Public Assessment Report

Decentralised Procedure

Oxcarbazepine 150mg, 300mg & 600mg Film Coated Tablets
UK/H/1304/001-003/DC

UK licence no: PL 00289/1084-6

TEVA UK Limited
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted TEVA UK Limited Marketing Authorisations (licences) for the medicinal products Oxcarbazepine 150mg, 300mg and 600mg Film Coated Tablets (PL 00289/1084-1086) on 3rd June 2009. This is a prescription-only medicine used to treatment of epilepsy. It is designed to help control seizures or fits in patients who have epilepsy. Oxcarbazepine is used to treat certain types of epilepsy in adults and children aged 6 years and over.

The tablets contain the active ingredient, oxcarbazepine. Oxcarbazepine belongs to a group of medicines called anticonvulsants, which are used in the treatment of epilepsy.

The mechanism of action of oxcarbazepine is thought to be mainly based on blockade of sodium channels and thus stabilising electrical activity in the brain.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Oxcarbazepine 150mg, 300mg and 600mg Film Coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module 1: Information about initial procedure</th>
<th>Page 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>Page 5</td>
</tr>
<tr>
<td>Module 3: Product Information Leaflet</td>
<td>Page 35</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>Page 37</td>
</tr>
<tr>
<td>Module 5: Scientific Discussion</td>
<td>Page 40</td>
</tr>
<tr>
<td>1 Introduction</td>
<td>Page 40</td>
</tr>
<tr>
<td>2 Quality aspects</td>
<td>Page 42</td>
</tr>
<tr>
<td>3 Pre-clinical aspects</td>
<td>Page 44</td>
</tr>
<tr>
<td>4 Clinical aspects</td>
<td>Page 44</td>
</tr>
<tr>
<td>5 Overall conclusions</td>
<td>Page 49</td>
</tr>
<tr>
<td>Module 6 Steps taken after initial procedure</td>
<td>Page 50</td>
</tr>
</tbody>
</table>
# Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Oxcarbazepine 150mg, 300mg &amp; 600 mg Film-coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Oxcarbazepine</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Film-Coated Tablet</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>150mg, 300mg and 600mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>TEVA UK Limited</td>
</tr>
<tr>
<td><strong>RMS</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Austria, Bulgaria, Cyprus, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Lithuania, Latvia, Malta, The Netherlands, Norway, Poland, Sweden.</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/1304/001-003/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 6th May 2009</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Oxcarbazepine 150 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 150 mg oxcarbazepine.

Excipients
Each film-coated tablet contains 8.32 mg lactose and 0.02 mg sunset yellow aluminium lake (E110).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Yellow to dark yellow, film-coated capsule-shaped tablet. One side of the tablet is scored in half and debossed with "9" on one side of the score and "3" on the other. The other side of the tablet is scored in half and debossed with "72" on one side of the score and "81" on the other.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Oxcarbazepine is indicated for the treatment of partial seizures with or without secondarily generalised tonic-clonic seizures.

It is indicated for use as monotherapy or adjunctive therapy in adults and in children of 6 years of age and above.

4.2 Posology and method of administration
In mono- and adjunctive therapy, treatment with oxcarbazepine is initiated with a clinically effective dose given in two divided doses. The dose may be increased depending on the clinical response of the patient.

When other antiepileptic medicinal products are replaced by oxcarbazepine, the dose of the concomitant antiepileptic medicinal product(s) should be reduced gradually on initiation of oxcarbazepine therapy.

In adjunctive therapy, as the total antiepileptic medicinal product load of the patient is increased, the dose of concomitant antiepileptic medicinal product(s) may need to be reduced and/or the oxcarbazepine dose increased more slowly (see section 4.5).

Oxcarbazepine can be taken with or without food.

The following dosing recommendations apply to all patients, in the absence of impaired renal function (see section 5.2). Active substance plasma level monitoring is not necessary to optimise oxcarbazepine therapy. The tablets are scored and can be broken in two halves in order to make it easier for the patient to swallow the tablet. For children, who cannot swallow tablets or where the required dose cannot be administered using tablets, other strengths and pharmaceutical forms are available.

Adults
Monotherapy
Oxcarbazepine should be initiated with a dose of 600 mg/day (8-10 mg/kg/day) given in 2 divided doses. If clinically indicated, the dose may be increased by a maximum of 600 mg/day increments at approximately weekly intervals from the starting dose to achieve the desired clinical response. Therapeutic effects are seen at doses between 600 mg/day and 2,400 mg/day.

Controlled monotherapy trials in patients not currently being treated with antiepileptic medicinal
products showed 1,200 mg/day to be an effective dose; however, a dose of 2,400 mg/day has been shown to be effective in more refractory patients converted from other antiepileptic medicinal products to oxcarbazepine monotherapy. In a controlled hospital setting, dose increases up to 2,400 mg/day have been achieved over 48 hours.

**Adjunctive therapy**

Oxcarbazepine should be initiated with a dose of 600 mg/day (8-10 mg/kg/day) given in 2 divided doses. If clinically indicated, the dose may be increased by a maximum of 600 mg/day increments at approximately weekly intervals from the starting dose to achieve the desired clinical response. Therapeutic responses are seen at doses between 600 mg/day and 2,400 mg/day.

Daily doses from 600 to 2,400 mg/day have been shown to be effective in a controlled adjunctive therapy trial, although most patients were not able to tolerate the 2,400 mg/day dose without reduction of concomitant antiepileptic medicinal products, mainly because of CNS-related adverse events. Daily doses above 2,400 mg/day have not been studied systematically in clinical trials.

**Elderly**

Adjustment of the dose is recommended in the elderly with compromised renal function (see 'Patients with renal impairment'). For patients at risk of hyponatraemia, see section 4.4.

**Children**

In mono- and adjunctive therapy, oxcarbazepine should be initiated with a dose of 8-10 mg/kg/day given in 2 divided doses. In adjunctive therapy, therapeutic effects were seen at a median maintenance dose of approximately 30 mg/kg/day. If clinically indicated, the dose may be increased by a maximum of 10 mg/kg/day increments at approximately weekly intervals from the starting dose, to a maximum dose of 46 mg/kg/day, to achieve the desired clinical response (see section 5.2).

Oxcarbazepine is recommended for use in children of 6 years of age and above. Safety and efficacy have been evaluated in controlled clinical trials involving approximately 230 children aged less than 6 years (down to 1 month). Oxcarbazepine is not recommended in children aged less than 6 years since safety and efficacy have not been adequately demonstrated.

All the above dosing recommendations (adults, elderly and children) are based on the doses studied in clinical trials for all age groups. However, lower initiation doses may be considered where appropriate.

**Patients with hepatic impairment**

No dosage adjustment is required for patients with mild to moderate hepatic impairment.

Oxcarbazepine has not been studied in patients with severe hepatic impairment, therefore, caution should be exercised when dosing severely impaired patients (see section 5.2).

**Patients with renal impairment**

In patients with impaired renal function (creatinine clearance less than 30 ml/min) oxcarbazepine therapy should be initiated at half the usual starting dose (300 mg/day) and increased, in at least weekly intervals, to achieve the desired clinical response (see section 5.2).

Dose escalation in renally impaired patients may require more careful observation.

4.3 **Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

4.4 **Special warnings and precautions for use**

**Hypersensitivity**

Class I (immediate) hypersensitivity reactions including rash, pruritus, urticaria, angioedema and reports of anaphylaxis have been received in the post-marketing period. Cases of anaphylaxis and angioedema involving the larynx, glottis, lips and eyelids have been reported in patients after taking the first or subsequent doses of oxcarbazepine. If a patient develops these reactions after treatment with oxcarbazepine, the medicinal product should be discontinued and an alternative treatment started.

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25-30% of these patients may experience hypersensitivity reactions (e.g. severe skin reactions) with oxcarbazepine (see section 4.8).
Hypersensitivity reactions, including multi-organ hypersensitivity reactions, may also occur in patients without history of hypersensitivity to carbamazepine. Such reactions can affect the skin, liver, blood and lymphatic system or other organs, either individually or together in the context of a systemic reaction (see section 4.8). In general, if signs and symptoms suggestive of hypersensitivity reactions occur (see section 4.8), oxcarbazepine should be withdrawn immediately.

**Dermatological effects**

Serious dermatological reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell’s syndrome) and erythema multiforme, have been reported very rarely in association with oxcarbazepine use. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and very rarely be fatal. Oxcarbazepine-associated cases occurred in both children and adults. The median time to onset was 19 days. Several isolated cases of recurrence of the serious skin reaction when rechallenged with oxcarbazepine were reported. Patients who develop a skin reaction with it should be promptly evaluated and oxcarbazepine withdrawn immediately unless the rash is clearly not related. In case of treatment withdrawal, consideration should be given to replacing oxcarbazepine with other antiepileptic therapy to avoid withdrawal seizures. Oxcarbazepine should not be restarted in patients who discontinued treatment due to a hypersensitivity reaction (see section 4.3).

**Hyponatraemia**

Serum sodium levels below 125 mmol/l, usually asymptomatic and not requiring adjustment of therapy, have been observed in up to 2.7% of oxcarbazepine-treated patients. Experience from clinical trials shows that serum sodium levels returned towards normal when the oxcarbazepine dosage was reduced, discontinued or the patient was treated conservatively (e.g. restricted fluid intake). In patients with pre-existing renal conditions associated with low sodium or in patients treated concomitantly with sodium-lowering medicinal products (e.g. diuretics, desmopressin) as well as NSAIDs (e.g. indomethacin), serum sodium levels should be measured prior to initiating therapy. Thereafter, serum sodium levels should be measured after approximately two weeks and then at monthly intervals for the first three months during therapy, or according to clinical need. These risk factors may apply especially to elderly patients. For patients on oxcarbazepine therapy when starting on sodium-lowering medicinal products, the same approach for sodium checks should be followed. In general, if clinical symptoms suggestive of hyponatraemia occur on oxcarbazepine therapy (see section 4.8), serum sodium measurement may be considered. Other patients may have serum sodium assessed as part of their routine laboratory studies.

