syndrome (IBS). Symptoms include chronic abdominal cramps and diarrhoea or constipation.

Rare side effects are:
- Reduction in blood platelets which increases risk of bleeding or bruising
- Severe pain in the back and stomach
- Reduction in white blood cells which makes infections more likely

The use of Exalief 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.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE EXALIEF

Keep out of the reach and sight of children.

Do not use Exalief after the expiry date, which is stated on the blister package 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Exalief 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 Exalief looks like and contents of the pack
Exalief 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 scoreline is only to facilitate breaking the tablet into two for ease of swallowing, and it does not divide the tablet into two equal doses.

The tablets are packaged in blisters in cardboard boxes containing 7, 14 or 28 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
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Portugal
tel: +351 22 986 61 00
fax: +351 22 986 61 99
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For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last approved in MMM/YYYY

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

Exalief 600 mg tablets

Eslicarbazepine acetate

Read all of this leaflet carefully before you start taking this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT EXALIEF IS AND WHAT IT IS USED FOR

Exalief belongs to a group of medicines called anti-epileptics used to treat epilepsy, a condition where someone has repeated seizures or fits.

Exalief 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).

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

2. BEFORE YOU TAKE EXALIEF

Do not take Exalief if:
- you are allergic (hypersensitive) to the active substance (eslicarbazepine acetate), to other carboxamide derivatives (e.g. carbamazepine or oxcarbazepine, medicines used to treat epilepsy) or to any of the other ingredients
- you suffer from a certain type of heart rhythm disorder (second or third degree atrioventricular (AV) block)

Take special care with Exalief
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.
- 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. Exalief is not recommended in patients with severe renal disease.
- you have liver problems. Exalief is not recommended in patients with severe liver problems.

- 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.
- you suffer from a heart disease such as heart failure or heart attack.
- you suffer from seizures that begin with a widespread electric discharge that involves both sides of the brain

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

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 Exalief, contact your doctor immediately.

Children
Exalief is not to be given to children and adolescents.

Taking other medicines
- Tell your doctor if you are taking phenytoin (a medicine used to treat epilepsy) since your dose may need to be adjusted.
- Tell your doctor if you are taking carbamazepine (a medicine used to treat epilepsy) since your dose may have to be adjusted and the following side effects of Exalief may occur in higher frequency: seeing double, abnormal coordination and dizziness.
- Tell your doctor if you are taking simvastatin (a medicine used to lower cholesterol levels) since your dose may have to be adjusted.
- Tell your doctor if you are taking the blood thinner - warfarin.
- Tell your doctor if you are taking tricyclic antidepressants e.g. amitriptyline.
- Tell your doctor if you are taking hormonal/oral contraceptives. Exalief 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 Exalief up to the end of the current menstrual cycle after stopping treatment.
- Do not take oxcarbazepine (a medicine used to treat epilepsy) with Exalief, as it is not known whether it is safe to take these medicines together.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is just in case any of them interfere with how Exalief works or how Exalief interferes with their effect.

Taking Exalief with food and drink
Exalief tablets may be taken with or without food.

Pregnancy and breast-feeding
Tell your doctor immediately if you are pregnant or planning to become pregnant. You must only take Exalief during pregnancy if your doctor tells you.

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 Exalief. It is not known whether it passes into breast milk.

See **'**Taking other medicines' section for advice about contraception.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Exalief 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 EXALIEF

Always take Exalief exactly as your doctor has told you. You should 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 dose 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 Exalief, your dose may be increased to 1200 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 Exalief. Your doctor will work out the correct dose for you. Exalief is not recommended if you have severe kidney problems.

Patients with liver problems
The dose is the same as for adults. However, Exalief is not recommended if you have severe liver problems. Please talk to your doctor if you are unsure about the dose you should be taking.

Method and route of administration
Swallow the tablet with a glass of water.

If you take more Exalief than you should
If you accidently take more Exalief 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 Exalief
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 the one you have missed.

If you stop taking Exalief
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 Exalief for. Should your doctor decide to stop your treatment with Exalief 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 product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

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

The following side effects can be very serious. If they happen to you stop taking Exalief 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

The frequency of possible side effects listed below is defined as using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)

Very common side effects are:

- Feeling dizzy or sleepy

Common 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
- Clumsiness
- Skin rash
- Numbness and tingling in hands and feet

Uncommon side effects are:

- Hypersensitivity
- Worsening of seizures
- Underactive thyroid gland. Symptoms include cold intolerance, large tongue, thin and brittle fingernails or hair and low body temperature.
- Increased levels of circulating fats in your blood
- Difficulty in sleeping
- Liver problems
- High or low blood pressure or a fall in blood pressure on standing up
- Blood tests showing that you have low levels of salts or sodium in your blood or a reduction in red blood cells
- Dehydration
- Eye movement changes, fuzzy vision, red eye or eye pain
- Having falls
- 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
- Agitated
- Irritability
- Mood changes or hallucinations
- Difficulty in speaking
- Nosebleed
- Chest pain
- Weight loss and general ill health (Cachexia)
- Feeling numb in any part of your body
- Burning sensation

- Disturbances in the sense of smell and/or tasting
- Ear pain or ringing in the ears
- Swelling in your legs and arms
- Heart burn, stomach upset, abdominal pain, abdominal bloating and discomfort or dry mouth
- Blood in faeces
- Inflamed gums, mouth inflammation or toothache
- Painful swallowing
- Sweating or having dry skin
- Nail or skin changes (e.g. red skin)
- Hair loss
- Having irregular periods
- Increased urine production during night time
- Urinary tract infection
- Feeling generally unwell or having chills
- Increased or decreased appetite
- Weight loss or extreme weight gain
- Muscle pain
- Back pain or neck pain
- Cold limbs
- Faster, slower or irregular heart beat
- Feeling sleepy
- Neurological movement disorder where your muscles contract causing twisting and repetitive movements or abnormal postures. Symptoms include tremors, pain, cramping.
- Irritable Bowel Syndrome (IBS). Symptoms include chronic abdominal cramps and diarrhoea or constipation.

Rare side effects are:
- Reduction in blood platelets which increases risk of bleeding or bruising
- Severe pain in the back and stomach
- Reduction in white blood cells which makes infections more likely

The use of Exalief 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.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE EXALIEF

Keep out of the reach and sight of children.

Do not use Exalief after the expiry date, which is stated on the blister package, 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Exalief 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 Exalief looks like and contents of the pack
Exalief 600 mg tablets are white and oblong. The tablets have 'ESL 600'engraved on one side and are scored on the other side, enabling the tablets to be divided into equal halves.

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

This leaflet was last approved in MMM/YYYY

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

Exalief 800 mg tablets

Eslicarbazepine acetate

Read all of this leaflet carefully before you start taking this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT EXALIEF IS AND WHAT IT IS USED FOR

Exalief belongs to a group of medicines called anti-epileptics used to treat epilepsy, a condition where someone has repeated seizures or fits.

Exalief 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).

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

2. BEFORE YOU TAKE EXALIEF

Do not take Exalief if:
- you are allergic (hypersensitive) to the active substance (eslicarbazepine acetate), to other carboxamide derivatives (e.g. carbamazepine or oxcarbazepine, medicines used to treat epilepsy) or to any of the other ingredients
- you suffer from a certain type of heart rhythm disorder (second or third degree atrioventricular (AV) block)

Take special care with Exalief
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.
- 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. Exalief is not recommended in patients with severe renal disease.
- you have liver problems. Exalief is not recommended in patients with severe liver problems.

- 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.
- you suffer from a heart disease such as heart failure or heart attack.
- you suffer from seizures that begin with a widespread electric discharge that involves both sides of the brain

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

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 Exalief, contact your doctor immediately.

Children
Exalief is not to be given to children and adolescents.

Taking other medicines
- Tell your doctor if you are taking phenytoin (a medicine used to treat epilepsy) since your dose may need to be adjusted.
- Tell your doctor if you are taking carbamazepine (a medicine used to treat epilepsy) since your dose may have to be adjusted and the following side effects of Exalief may occur in higher frequency: seeing double, abnormal coordination and dizziness.
- Tell your doctor if you are taking simvastatin (a medicine used to lower cholesterol levels) since your dose may have to be adjusted
- Tell your doctor if you are taking the blood thinner - warfarin.
- Tell your doctor if you are taking tricyclic antidepressants e.g. amitriptyline.
- Tell your doctor if you are taking hormonal/oral contraceptives. Exalief 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 Exalief up to the end of the current menstrual cycle after stopping treatment.
- Do not take oxcarbazepine (a medicine used to treat epilepsy) with Exalief, as it is not known whether it is safe to take these medicines together.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is just in case any of them interfere with how Exalief works or how Exalief interferes with their effect.