All patients with cardiac insufficiency and secondary heart failure should have regular weight measurements to determine occurrence of fluid retention. In case of fluid retention or worsening of the cardiac condition, serum sodium should be checked. If hyponatraemia is observed, water restriction is an important counter-measurement. As oxcarbazepine may, very rarely, lead to impairment of cardiac conduction, patients with pre-existing conduction disturbances (e.g. atrioventricular-block, arrhythmia) should be followed carefully.

**Hepatic function**

Very rare cases of hepatitis have been reported, which in most of the cases resolved favourably. When a hepatic event is suspected, liver function should be evaluated and discontinuation of oxcarbazepine should be considered.

**Haematological effects**

Very rare reports of agranulocytosis, aplastic anaemia and pancytopenia have been seen in patients treated with oxcarbazepine during post-marketing experience (see section 4.8).

Discontinuation of the medicinal product should be considered if any evidence of significant bone marrow depression develops.

**Hormonal contraceptives**

Female patients of child-bearing age should be warned that the concurrent use of oxcarbazepine with hormonal contraceptives may render this type of contraceptive ineffective (see section 4.5). Additional non-hormonal forms of contraception are recommended when using oxcarbazepine.

**Alcohol**

Caution should be exercised if alcohol is taken in combination with oxcarbazepine therapy, due to a possible additive sedative effect.
Withdrawal
Oxcarbazepine should be withdrawn gradually to minimise the potential of increased seizure frequency.

Suicidal ideation
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic agents 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 oxcarbazepine. 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.

Excipients
This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains sunset yellow aluminium lake (E110) and may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Enzyme induction
Oxcarbazepine and its pharmacologically active metabolite (the monohydroxy derivative, MHD) are weak inducers in vitro and in vivo of the cytochrome P450 enzymes CYP3A4 and CYP3A5 responsible for the metabolism of a very large number of substances, for example, immunosuppressants (e.g. ciclosporin, tacrolimus), oral contraceptives (see below), and some other antiepileptic medicinal products (e.g. carbamazepine) resulting in a lower plasma concentration of these medicinal products (see table below summarizing results with other antiepileptic medicinal products).

In vitro, oxcarbazepine and MHD are weak inducers of UDP-glucuronyl transferases (effects on specific enzymes in this family are not known). Therefore, in vivo oxcarbazepine and MHD may have a small inducing effect on the metabolism of medicinal products which are mainly eliminated by conjugation through the UDP-glucuronyl transferases. When initiating treatment with oxcarbazepine or changing the dose, it may take 2 to 3 weeks to reach the new level of induction.

In case of discontinuation of oxcarbazepine therapy, a dose reduction of the concomitant medications may be necessary and should be decided upon by clinical and/or plasma level monitoring. The induction is likely to gradually decrease over 2 to 3 weeks after discontinuation.

Hormonal contraceptives: Oxcarbazepine was shown to have an influence on the two components, ethinyloestradiol (EO) and levonorgestrel (LNG), of an oral contraceptive. The mean AUC values of EO and LNG were decreased by 48-52% and 32-52% respectively. Therefore, concurrent use of oxcarbazepine with hormonal contraceptives may render these contraceptives ineffective (see section 4.4). Another reliable contraceptive method should be used.

Enzyme inhibition
Oxcarbazepine and MHD inhibit CYP2C19. Therefore, interactions could arise when co-administering high doses of oxcarbazepine with medicinal products that are mainly metabolised by CYP2C19 (e.g. phenytoin). Phenytoin plasma levels increased by up to 40% when oxcarbazepine was given at doses above 1,200 mg/day (see table below summarizing results with other anticonvulsants). In this case, a reduction of co-administered phenytoin may be required (see section 4.2).

Antiepileptic medicinal products
Potential interactions between oxcarbazepine and other antiepileptic medicinal products were assessed in clinical studies. The effect of these interactions on mean AUCs and \( C_{\text{max}} \) are summarised in the following table.
Summary of antiepileptic medicinal product interactions with oxcarbazepine

<table>
<thead>
<tr>
<th>Antiepileptic medicinal product co-administered</th>
<th>Influence of oxcarbazepine on antiepileptic medicinal product concentration</th>
<th>Influence of antiepileptic medicinal product on MHD concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>0-22% decrease (30% increase of carbamazepine-epoxide)</td>
<td>40% decrease</td>
</tr>
<tr>
<td>Clobazam</td>
<td>Not studied</td>
<td>No influence</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Not studied</td>
<td>No influence</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Slight decrease*</td>
<td>No influence</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>14-15% increase</td>
<td>30-31% decrease</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>0-40% increase</td>
<td>29-35% decrease</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>No influence</td>
<td>0-18% decrease</td>
</tr>
</tbody>
</table>

* Preliminary results indicate that oxcarbazepine may result in lower lamotrigine concentrations, possibly of importance in children, but the interaction potential of oxcarbazepine appears lower than seen with concomitant enzyme-inducing substances (carbamazepine, phenobarbitone, and phenytoin).

Strong inducers of cytochrome P450 enzymes (i.e. carbamazepine, phenytoin and phenobarbitone) have been shown to decrease the plasma levels of MHD (29-40%) in adults; in children 4 to 12 years of age, MHD clearance increased by approximately 35% when given one of the three enzyme-inducing antiepileptic medicinal products compared to monotherapy. Concomitant therapy of oxcarbazepine and lamotrigine has been associated with an increased risk of adverse events (nausea, somnolence, dizziness and headache). When one or several antiepileptic medicinal products are concurrently administered with oxcarbazepine, a careful dose adjustment and/or plasma level monitoring may be considered on a case by case basis, notably in paediatric patients treated concomitantly with lamotrigine.

No auto-induction has been observed with oxcarbazepine.

Other medicinal product interactions

- Cimetidine, erythromycin, viloxazine, warfarin and dextropropoxyphene had no effect on the pharmacokinetics of MHD.

- The interaction between oxcarbazepine and monoamine oxidase inhibitors (MAOIs) is theoretically possible based on a structural relationship of oxcarbazepine to tricyclic antidepressants.

- Patients on tricyclic antidepressant therapy were included in clinical trials and no clinically relevant interactions have been observed.

- The combination of lithium and oxcarbazepine might cause enhanced neurotoxicity.

4.6 Pregnancy and lactation

Pregnancy

- Risk related to epilepsy and antiepileptic medicinal products in general:
  - It has been shown that in the offspring of women with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. In the treated population, an increase in malformations has been noted with polytherapy; however, the extent to which the treatment and/or the illness is responsible has not been elucidated.

- Moreover, effective antiepileptic therapy must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the fetus.

- Risk related to oxcarbazepine:
  - Clinical data on exposure during pregnancy are still insufficient to assess the teratogenic potential of oxcarbazepine. In animal studies, increased embryo mortality, delayed growth and malformations were observed at maternally toxic dose levels (see section 5.3).

Taking these data into consideration:

- If women receiving oxcarbazepine become pregnant or plan to become pregnant, the use of this product 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 of antenatal screening.

• During pregnancy, an effective antiepileptic oxcarbazepine treatment must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the fetus.

**Monitoring and prevention:**
Antiepileptic medicinal products may contribute to folic acid deficiency, a possible contributory cause of fetal abnormality. Folic acid supplementation is recommended before and during pregnancy. As the efficacy of this supplementation is not proved, 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 agents have been reported. As a precaution, vitamin K$_1$ should be administered as a preventive measure in the last few weeks of pregnancy and to the newborn.

**Lactation**
Oxcarbazepine and its active metabolite (MHD) are excreted in human breast milk. A milk-to-plasma concentration ratio of 0.5 was found for both. The effects on the infant exposed to oxcarbazepine by this route are unknown. Therefore, it should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

The use of oxcarbazepine has been associated with adverse reactions such as dizziness or somnolence (see section 4.8). Therefore, patients should be advised that their physical and/or mental abilities required for operating machinery or driving a car might be impaired.

4.8 Undesirable effects

The most commonly reported adverse reactions are somnolence, headache, dizziness, diplopia, nausea, vomiting and fatigue occurring in more than 10% of patients.

The adverse event profile by body system is based on adverse events from clinical trials assessed as related to oxcarbazepine. In addition, clinically meaningful reports on adverse experiences from named patient programs and postmarketing experience were taken into account.

Frequency estimate: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very rare</strong></td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
</tr>
</tbody>
</table>

**Metabolism and nutrition disorders**

<table>
<thead>
<tr>
<th>Common</th>
<th>Hyponatraemia</th>
</tr>
</thead>
</table>

| Very rare | Hyponatraemia associated with signs and symptoms such as seizures, confusion, depressed level of consciousness, encephalopathy (see also Nervous system disorders for further adverse events), vision disorders |
(e.g. blurred vision), vomiting, nausea†

Psychiatric disorders

Common Confusional state, depression, apathy, agitation (e.g. nervousness), affect lability

Nervous system disorders

Very common Somnolence, headache, dizziness

Common Ataxia, tremor, nystagmus, disturbance in attention, amnesia

Eye disorders

Very common Diplopia

Common Vision blurred, visual disturbance

Ear and labyrinth disorders

Common Vertigo

Cardiac disorders

Very rare Arrhythmia, atrioventricular block

Vascular disorders

Unknown Hypertension

Gastrointestinal disorders

Very common Nausea, vomiting

Common Diarrhoea, constipation, abdominal pain

Very rare Pancreatitis and/or lipase and/or amylase increase

Hepato-biliary disorders

Very rare Hepatitis

Skin and subcutaneous tissue disorders

Common Rash, alopecia, acne

Uncommon Urticaria

Very rare Angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell’s syndrome), erythema multiforme (see section 4.4)

Musculoskeletal, connective tissue and bone disorders

Very rare Systemic lupus erythematosus

General disorders and administration site conditions

Very common Fatigue

Common Asthenia

Investigations

Uncommon Hepatic enzymes increased, blood alkaline phosphatase increased

†Very rarely, clinically significant hyponatraemia (sodium <125 mmol/l) can develop during oxcarbazepine use. It generally occurred during the first 3 months of treatment, although there were patients who first developed a serum sodium <125 mmol/l more than 1 year after initiation of therapy (see section 4.4).

4.9 Overdose

Isolated cases of overdose have been reported. The maximum dose taken was approximately 24,000 mg. All patients recovered with symptomatic treatment. Symptoms of overdose include somnolence, dizziness, nausea, vomiting, hyperkinesia, hyponatraemia, ataxia and nystagmus. There is no specific antidote. Symptomatic and supportive treatment should be administered as appropriate. Removal of the medicinal product by gastric lavage and/or inactivation by administering activated charcoal should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Carboxamide derivatives

ATC code: N03A F02

Pharmacodynamic effects

The pharmacological activity of oxcarbazepine is primarily exerted through the metabolite (MHD) (see section 5.2). The mechanism of action of oxcarbazepine and MHD is thought to be mainly based on blockade of voltage-sensitive sodium channels, thus resulting in stabilisation of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminishment of propagation of synaptic impulses. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may also contribute to the anticonvulsant effects. No significant interactions with brain neurotransmitter or modulator receptor sites were found.
Oxcarbazepine and its active metabolite (MHD), are potent and efficacious anticonvulsants in animals. They protected rodents against generalised tonic-clonic and, to a lesser degree, clonic seizures, and abolished or reduced the frequency of chronically recurring partial seizures in Rhesus monkeys with aluminium implants. No tolerance (i.e. attenuation of anticonvulsive activity) against tonic-clonic seizures was observed when mice and rats were treated daily for 5 days or 4 weeks, respectively, with oxcarbazepine or MHD.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, oxcarbazepine is completely absorbed and extensively metabolised to its pharmacologically active metabolite (MHD).

After single dose administration of 600 mg oxcarbazepine to healthy male volunteers under fasted conditions, the mean $C_{\text{max}}$ value of MHD was 34 µmol/l, with a corresponding median $t_{\text{max}}$ of 4.5 hours.

In a mass balance study in man, only 2% of total radioactivity in plasma was due to unchanged oxcarbazepine, approximately 70% was due to MHD, and the remainder attributable to minor secondary metabolites which were rapidly eliminated.

Food has no effect on the rate and extent of absorption of oxcarbazepine, therefore, it can be taken with or without food.

Distribution
The apparent volume of distribution of MHD is 49 litres.

Approximately 40% of MHD is bound to serum proteins, predominantly to albumin. Binding was independent of the serum concentration within the therapeutically relevant range. Oxcarbazepine and MHD do not bind to alpha-1-acid glycoprotein.

Oxcarbazepine and MHD cross the placenta. Neonatal and maternal plasma MHD concentrations were similar in one case.

Biotransformation
Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to MHD, which is primarily responsible for its pharmacological effect. MHD is metabolised further by conjugation with glucuronic acid. Minor amounts (4% of the dose) are oxidised to the pharmacologically inactive metabolite (10, 11-dihydroxy derivative, DHD).

Elimination
Oxcarbazepine is cleared from the body mostly in the form of metabolites which are predominantly excreted by the kidneys. More than 95% of the dose appears in the urine, with less than 1% as unchanged oxcarbazepine. Faecal excretion accounts for less than 4% of the administered dose. Approximately 80% of the dose is excreted in the urine either as glucuronides of MHD (49%) or as unchanged MHD (27%), whereas the inactive DHD accounts for approximately 3% and conjugates of oxcarbazepine account for 13% of the dose.

Oxcarbazepine is rapidly eliminated from the plasma with apparent half-life values between 1.3 and 2.3 hours. In contrast, the apparent plasma half-life of MHD averaged 9.3 ± 1.8 h.

Dose-proportionality
Steady-state plasma concentrations of MHD are reached within 2-3 days in patients when oxcarbazepine is given twice a day. At steady-state, the pharmacokinetics of MHD are linear and show dose-proportionality across the dose range of 300 to 2,400 mg/day.

Special populations
Patients with hepatic impairment
The pharmacokinetics and metabolism of oxcarbazepine and MHD were evaluated in healthy volunteers and hepatically-impaired subjects after a single 900 mg oral dose. Mild to moderate hepatic impairment did not affect the pharmacokinetics of oxcarbazepine and MHD. Oxcarbazepine has not been studied in patients with severe hepatic impairment.
Patients with renal impairment
There is a linear correlation between creatinine clearance and the renal clearance of MHD. When oxcarbazepine is administered as a single 300 mg dose, in renal impaired patients (creatinine clearance < 30 ml/min) the elimination half-life of MHD is prolonged by 60-90% (16 to 19 hours) with a two fold increase in AUC compared to adults with normal renal function (10 hours).

Children
The pharmacokinetics of oxcarbazepine were evaluated in clinical trials in paediatric patients taking it in the dose range 10-60 mg/kg/day. Weight-adjusted MHD clearance decreases as age and weight increase approaching that of adults. The mean weight clearance in children 4 to 12 years of age is approximately 40% higher that that of adults. Therefore MHD exposure in these children is expected to be about two-thirds that of adults when treated with a similar weight-adjusted dose. As weight increases, for patients 13 years of age and above, weight-adjusted MHD clearance is expected to reach that of adults.

Elderly
Following administration of single (300 mg) and multiple doses (600 mg/day) of oxcarbazepine in elderly volunteers (60-82 years of age), the maximum plasma concentrations and AUC values of MHD were 30-60% higher than in younger volunteers (18-32 years of age). Comparisons of creatinine clearances in young and elderly volunteers indicate that the difference was due to age-related reductions in creatinine clearance. No special dose recommendations are necessary because therapeutic doses are individually adjusted.

Gender
No gender-related pharmacokinetic differences have been observed in children, adults, or the elderly.

5.3 Preclinical safety data
Preclinical data indicated no special hazard for humans based on repeated-dose toxicity, safety pharmacology and genotoxicity studies with oxcarbazepine and the pharmacologically active metabolite, monohydroxy derivative (MHD).

Evidence of nephrotoxicity was noted in repeated dose toxicity rat studies but not in dog or mice studies. As there are no reports of such changes in patients, the clinical relevance of this finding in rats remains unknown.

Immunostimulatory tests in mice showed that MHD (and to a lesser extent oxcarbazepine) can induce delayed hypersensitivity.

Animal studies revealed effects such as increases in the incidence of embryo mortality and some delay in antenatal and/or postnatal growth at maternally toxic dose levels. There was an increase in rat fetal malformations in one of the eight embryo toxicity studies, which were conducted with either oxcarbazepine or the pharmacologically active metabolite (MHD), at a dose which also showed maternal toxicity (see section 4.6).

In the carcinogenicity studies, liver (rats and mice), testicular and female genital tract granular cell (rats) tumours were induced in treated animals. The occurrence of liver tumours was most likely a consequence of the induction of hepatic microsomal enzymes; an inductive effect which, although it cannot be excluded, is weak or absent in patients treated with oxcarbazepine. Testicular tumours may have been induced by elevated luteinizing hormone concentrations. Due to the absence of such an increase in humans, these tumours are considered to be of no clinical relevance. A dose-related increase in the incidence of granular cell tumours of the female genital tract (cervix and vagina) was noted in the rat carcinogenicity study with MHD. These effects occurred at exposure levels comparable with the anticipated clinical exposure. The mechanism for the development of these tumours has not been elucidated. Thus, the clinical relevance of these tumours is unknown.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Tablet core
Lactose monohydrate
Maize starch
Crospovidone
Povidone (K-30)
Cellulose, microcrystalline
Sodium starch glycolate (Type A)
Silica, colloidal anhydrous
Magnesium stearate

**Tablet film-coating**
Hypermellose
Macrogol 6000
Macrogol 400
Titanium dioxide (E171)
Iron oxide, yellow (E172)
Sunset yellow aluminium lake (E110)

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**
Transparent PVC/PVdC – Aluminium blisters:

Blisters in packs containing 1, 30, 50, 56, 100, 200 & 500 film-coated tablets. Hospital pack: 500 film-coated tablets.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORIZATION HOLDER**
Teva UK Limited,
Brampton Road,
Hampden Park,
Eastbourne, BN22 9AG
United Kingdom

8 **MARKETING AUTHORIZATION NUMBER(S)**
PL 00289/1084

9 **DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION**
03/06/2009

10 **DATE OF REVISION OF THE TEXT**
03/06/2009
1 NAME OF THE MEDICINAL PRODUCT
Oxcarbazepine 300 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 300 mg oxcarbazepine.

Excipients
Each film-coated tablet contains 16.63 mg lactose and 0.04 mg sunset yellow aluminium lake (E110).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Yellow to dark yellow, film-coated capsule-shaped tablet. One side of the tablet is scored in half and debossed with "9" on one side of the score and "3" on the other. The other side of the tablet is scored in half and debossed with "72" on one side of the score and "82" on the other.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Oxcarbazepine is indicated for the treatment of partial seizures with or without secondarily generalised tonic-clonic seizures.

It is indicated for use as monotherapy or adjunctive therapy in adults and in children of 6 years of age and above.

4.2 Posology and method of administration
In mono- and adjunctive therapy, treatment with oxcarbazepine is initiated with a clinically effective dose given in two divided doses. The dose may be increased depending on the clinical response of the patient.

When other antiepileptic medicinal products are replaced by oxcarbazepine, the dose of the concomitant antiepileptic medicinal product(s) should be reduced gradually on initiation of oxcarbazepine therapy.

In adjunctive therapy, as the total antiepileptic medicinal product load of the patient is increased, the dose of concomitant antiepileptic medicinal product(s) may need to be reduced and/or the oxcarbazepine dose increased more slowly (see section 4.5).

Oxcarbazepine can be taken with or without food.

The following dosing recommendations apply to all patients, in the absence of impaired renal function (see section 5.2). Active substance plasma level monitoring is not necessary to optimise oxcarbazepine therapy. The tablets are scored and can be broken in two halves in order to make it easier for the patient to swallow the tablet. For children, who cannot swallow tablets or where the required dose cannot be administered using tablets, other strengths and pharmaceutical forms are available.

Adults
Monotherapy
Oxcarbazepine should be initiated with a dose of 600 mg/day (8-10 mg/kg/day) given in 2 divided doses. If clinically indicated, the dose may be increased by a maximum of 600 mg/day increments at approximately weekly intervals from the starting dose to achieve the desired clinical response. Therapeutic effects are seen at doses between 600 mg/day and 2,400 mg/day.