Taking Exalief with food and drink
Exalief tablets may be taken with or without food.

Pregnancy and breast-feeding
Tell your doctor immediately if you are pregnant or planning to become pregnant. You must only take Exalief during pregnancy if your doctor tells you.

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 Exalief. It is not known whether it passes into breast milk.

See **'**Taking other medicines' section for advice about contraception.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Exalief 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 EXALIEF

Always take Exalief exactly as your doctor has told you. You should 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 dose 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 Exalief, your dose may be increased to 1200 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 Exalief. Your doctor will work out the correct dose for you. Exalief is not recommended if you have severe kidney problems.

Patients with liver problems
The dose is the same as for adults. However, Exalief is not recommended if you have severe liver problems. Please talk to your doctor if you are unsure about the dose you should be taking.

Method and route of administration
Swallow the tablet with a glass of water.

If you take more Exalief than you should
If you accidently take more Exalief 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 Exalief
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 the one you have missed.

If you stop taking Exalief
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 Exalief for. Should your doctor decide to stop your treatment with Exalief 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 product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

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

The following side effects can be very serious. If they happen to you stop taking Exalief 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

The frequency of possible side effects listed below is defined as using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)

Very common side effects are:

- Feeling dizzy or sleepy

Common 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
- Clumsiness
- Skin rash
- Numbness and tingling in hands and feet

Uncommon side effects are:

- Hypersensitivity
- Worsening of seizures
- Underactive thyroid gland. Symptoms include cold intolerance, large tongue, thin and brittle fingernails or hair and low body temperature.
- Increased levels of circulating fats in your blood
- Difficulty in sleeping
- Liver problems
- High or low blood pressure or a fall in blood pressure on standing up
- Blood tests showing that you have low levels of salts or sodium in your blood or a reduction in red blood cells
- Dehydration
- Eye movement changes, fuzzy vision, red eye or eye pain
- Having falls
- 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
- Agitated
- Irritability
- Mood changes or hallucinations
- Difficulty in speaking
- Nosebleed
- Chest pain
- Weight loss and general ill health (Cachexia)
- Feeling numb in any part of your body
- Burning sensation

- Disturbances in the sense of smell and/or tasting
- Ear pain or ringing in the ears
- Swelling in your legs and arms
- Heart burn, stomach upset, abdominal pain, abdominal bloating and discomfort or dry mouth
- Blood in faeces
- Inflamed gums, mouth inflammation or toothache
- Painful swallowing
- Sweating or having dry skin
- Nail or skin changes (e.g. red skin)
- Hair loss
- Having irregular periods
- Increased urine production during night time
- Urinary tract infection
- Feeling generally unwell or having chills
- Increased or decreased appetite
- Weight loss or extreme weight gain
- Muscle pain
- Back pain or neck pain
- Cold limbs
- Faster, slower or irregular heart beat
- Feeling sleepy
- Neurological movement disorder where your muscles contract causing twisting and repetitive movements or abnormal postures. Symptoms include tremors, pain, cramping.
- Irritable Bowel Syndrome (IBS). Symptoms include chronic abdominal cramps and diarrhoea or constipation.

Rare side effects are:
- Reduction in blood platelets which increases risk of bleeding or bruising
- Severe pain in the back and stomach
- Reduction in white blood cells which makes infections more likely

The use of Exalief 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.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE EXALIEF

Keep out of the reach and sight of children.

Do not use Exalief after the expiry date, which is stated on the blister package, 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Exalief 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 Exalief looks like and contents of the pack
Exalief 800 mg tablets are white and oblong. The tablets have 'ESL 800'engraved on one side and are scored on the other side, enabling the tablets to be divided into equal halves.

The tablets are packaged in blisters in cardboard boxes containing 20, 30, 60 or 90 tablets, and in HDPE bottles with child resistant closure in cardboard boxes containing 90 tablets.

Not all pack sizes may be marketed.

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

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