Controlled monotherapy trials in patients not currently being treated with antiepileptic medicinal products showed 1,200 mg/day to be an effective dose; however, a dose of 2,400 mg/day has been shown to be effective in more refractory patients converted from other antiepileptic medicinal products to oxcarbazepine monotherapy. In a controlled hospital setting, dose increases up to 2,400 mg/day have been achieved over 48 hours.
Adjunctive therapy
Oxcarbazepine should be initiated with a dose of 600 mg/day (8-10 mg/kg/day) given in 2 divided doses. If clinically indicated, the dose may be increased by a maximum of 600 mg/day increments at approximately weekly intervals from the starting dose to achieve the desired clinical response. Therapeutic responses are seen at doses between 600 mg/day and 2,400 mg/day.

Daily doses from 600 to 2,400 mg/day have been shown to be effective in a controlled adjunctive therapy trial, although most patients were not able to tolerate the 2,400 mg/day dose without reduction of concomitant antiepileptic medicinal products, mainly because of CNS-related adverse events. Daily doses above 2,400 mg/day have not been studied systematically in clinical trials.

Elderly
Adjustment of the dose is recommended in the elderly with compromised renal function (see 'Patients with renal impairment'). For patients at risk of hyponatraemia, see section 4.4.

Children
In mono- and adjunctive therapy, oxcarbazepine should be initiated with a dose of 8-10 mg/kg/day given in 2 divided doses. In adjunctive therapy, therapeutic effects were seen at a median maintenance dose of approximately 30 mg/kg/day. If clinically indicated, the dose may be increased by a maximum of 10 mg/kg/day increments at approximately weekly intervals from the starting dose, to a maximum dose of 46 mg/kg/day, to achieve the desired clinical response (see section 5.2).

Oxcarbazepine is recommended for use in children of 6 years of age and above. Safety and efficacy have been evaluated in controlled clinical trials involving approximately 230 children aged less than 6 years (down to 1 month). Oxcarbazepine is not recommended in children aged less than 6 years since safety and efficacy have not been adequately demonstrated.

All the above dosing recommendations (adults, elderly and children) are based on the doses studied in clinical trials for all age groups. However, lower initiation doses may be considered where appropriate.

Patients with hepatic impairment
No dosage adjustment is required for patients with mild to moderate hepatic impairment.

Oxcarbazepine has not been studied in patients with severe hepatic impairment, therefore, caution should be exercised when dosing severely impaired patients (see section 5.2).

Patients with renal impairment
In patients with impaired renal function (creatinine clearance less than 30 ml/min) oxcarbazepine therapy should be initiated at half the usual starting dose (300 mg/day) and increased, in at least weekly intervals, to achieve the desired clinical response (see section 5.2).

Dose escalation in renally impaired patients may require more careful observation.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use
Hypersensitivity

Class I (immediate) hypersensitivity reactions including rash, pruritus, urticaria, angioedema and reports of anaphylaxis have been received in the post-marketing period. Cases of anaphylaxis and angioedema involving the larynx, glottis, lips and eyelids have been reported in patients after taking the first or subsequent doses of oxcarbazepine. If a patient develops these reactions after treatment with oxcarbazepine, the medicinal product should be discontinued and an alternative treatment started.

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25-30% of these patients may experience hypersensitivity reactions (e.g. severe skin reactions) with oxcarbazepine (see section 4.8).

Hypersensitivity reactions, including multi-organ hypersensitivity reactions, may also occur in patients without history of hypersensitivity to carbamazepine. Such reactions can affect the skin, liver, blood and lymphatic system or other organs, either individually or together in the context of a systemic reaction (see section 4.8). In general, if signs and symptoms suggestive of hypersensitivity reactions
occur (see section 4.8), oxcarbazepine should be withdrawn immediately.

**Dermatological effects**
Serious dermatological reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) and erythema multiforme, have been reported very rarely in association with oxcarbazepine use. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and very rarely be fatal. Oxcarbazepine-associated cases occurred in both children and adults. The median time to onset was 19 days. Several isolated cases of recurrence of the serious skin reaction when rechallenged with oxcarbazepine were reported. Patients who develop a skin reaction with it should be promptly evaluated and oxcarbazepine withdrawn immediately unless the rash is clearly not related. In case of treatment withdrawal, consideration should be given to replacing oxcarbazepine with other antiepileptic therapy to avoid withdrawal seizures. Oxcarbazepine should not be restarted in patients who discontinued treatment due to a hypersensitivity reaction (see section 4.3).

**Hyponatraemia**
Serum sodium levels below 125 mmol/l, usually asymptomatic and not requiring adjustment of therapy, have been observed in up to 2.7% of oxcarbazepine-treated patients. Experience from clinical trials shows that serum sodium levels returned towards normal when the oxcarbazepine dosage was reduced, discontinued or the patient was treated conservatively (e.g. restricted fluid intake). In patients with pre-existing renal conditions associated with low sodium or in patients treated concomitantly with sodium-lowering medicinal products (e.g. diuretics, desmopressin) as well as NSAIDs (e.g. indometacin), serum sodium levels should be measured prior to initiating therapy. Thereafter, serum sodium levels should be measured after approximately two weeks and then at monthly intervals for the first three months during therapy, or according to clinical need. These risk factors may apply especially to elderly patients. For patients on oxcarbazepine therapy when starting on sodium-lowering medicinal products, the same approach for sodium checks should be followed. In general, if clinical symptoms suggestive of hyponatraemia occur on oxcarbazepine therapy (see section 4.8), serum sodium measurement may be considered. Other patients may have serum sodium assessed as part of their routine laboratory studies.

All patients with cardiac insufficiency and secondary heart failure should have regular weight measurements to determine occurrence of fluid retention. In case of fluid retention or worsening of the cardiac condition, serum sodium should be checked. If hyponatraemia is observed, water restriction is an important counter-measurement. As oxcarbazepine may, very rarely, lead to impairment of cardiac conduction, patients with pre-existing conduction disturbances (e.g. atrioventricular-block, arrhythmia) should be followed carefully.

**Hepatic function**
Very rare cases of hepatitis have been reported, which in most of the cases resolved favourably. When a hepatic event is suspected, liver function should be evaluated and discontinuation of oxcarbazepine should be considered.

**Haematological effects**
Very rare reports of agranulocytosis, aplastic anaemia and pancytopenia have been seen in patients treated with oxcarbazepine during post-marketing experience (see section 4.8).

Discontinuation of the medicinal product should be considered if any evidence of significant bone marrow depression develops.

**Hormonal contraceptives**
Female patients of child-bearing age should be warned that the concurrent use of oxcarbazepine with hormonal contraceptives may render this type of contraceptive ineffective (see section 4.5). Additional non-hormonal forms of contraception are recommended when using oxcarbazepine.

**Alcohol**
Caution should be exercised if alcohol is taken in combination with oxcarbazepine therapy, due to a possible additive sedative effect.

**Withdrawal**
Oxcarbazepine should be withdrawn gradually to minimise the potential of increased seizure frequency.
Suicidal ideation
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic agents 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 oxcarbazepine. 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.

Excipients
This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains sunset yellow aluminium lake (E110) and may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Enzyme induction
Oxcarbazepine and its pharmacologically active metabolite (the monohydroxy derivative, MHD) are weak inducers in vitro and in vivo of the cytochrome P450 enzymes CYP3A4 and CYP3A5 responsible for the metabolism of a very large number of substances, for example, immunosuppressants (e.g. ciclosporin, tacrolimus), oral contraceptives (see below), and some other antiepileptic medicinal products (e.g. carbamazepine) resulting in a lower plasma concentration of these medicinal products (see table below summarizing results with other antiepileptic medicinal products).

In vitro, oxcarbazepine and MHD are weak inducers of UDP-glucuronyl transferases (effects on specific enzymes in this family are not known). Therefore, in vivo oxcarbazepine and MHD may have a small inducing effect on the metabolism of medicinal products which are mainly eliminated by conjugation through the UDP-glucuronyl transferases. When initiating treatment with oxcarbazepine or changing the dose, it may take 2 to 3 weeks to reach the new level of induction.

In case of discontinuation of oxcarbazepine therapy, a dose reduction of the concomitant medications may be necessary and should be decided upon by clinical and/or plasma level monitoring. The induction is likely to gradually decrease over 2 to 3 weeks after discontinuation.

Hormonal contraceptives: Oxcarbazepine was shown to have an influence on the two components, ethinyloestradiol (EO) and levonorgestrel (LNG), of an oral contraceptive. The mean AUC values of EO and LNG were decreased by 48-52% and 32-52% respectively. Therefore, concurrent use of oxcarbazepine with hormonal contraceptives may render these contraceptives ineffective (see section 4.4). Another reliable contraceptive method should be used.

Enzyme inhibition
Oxcarbazepine and MHD inhibit CYP2C19. Therefore, interactions could arise when co-administering high doses of oxcarbazepine with medicinal products that are mainly metabolised by CYP2C19 (e.g. phenytoin). Phenytoin plasma levels increased by up to 40% when oxcarbazepine was given at doses above 1,200 mg/day (see table below summarizing results with other anticonvulsants). In this case, a reduction of co-administered phenytoin may be required (see section 4.2).

Antiepileptic medicinal products
Potential interactions between oxcarbazepine and other antiepileptic medicinal products were assessed in clinical studies. The effect of these interactions on mean AUCs and Cmax are summarised in the following table.
### Summary of antiepileptic medicinal product interactions with oxcarbazepine

<table>
<thead>
<tr>
<th>Antiepileptic medicinal product co-administered</th>
<th>Influence of oxcarbazepine on antiepileptic medicinal product concentration</th>
<th>Influence of antiepileptic medicinal product on MHD concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>0-22% decrease (30% increase of carbamazepine-epoxide)</td>
<td>40% decrease</td>
</tr>
<tr>
<td>Clobazam</td>
<td>Not studied</td>
<td>No influence</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Not studied</td>
<td>No influence</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Slight decrease*</td>
<td>No influence</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>14-15% increase</td>
<td>30-31% decrease</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>0-40% increase</td>
<td>29-35% decrease</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>No influence</td>
<td>0-18% decrease</td>
</tr>
</tbody>
</table>

* Preliminary results indicate that oxcarbazepine may result in lower lamotrigine concentrations, possibly of importance in children, but the interaction potential of oxcarbazepine appears lower than seen with concomitant enzyme-inducing substances (carbamazepine, phenobarbitone, and phenytoin).

Strong inducers of cytochrome P450 enzymes (i.e. carbamazepine, phenytoin and phenobarbitone) have been shown to decrease the plasma levels of MHD (29-40%) in adults; in children 4 to 12 years of age, MHD clearance increased by approximately 35% when given one of the three enzyme-inducing antiepileptic medicinal products compared to monotherapy. Concomitant therapy of oxcarbazepine and lamotrigine has been associated with an increased risk of adverse events (nausea, somnolence, dizziness and headache). When one or several antiepileptic medicinal products are concurrently administered with oxcarbazepine, a careful dose adjustment and/or plasma level monitoring may be considered on a case by case basis, notably in paediatric patients treated concomitantly with lamotrigine.

No auto-induction has been observed with oxcarbazepine.

### Other medicinal product interactions

- Cimetidine, erythromycin, viloxazine, warfarin and dextropropoxyphene had no effect on the pharmacokinetics of MHD.

The interaction between oxcarbazepine and monoamine oxidase inhibitors (MAOIs) is theoretically possible based on a structural relationship of oxcarbazepine to tricyclic antidepressants.

Patients on tricyclic antidepressant therapy were included in clinical trials and no clinically relevant interactions have been observed.

The combination of lithium and oxcarbazepine might cause enhanced neurotoxicity.

### 4.6 Pregnancy and lactation

#### Pregnancy

**Risk related to epilepsy and antiepileptic medicinal products in general:**

It has been shown that in the offspring of women with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. In the treated population, an increase in malformations has been noted with polytherapy; however, the extent to which the treatment and/or the illness is responsible has not been elucidated.

Moreover, effective antiepileptic therapy must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the fetus.

**Risk related to oxcarbazepine:**

Clinical data on exposure during pregnancy are still insufficient to assess the teratogenic potential of oxcarbazepine. In animal studies, increased embryo mortality, delayed growth and malformations were observed at maternally toxic dose levels (see section 5.3).

Taking these data into consideration:

- If women receiving oxcarbazepine become pregnant or plan to become pregnant, the use of this product 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 of antenatal screening.

During pregnancy, an effective antiepileptic oxcarbazepine treatment must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the fetus.

**Monitoring and prevention:**
Antiepileptic medicinal products may contribute to folic acid deficiency, a possible contributory cause of fetal abnormality. Folic acid supplementation is recommended before and during pregnancy. As the efficacy of this supplementation is not proved, 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 agents 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.

**Lactation**
Oxcarbazepine and its active metabolite (MHD) are excreted in human breast milk. A milk-to-plasma concentration ratio of 0.5 was found for both. The effects on the infant exposed to oxcarbazepine by this route are unknown. Therefore, it should not be used during breast-feeding.

**4.7 Effects on ability to drive and use machines**
The use of oxcarbazepine has been associated with adverse reactions such as dizziness or somnolence (see section 4.8). Therefore, patients should be advised that their physical and/or mental abilities required for operating machinery or driving a car might be impaired.

**4.8 Undesirable effects**
The most commonly reported adverse reactions are somnolence, headache, dizziness, diplopia, nausea, vomiting and fatigue occurring in more than 10% of patients.

The adverse event profile by body system is based on adverse events from clinical trials assessed as related to oxcarbazepine. In addition, clinically meaningful reports on adverse experiences from named patient programs and postmarketing experience were taken into account.

Frequency estimate: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td>Leucopenia</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
</tr>
<tr>
<td>Bone marrow depression, aplastic anaemia, agranulocytosis, pancytopenia, neutropenia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very rare</strong></td>
</tr>
<tr>
<td>Hypersensitivity (including multi-organ hypersensitivity) characterised by features such as rash, fever. Other organs or systems may be affected such as the blood and lymphatic system (e.g. eosinophilia, thrombocytopenia, leucopenia, lymphadenopathy, splenomegaly), liver (e.g. abnormal liver function tests, hepatitis), muscles and joints (e.g. joint swelling, myalgia, arthralgia), nervous system (e.g. hepatic encephalopathy), kidney (e.g. proteinuria, interstitial nephritis, renal failure), lungs (e.g. dyspnoea, pulmonary oedema, asthma, bronchospasm, interstitial lung disease), angioedema.</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
</tr>
<tr>
<td>Anaphylactic reactions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Hyponatraemia</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
</tr>
<tr>
<td>Hyponatraemia associated with signs and symptoms such as seizures, confusion, depressed level of consciousness,</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Hyponatraemia</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
</tr>
<tr>
<td>Hyponatraemia associated with signs and symptoms such as seizures, confusion, depressed level of consciousness,</td>
</tr>
</tbody>
</table>
### 4.9 Overdose

Isolated cases of overdose have been reported. The maximum dose taken was approximately 24,000 mg. All patients recovered with symptomatic treatment. Symptoms of overdose include somnolence, dizziness, nausea, vomiting, hyperkinesia, hyponatraemia, ataxia and nystagmus. There is no specific antidote. Symptomatic and supportive treatment should be administered as appropriate. Removal of the medicinal product by gastric lavage and/or inactivation by administering activated charcoal should be considered.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

**Pharmacodynamic effects**

The pharmacological activity of oxcarbazepine is primarily exerted through the metabolite (MHD) (see section 5.2). The mechanism of action of oxcarbazepine and MHD is thought to be mainly based on blockade of voltage-sensitive sodium channels, thus resulting in stabilisation of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminishment of propagation of synaptic

---

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusional state, depression, apathy, agitation (e.g. nervousness), affect lability</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Very common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence, headache, dizziness</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia, tremor, nystagmus, disturbance in attention, amnesia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Very common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diplopia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision blurred, visual disturbance</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertigo</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia, atrioventricular block</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Very common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, vomiting</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea, constipation, abdominal pain</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis and/or lipase and/or amylase increase</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash, alopecia, acne</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell’s syndrome), erythema multiforme (see section 4.4)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Very common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Very common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic enzymes increased, blood alkaline phosphatase increased</td>
<td></td>
</tr>
</tbody>
</table>

---

†Very rarely, clinically significant hyponatraemia (sodium <125 mmol/l) can develop during oxcarbazepine use. It generally occurred during the first 3 months of treatment, although there were patients who first developed a serum sodium <125 mmol/l more than 1 year after initiation of therapy (see section 4.4).
impulses. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may also contribute to the anticonvulsant effects. No significant interactions with brain neurotransmitter or modulator receptor sites were found.

Oxcarbazepine and its active metabolite (MHD), are potent and efficacious anticonvulsants in animals. They protected rodents against generalised tonic-clonic and, to a lesser degree, clonic seizures, and abolished or reduced the frequency of chronically recurring partial seizures in Rhesus monkeys with aluminium implants. No tolerance (i.e. attenuation of anticonvulsive activity) against tonic-clonic seizures was observed when mice and rats were treated daily for 5 days or 4 weeks, respectively, with oxcarbazepine or MHD.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, oxcarbazepine is completely absorbed and extensively metabolised to its pharmacologically active metabolite (MHD).

After single dose administration of 600 mg oxcarbazepine to healthy male volunteers under fasted conditions, the mean $C_{\text{max}}$ value of MHD was 34 µmol/l, with a corresponding median $t_{\text{max}}$ of 4.5 hours.

In a mass balance study in man, only 2% of total radioactivity in plasma was due to unchanged oxcarbazepine, approximately 70% was due to MHD, and the remainder attributable to minor secondary metabolites which were rapidly eliminated.

Food has no effect on the rate and extent of absorption of oxcarbazepine, therefore, it can be taken with or without food.

Distribution
The apparent volume of distribution of MHD is 49 litres.

Approximately 40% of MHD is bound to serum proteins, predominantly to albumin. Binding was independent of the serum concentration within the therapeutically relevant range. Oxcarbazepine and MHD do not bind to alpha-1-acid glycoprotein.

Oxcarbazepine and MHD cross the placenta. Neonatal and maternal plasma MHD concentrations were similar in one case.

Biotransformation
Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to MHD, which is primarily responsible for its pharmacological effect. MHD is metabolised further by conjugation with glucuronic acid. Minor amounts (4% of the dose) are oxidised to the pharmacologically inactive metabolite (10, 11-dihydroxy derivative, DHD).

Elimination
Oxcarbazepine is cleared from the body mostly in the form of metabolites which are predominantly excreted by the kidneys. More than 95% of the dose appears in the urine, with less than 1% as unchanged oxcarbazepine. Faecal excretion accounts for less than 4% of the administered dose. Approximately 80% of the dose is excreted in the urine either as glucuronides of MHD (49%) or as unchanged MHD (27%), whereas the inactive DHD accounts for approximately 3% and conjugates of oxcarbazepine account for 13% of the dose.

Oxcarbazepine is rapidly eliminated from the plasma with apparent half-life values between 1.3 and 2.3 hours. In contrast, the apparent plasma half-life of MHD averaged 9.3 ± 1.8 h.

Dose-proportionality
Steady-state plasma concentrations of MHD are reached within 2-3 days in patients when oxcarbazepine is given twice a day. At steady-state, the pharmacokinetics of MHD are linear and show dose-proportionality across the dose range of 300 to 2,400 mg/day.

Special populations
Patients with hepatic impairment
The pharmacokinetics and metabolism of oxcarbazepine and MHD were evaluated in healthy volunteers and hepatically-impaired subjects after a single 900 mg oral dose. Mild to moderate hepatic impairment did not affect the pharmacokinetics of oxcarbazepine and MHD. Oxcarbazepine has not
been studied in patients with severe hepatic impairment.

**Patients with renal impairment**

There is a linear correlation between creatinine clearance and the renal clearance of MHD. When oxcarbazepine is administered as a single 300 mg dose, in renally impaired patients (creatinine clearance < 30 ml/min) the elimination half-life of MHD is prolonged by 60-90% (16 to 19 hours) with a two fold increase in AUC compared to adults with normal renal function (10 hours).

**Children**

The pharmacokinetics of oxcarbazepine were evaluated in clinical trials in paediatric patients taking it in the dose range 10-60 mg/kg/day. Weight-adjusted MHD clearance decreases as age and weight increase approaching that of adults. The mean weight clearance in children 4 to 12 years of age is approximately 40% higher that that of adults. Therefore MHD exposure in these children is expected to be about two-thirds that of adults when treated with a similar weight-adjusted dose. As weight increases, for patients 13 years of age and above, weight-adjusted MHD clearance is expected to reach that of adults.

**Elderly**

Following administration of single (300 mg) and multiple doses (600 mg/day) of oxcarbazepine in elderly volunteers (60-82 years of age), the maximum plasma concentrations and AUC values of MHD were 30-60% higher than in younger volunteers (18-32 years of age). Comparisons of creatinine clearances in young and elderly volunteers indicate that the difference was due to age-related reductions in creatinine clearance. No special dose recommendations are necessary because therapeutic doses are individually adjusted.

**Gender**

No gender-related pharmacokinetic differences have been observed in children, adults, or the elderly.

5.3 Preclinical safety data

Preclinical data indicated no special hazard for humans based on repeated-dose toxicity, safety pharmacology and genotoxicity studies with oxcarbazepine and the pharmacologically active metabolite, monohydroxy derivative (MHD).

Evidence of nephrotoxicity was noted in repeated dose toxicity rat studies but not in dog or mice studies. As there are no reports of such changes in patients, the clinical relevance of this finding in rats remains unknown.

Immunostimulatory tests in mice showed that MHD (and to a lesser extent oxcarbazepine) can induce delayed hypersensitivity.

Animal studies revealed effects such as increases in the incidence of embryo mortality and some delay in antenatal and/or postnatal growth at maternally toxic dose levels. There was an increase in rat fetal malformations in one of the eight embryo toxicity studies, which were conducted with either oxcarbazepine or the pharmacologically active metabolite (MHD), at a dose which also showed maternal toxicity (see section 4.6).

In the carcinogenicity studies, liver (rats and mice), testicular and female genital tract granular cell (rats) tumours were induced in treated animals. The occurrence of liver tumours was most likely a consequence of the induction of hepatic microsomal enzymes; an inductive effect which, although it cannot be excluded, is weak or absent in patients treated with oxcarbazepine. Testicular tumours may have been induced by elevated luteinizing hormone concentrations. Due to the absence of such an increase in humans, these tumours are considered to be of no clinical relevance. A dose-related increase in the incidence of granular cell tumours of the female genital tract (cervix and vagina) was noted in the rat carcinogenicity study with MHD. These effects occurred at exposure levels comparable with the anticipated clinical exposure. The mechanism for the development of these tumours has not been elucidated. Thus, the clinical relevance of these tumours is unknown.

### PHARMACEUTICAL PARTICULARS

6.1 List of excipients

*Tablet core*
- Lactose monohydrate
- Maize starch
- Crospovidone
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
Transparent PVC/PVdC – Aluminium blisters:

Blisters in packs containing 1, 30, 50, 56, 100, 200 & 500 film-coated tablets. Hospital packs: 50 & 500 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Oxcarbazepine 600 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 600 mg oxcarbazepine.

Excipients
Each film-coated tablet contains 33.25 mg lactose and 0.08 mg sunset yellow aluminium lake (E110).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Yellow to dark yellow, film-coated capsule-shaped tablet. One side of the tablet is scored in half and debossed with "9" on one side of the score and "3" on the other. The other side of the tablet is scored in half and debossed with "72" on one side of the score and "83" on the other.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Oxcarbazepine is indicated for the treatment of partial seizures with or without secondarily generalised tonic-clonic seizures.

It is indicated for use as monotherapy or adjunctive therapy in adults and in children of 6 years of age and above.

4.2 Posology and method of administration
In mono- and adjunctive therapy, treatment with oxcarbazepine is initiated with a clinically effective dose given in two divided doses. The dose may be increased depending on the clinical response of the patient.

When other antiepileptic medicinal products are replaced by oxcarbazepine, the dose of the concomitant antiepileptic medicinal product(s) should be reduced gradually on initiation of oxcarbazepine therapy.

In adjunctive therapy, as the total antiepileptic medicinal product load of the patient is increased, the dose of concomitant antiepileptic medicinal product(s) may need to be reduced and/or the oxcarbazepine dose increased more slowly (see section 4.5).

Oxcarbazepine can be taken with or without food.

The following dosing recommendations apply to all patients, in the absence of impaired renal function (see section 5.2). Active substance plasma level monitoring is not necessary to optimise oxcarbazepine therapy. The tablets are scored and can be broken in two halves in order to make it easier for the patient to swallow the tablet. For children, who cannot swallow tablets or where the required dose cannot be administered using tablets, other strengths and pharmaceutical forms are available.

Adults
Monotherapy
Oxcarbazepine should be initiated with a dose of 600 mg/day (8-10 mg/kg/day) given in 2 divided doses. If clinically indicated, the dose may be increased by a maximum of 600 mg/day increments at approximately weekly intervals from the starting dose to achieve the desired clinical response. Therapeutic effects are seen at doses between 600 mg/day and 2,400 mg/day.

Controlled monotherapy trials in patients not currently being treated with antiepileptic medicinal products showed 1,200 mg/day to be an effective dose; however, a dose of 2,400 mg/day has been
shown to be effective in more refractory patients converted from other antiepileptic medicinal products to oxcarbazepine monotherapy. In a controlled hospital setting, dose increases up to 2,400 mg/day have been achieved over 48 hours.

Adjunctive therapy
Oxcarbazepine should be initiated with a dose of 600 mg/day (8-10 mg/kg/day) given in 2 divided doses. If clinically indicated, the dose may be increased by a maximum of 600 mg/day increments at approximately weekly intervals from the starting dose to achieve the desired clinical response. Therapeutic responses are seen at doses between 600 mg/day and 2,400 mg/day.

Daily doses from 600 to 2,400 mg/day have been shown to be effective in a controlled adjunctive therapy trial, although most patients were not able to tolerate the 2,400 mg/day dose without reduction of concomitant antiepileptic medicinal products, mainly because of CNS-related adverse events. Daily doses above 2,400 mg/day have not been studied systematically in clinical trials.

Elderly
Adjustment of the dose is recommended in the elderly with compromised renal function (see 'Patients with renal impairment'). For patients at risk of hyponatraemia, see section 4.4.

Children
In mono- and adjunctive therapy, oxcarbazepine should be initiated with a dose of 8-10 mg/kg/day given in 2 divided doses. In adjunctive therapy, therapeutic effects were seen at a median maintenance dose of approximately 30 mg/kg/day. If clinically indicated, the dose may be increased by a maximum of 10 mg/kg/day increments at approximately weekly intervals from the starting dose, to a maximum dose of 46 mg/kg/day, to achieve the desired clinical response (see section 5.2). Oxcarbazepine is recommended for use in children of 6 years of age and above. Safety and efficacy have been evaluated in controlled clinical trials involving approximately 230 children aged less than 6 years (down to 1 month). Oxcarbazepine is not recommended in children aged less than 6 years since safety and efficacy have not been adequately demonstrated.

All the above dosing recommendations (adults, elderly and children) are based on the doses studied in clinical trials for all age groups. However, lower initiation doses may be considered where appropriate.

Patients with hepatic impairment
No dosage adjustment is required for patients with mild to moderate hepatic impairment.

Oxcarbazepine has not been studied in patients with severe hepatic impairment, therefore, caution should be exercised when dosing severely impaired patients (see section 5.2).

Patients with renal impairment
In patients with impaired renal function (creatinine clearance less than 30 ml/min) oxcarbazepine therapy should be initiated at half the usual starting dose (300 mg/day) and increased, in at least weekly intervals, to achieve the desired clinical response (see section 5.2).

Dose escalation in renally impaired patients may require more careful observation.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use
Hypersensitivity
Class I (immediate) hypersensitivity reactions including rash, pruritus, urticaria, angioedema and reports of anaphylaxis have been received in the post-marketing period. Cases of anaphylaxis and angioedema involving the larynx, glottis, lips and eyelids have been reported in patients after taking the first or subsequent doses of oxcarbazepine. If a patient develops these reactions after treatment with oxcarbazepine, the medicinal product should be discontinued and an alternative treatment started.

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25-30% of these patients may experience hypersensitivity reactions (e.g. severe skin reactions) with oxcarbazepine (see section 4.8).

Hypersensitivity reactions, including multi-organ hypersensitivity reactions, may also occur in patients
without history of hypersensitivity to carbamazepine. Such reactions can affect the skin, liver, blood and lymphatic system or other organs, either individually or together in the context of a systemic reaction (see section 4.8). In general, if signs and symptoms suggestive of hypersensitivity reactions occur (see section 4.8), oxcarbazepine should be withdrawn immediately.

**Dermatological effects**

Serious dermatological reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell’s syndrome) and erythema multiforme, have been reported very rarely in association with oxcarbazepine use. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and very rarely be fatal. Oxcarbazepine-associated cases occurred in both children and adults. The median time to onset was 19 days. Several isolated cases of recurrence of the serious skin reaction when rechallenged with oxcarbazepine were reported. Patients who develop a skin reaction with it should be promptly evaluated and oxcarbazepine withdrawn immediately unless the rash is clearly not related. In case of treatment withdrawal, consideration should be given to replacing oxcarbazepine with other antiepileptic therapy to avoid withdrawal seizures. Oxcarbazepine should not be restarted in patients who discontinued treatment due to a hypersensitivity reaction (see section 4.3).

**Hyponatraemia**

Serum sodium levels below 125 mmol/l, usually asymptomatic and not requiring adjustment of therapy, have been observed in up to 2.7% of oxcarbazepine-treated patients. Experience from clinical trials shows that serum sodium levels returned towards normal when the oxcarbazepine dosage was reduced, discontinued or the patient was treated conservatively (e.g. restricted fluid intake). In patients with pre-existing renal conditions associated with low sodium or in patients treated concomitantly with sodium-lowering medicinal products (e.g. diuretics, desmopressin) as well as NSAIDs (e.g. indometacin), serum sodium levels should be measured prior to initiating therapy. Thereafter, serum sodium levels should be measured after approximately two weeks and then at monthly intervals for the first three months during therapy, or according to clinical need. These risk factors may apply especially to elderly patients. For patients on oxcarbazepine therapy when starting on sodium-lowering medicinal products, the same approach for sodium checks should be followed. In general, if clinical symptoms suggestive of hyponatraemia occur on oxcarbazepine therapy (see section 4.8), serum sodium measurement may be considered. Other patients may have serum sodium assessed as part of their routine laboratory studies.

All patients with cardiac insufficiency and secondary heart failure should have regular weight measurements to determine occurrence of fluid retention. In case of fluid retention or worsening of the cardiac condition, serum sodium should be checked. If hyponatraemia is observed, water restriction is an important counter-measurement. As oxcarbazepine may, very rarely, lead to impairment of cardiac conduction, patients with pre-existing conduction disturbances (e.g. atrioventricular-block, arrhythmia) should be followed carefully.

**Hepatic function**

Very rare cases of hepatitis have been reported, which in most of the cases resolved favourably. When a hepatic event is suspected, liver function should be evaluated and discontinuation of oxcarbazepine should be considered.

**Haematological effects**

Very rare reports of agranulocytosis, aplastic anaemia and pancytopenia have been seen in patients treated with oxcarbazepine during post-marketing experience (see section 4.8).

Discontinuation of the medicinal product should be considered if any evidence of significant bone marrow depression develops.

**Hormonal contraceptives**

Female patients of child-bearing age should be warned that the concurrent use of oxcarbazepine with hormonal contraceptives may render this type of contraceptive ineffective (see section 4.5). Additional non-hormonal forms of contraception are recommended when using oxcarbazepine.

**Alcohol**

Caution should be exercised if alcohol is taken in combination with oxcarbazepine therapy, due to a possible additive sedative effect.
Withdrawal
Oxcarbazepine should be withdrawn gradually to minimise the potential of increased seizure frequency.

Suicidal ideation
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic agents 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 oxcarbazepine. 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.

Excipients
This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains sunset yellow aluminium lake (E110) and may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Enzyme induction
Oxcarbazepine and its pharmacologically active metabolite (the monohydroxy derivative, MHD) are weak inducers in vitro and in vivo of the cytochrome P450 enzymes CYP3A4 and CYP3A5 responsible for the metabolism of a very large number of substances, for example, immunosuppressants (e.g. ciclosporin, tacrolimus), oral contraceptives (see below), and some other antiepileptic medicinal products (e.g. carbamazepine) resulting in a lower plasma concentration of these medicinal products (see table below summarizing results with other antiepileptic medicinal products).

In vitro, oxcarbazepine and MHD are weak inducers of UDP-glucuronyl transferases (effects on specific enzymes in this family are not known). Therefore, in vivo oxcarbazepine and MHD may have a small inducing effect on the metabolism of medicinal products which are mainly eliminated by conjugation through the UDP-glucuronyl transferases. When initiating treatment with oxcarbazepine or changing the dose, it may take 2 to 3 weeks to reach the new level of induction.

In case of discontinuation of oxcarbazepine therapy, a dose reduction of the concomitant medications may be necessary and should be decided upon by clinical and/or plasma level monitoring. The induction is likely to gradually decrease over 2 to 3 weeks after discontinuation.

Hormonal contraceptives: Oxcarbazepine was shown to have an influence on the two components, ethinyloestradiol (EO) and levonorgestrel (LNG), of an oral contraceptive. The mean AUC values of EO and LNG were decreased by 48-52% and 32-52% respectively. Therefore, concurrent use of oxcarbazepine with hormonal contraceptives may render these contraceptives ineffective (see section 4.4). Another reliable contraceptive method should be used.

Enzyme inhibition
Oxcarbazepine and MHD inhibit CYP2C19. Therefore, interactions could arise when co-administering high doses of oxcarbazepine with medicinal products that are mainly metabolised by CYP2C19 (e.g. phenytoin). Phenytoin plasma levels increased by up to 40% when oxcarbazepine was given at doses above 1,200 mg/day (see table below summarizing results with other anticonvulsants). In this case, a reduction of co-administered phenytoin may be required (see section 4.2).

Antiepileptic medicinal products
Potential interactions between oxcarbazepine and other antiepileptic medicinal products were assessed in clinical studies. The effect of these interactions on mean AUCs and $C_{\text{max}}$ are summarised in the following table.
Summary of antiepileptic medicinal product interactions with oxcarbazepine

<table>
<thead>
<tr>
<th>Antiepileptic medicinal product co-administered</th>
<th>Influence of oxcarbazepine on antiepileptic medicinal product concentration</th>
<th>Influence of antiepileptic medicinal product on MHD concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>0-22% decrease (30% increase of carbamazepine-epoxide)</td>
<td>40% decrease</td>
</tr>
<tr>
<td>Clobazam</td>
<td>Not studied</td>
<td>No influence</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Not studied</td>
<td>No influence</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Slight decrease*</td>
<td>No influence</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>14-15% increase</td>
<td>30-31% decrease</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>0-40% increase</td>
<td>29-35% decrease</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>No influence</td>
<td>0-18% decrease</td>
</tr>
</tbody>
</table>

* Preliminary results indicate that oxcarbazepine may result in lower lamotrigine concentrations, possibly of importance in children, but the interaction potential of oxcarbazepine appears lower than seen with concomitant enzyme-inducing substances (carbamazepine, phenobarbitone, and phenytoin).

Strong inducers of cytochrome P450 enzymes (i.e. carbamazepine, phenytoin and phenobarbitone) have been shown to decrease the plasma levels of MHD (29-40%) in adults; in children 4 to 12 years of age, MHD clearance increased by approximately 35% when given one of the three enzyme-inducing antiepileptic medicinal products compared to monotherapy. Concomitant therapy of oxcarbazepine and lamotrigine has been associated with an increased risk of adverse events (nausea, somnolence, dizziness and headache). When one or several antiepileptic medicinal products are concurrently administered with oxcarbazepine, a careful dose adjustment and/or plasma level monitoring may be considered on a case by case basis, notably in paediatric patients treated concomitantly with lamotrigine.

No auto-induction has been observed with oxcarbazepine.

Other medicinal product interactions

Cimetidine, erythromycin, viloxazine, warfarin and dextropropoxyphene had no effect on the pharmacokinetics of MHD.

The interaction between oxcarbazepine and monoamine oxidase inhibitors (MAOIs) is theoretically possible based on a structural relationship of oxcarbazepine to tricyclic antidepressants.

Patients on tricyclic antidepressant therapy were included in clinical trials and no clinically relevant interactions have been observed.

The combination of lithium and oxcarbazepine might cause enhanced neurotoxicity.

4.6 Pregnancy and lactation

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general:

It has been shown that in the offspring of women with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. In the treated population, an increase in malformations has been noted with polytherapy; however, the extent to which the treatment and/or the illness is responsible has not been elucidated.

Moreover, effective antiepileptic therapy must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the fetus.

Risk related to oxcarbazepine:

Clinical data on exposure during pregnancy are still insufficient to assess the teratogenic potential of oxcarbazepine. In animal studies, increased embryo mortality, delayed growth and malformations were observed at maternally toxic dose levels (see section 5.3).

Taking these data into consideration:

- If women receiving oxcarbazepine become pregnant or plan to become pregnant, the use of this product 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 of antenatal screening.

• During pregnancy, an effective antiepileptic oxcarbazepine treatment must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the fetus.

**Monitoring and prevention:**
Antiepileptic medicinal products may contribute to folic acid deficiency, a possible contributory cause of fetal abnormality. Folic acid supplementation is recommended before and during pregnancy. As the efficacy of this supplementation is not proved, 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 agents 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.

**Lactation**
Oxcarbazepine and its active metabolite (MHD) are excreted in human breast milk. A milk-to-plasma concentration ratio of 0.5 was found for both. The effects on the infant exposed to oxcarbazepine by this route are unknown. Therefore, it should not be used during breast-feeding.

### 4.7 Effects on ability to drive and use machines
The use of oxcarbazepine has been associated with adverse reactions such as dizziness or somnolence (see section 4.8). Therefore, patients should be advised that their physical and/or mental abilities required for operating machinery or driving a car might be impaired.

### 4.8 Undesirable effects
The most commonly reported adverse reactions are somnolence, headache, dizziness, diplopia, nausea, vomiting and fatigue occurring in more than 10% of patients.

The adverse event profile by body system is based on adverse events from clinical trials assessed as related to oxcarbazepine. In addition, clinically meaningful reports on adverse experiences from named patient programs and postmarketing experience were taken into account.

Frequency estimate: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td>Leucopenia</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
</tr>
<tr>
<td>Bone marrow depression, aplastic anaemia, agranulocytosis, pancytopenia, neutropenia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very rare</strong></td>
</tr>
<tr>
<td>Hypersensitivity (including multi-organ hypersensitivity)</td>
</tr>
<tr>
<td>characterised by features such as rash, fever. Other organs or systems may be affected such as the blood and lymphatic system (e.g. eosinophilia, thrombocytopenia, leucopenia, lymphadenopathy, splenomegaly), liver (e.g. abnormal liver function tests, hepatitis), muscles and joints (e.g. joint swelling, myalgia, arthralgia), nervous system (e.g. hepatic encephalopathy), kidney (e.g. proteinuria, interstitial nephritis, renal failure), lungs (e.g. dyspnoea, pulmonary oedema, asthma, bronchospasm, interstitial lung disease), angioedema.</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
</tr>
<tr>
<td>Anaphylactic reactions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Hyponatraemia</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
</tr>
<tr>
<td>Hyponatraemia associated with signs and symptoms such as seizures, confusion, depressed level of consciousness,</td>
</tr>
</tbody>
</table>
encephalopathy (see also Nervous system disorders for further adverse events), vision disorders (e.g. blurred vision), vomiting, nausea

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Confusional state, depression, apathy, agitation (e.g. nervousness), affect lability</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Somnolence, headache, dizziness</td>
</tr>
<tr>
<td>Common</td>
<td>Ataxia, tremor, nystagmus, disturbance in attention, amnesia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eye disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Diplopia</td>
</tr>
<tr>
<td>Common</td>
<td>Vision blurred, visual disturbance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ear and labyrinth disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Vertigo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>Arrhythmia, atroventricular block</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td>Common</td>
<td>Diarrhoea, constipation, abdominal pain</td>
</tr>
<tr>
<td>Very rare</td>
<td>Pancreatitis and/or lipase and/or amylase increase</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepato-biliary disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>Hepatitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Rash, alopecia, acne</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Urticaria</td>
</tr>
<tr>
<td>Very rare</td>
<td>Angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell’s syndrome), erythema multiforme (see section 4.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal, connective tissue and bone disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>Systemic lupus erythematosus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Common</td>
<td>Asthenia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Hepatic enzymes increased, blood alkaline phosphatase increased</td>
</tr>
</tbody>
</table>

Very rarely, clinically significant hyponatraemia (sodium <125 mmol/l) can develop during oxcarbazepine use. It generally occurred during the first 3 months of treatment, although there were patients who first developed a serum sodium <125 mmol/l more than 1 year after initiation of therapy (see section 4.4).

4.9 Overdose
Isolated cases of overdose have been reported. The maximum dose taken was approximately 24,000 mg. All patients recovered with symptomatic treatment. Symptoms of overdose include somnolence, dizziness, nausea, vomiting, hyperkinesia, hyponatraemia, ataxia and nystagmus. There is no specific antidote. Symptomatic and supportive treatment should be administered as appropriate. Removal of the medicinal product by gastric lavage and/or inactivation by administering activated charcoal should be considered.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacaco-therapeutic group: Carboxamide derivatives

ATC code: N03A F02

Pharmacodynamic effects
The pharmacological activity of oxcarbazepine is primarily exerted through the metabolite (MHD) (see section 5.2). The mechanism of action of oxcarbazepine and MHD is thought to be mainly based on blockade of voltage-sensitive sodium channels, thus resulting in stabilisation of hyperexcited neural
membranes, inhibition of repetitive neuronal firing, and diminishment of propagation of synaptic impulses. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may also contribute to the anticonvulsant effects. No significant interactions with brain neurotransmitter or modulator receptor sites were found.

Oxcarbazepine and its active metabolite (MHD), are potent and efficacious anticonvulsants in animals. They protected rodents against generalised tonic-clonic and, to a lesser degree, clonic seizures, and abolished or reduced the frequency of chronically recurring partial seizures in Rhesus monkeys with aluminium implants. No tolerance (i.e. attenuation of anticonvulsive activity) against tonic-clonic seizures was observed when mice and rats were treated daily for 5 days or 4 weeks, respectively, with oxcarbazepine or MHD.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, oxcarbazepine is completely absorbed and extensively metabolised to its pharmacologically active metabolite (MHD).

After single dose administration of 600 mg oxcarbazepine to healthy male volunteers under fasted conditions, the mean $C_{max}$ value of MHD was 34 µmol/l, with a corresponding median $t_{max}$ of 4.5 hours.

In a mass balance study in man, only 2% of total radioactivity in plasma was due to unchanged oxcarbazepine, approximately 70% was due to MHD, and the remainder attributable to minor secondary metabolites which were rapidly eliminated.

Food has no effect on the rate and extent of absorption of oxcarbazepine, therefore, it can be taken with or without food.

Distribution
The apparent volume of distribution of MHD is 49 litres.

Approximately 40% of MHD is bound to serum proteins, predominantly to albumin. Binding was independent of the serum concentration within the therapeutically relevant range. Oxcarbazepine and MHD do not bind to alpha-1-acid glycoprotein.

Oxcarbazepine and MHD cross the placenta. Neonatal and maternal plasma MHD concentrations were similar in one case.

Biotransformation
Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to MHD, which is primarily responsible for its pharmacological effect. MHD is metabolised further by conjugation with glucuronic acid. Minor amounts (4% of the dose) are oxidised to the pharmacologically inactive metabolite (10, 11-dihydroxy derivative, DHD).

Elimination
Oxcarbazepine is cleared from the body mostly in the form of metabolites which are predominantly excreted by the kidneys. More than 95% of the dose appears in the urine, with less than 1% as unchanged oxcarbazepine. Faecal excretion accounts for less than 4% of the administered dose. Approximately 80% of the dose is excreted in the urine either as glucuronides of MHD (49%) or as unchanged MHD (27%), whereas the inactive DHD accounts for approximately 3% and conjugates of oxcarbazepine account for 13% of the dose.

Oxcarbazepine is rapidly eliminated from the plasma with apparent half-life values between 1.3 and 2.3 hours. In contrast, the apparent plasma half-life of MHD averaged 9.3 ± 1.8 h.

Dose-proportionality
Steady-state plasma concentrations of MHD are reached within 2-3 days in patients when oxcarbazepine is given twice a day. At steady-state, the pharmacokinetics of MHD are linear and show dose-proportionality across the dose range of 300 to 2,400 mg/day.

Special populations
Patients with hepatic impairment
The pharmacokinetics and metabolism of oxcarbazepine and MHD were evaluated in healthy volunteers and hepatically-impaired subjects after a single 900 mg oral dose. Mild to moderate hepatic
impairment did not affect the pharmacokinetics of oxcarbazepine and MHD. Oxcarbazepine has not been studied in patients with severe hepatic impairment.

**Patients with renal impairment**

There is a linear correlation between creatinine clearance and the renal clearance of MHD. When oxcarbazepine is administered as a single 300 mg dose, in renally impaired patients (creatinine clearance < 30 ml/min) the elimination half-life of MHD is prolonged by 60-90% (16 to 19 hours) with a two fold increase in AUC compared to adults with normal renal function (10 hours).

**Children**

The pharmacokinetics of oxcarbazepine were evaluated in clinical trials in paediatric patients taking it in the dose range 10-60 mg/kg/day. Weight-adjusted MHD clearance decreases as age and weight increase approaching that of adults. The mean weight clearance in children 4 to 12 years of age is approximately 40% higher than that of adults. Therefore MHD exposure in these children is expected to be about two-thirds that of adults when treated with a similar weight-adjusted dose. As weight increases, for patients 13 years of age and above, weight-adjusted MHD clearance is expected to reach that of adults.

**Elderly**

Following administration of single (300 mg) and multiple doses (600 mg/day) of oxcarbazepine in elderly volunteers (60-82 years of age), the maximum plasma concentrations and AUC values of MHD were 30-60% higher than in younger volunteers (18-32 years of age). Comparisons of creatinine clearances in young and elderly volunteers indicate that the difference was due to age-related reductions in creatinine clearance. No special dose recommendations are necessary because therapeutic doses are individually adjusted.

**Gender**

No gender-related pharmacokinetic differences have been observed in children, adults, or the elderly.

### 5.3 Preclinical safety data

Preclinical data indicated no special hazard for humans based on repeated-dose toxicity, safety pharmacology and genotoxicity studies with oxcarbazepine and the pharmacologically active metabolite, monohydroxy derivative (MHD).

Evidence of nephrotoxicity was noted in repeated dose toxicity rat studies but not in dog or mice studies. As there are no reports of such changes in patients, the clinical relevance of this finding in rats remains unknown.

Immunostimulatory tests in mice showed that MHD (and to a lesser extent oxcarbazepine) can induce delayed hypersensitivity.

Animal studies revealed effects such as increases in the incidence of embryo mortality and some delay in antenatal and/or postnatal growth at maternally toxic dose levels. There was an increase in rat fetal malformations in one of the eight embryo toxicity studies, which were conducted with either oxcarbazepine or the pharmacologically active metabolite (MHD), at a dose which also showed maternal toxicity (see section 4.6).

In the carcinogenicity studies, liver (rats and mice), testicular and female genital tract granular cell (rats) tumours were induced in treated animals. The occurrence of liver tumours was most likely a consequence of the induction of hepatic microsomal enzymes; an inductive effect which, although it cannot be excluded, is weak or absent in patients treated with oxcarbazepine. Testicular tumours may have been induced by elevated luteinizing hormone concentrations. Due to the absence of such an increase in humans, these tumours are considered to be of no clinical relevance. A dose-related increase in the incidence of granular cell tumours of the female genital tract (cervix and vagina) was noted in the rat carcinogenicity study with MHD. These effects occurred at exposure levels comparable with the anticipated clinical exposure. The mechanism for the development of these tumours has not been elucidated. Thus, the clinical relevance of these tumours is unknown.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

**Tablet core**

Lactose monohydrate

Maize starch
Crospovidone
Povidone (K-30)
Cellulose, microcrystalline
Sodium starch glycolate (Type A)
Silica, colloidal anhydrous
Magnesium stearate

Tablet film-coating
Hypromellose
Macrogol 6000
Macrogol 400
Titanium dioxide (E171)
Iron oxide, yellow (E172)
Sunset yellow aluminium lake (E110)

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
Transparent PVC/PVdC – Aluminium blisters:

Blisters in packs containing 1, 30, 50, 56, 100, 200 & 500 film-coated tablets. Hospital packs: 50 & 500 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Teva UK Limited,
Brampton Road,
Hampden Park,
Eastbourne, BN22 9AG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/1086

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
03/06/2009

10 DATE OF REVISION OF THE TEXT
03/06/2009
Module 3
PATIENT INFORMATION LEAFLET

OXCARB AZEPINE 150 mg, 300 mg & 600 mg FILM-COATED TABLETS

Package Leaflet Information for the Patient

This leaflet contains important information about the use of this medicine.

1. What Oxcabazepine film-coated Tablets are and what they are used for.
2. Before you take Oxcabazepine film-coated Tablets.
3. How to take Oxcabazepine film-coated Tablets.
4. Possible side effects.
5. How to store Oxcabazepine film-coated Tablets.
6. Further information.

1. What Oxcabazepine film-coated Tablets are and what they are used for.

Oxcabazepine belongs to a group of medicines called antiepileptic drugs, which are used in the treatment of epilepsy. It is designed to help control seizures in patients who have epilepsy.

Oxcabazepine is used to treat certain types of epilepsy such as absence attacks and convulsions in general.

Your doctor may prescribe Oxcabazepine alone or in combination with other epilepsy medicines.

2. Before you take Oxcabazepine film-coated Tablets.

Do not take Oxcabazepine film-coated Tablets if:

- You are allergic to Oxcabazepine or any of the other ingredients in this medicine.

Take special care with Oxcabazepine film-coated Tablets if:

- Your doctor tells you to.

If you are taking any other medicines, especially

- You have ever had kidney disease as indicated by your blood work in the past.

Oxcabazepine can reduce your blood levels of some of these medicines, which may affect your treatment.

- Your doctor tells you to.

- You have ever had kidney disease.

Oxcabazepine may increase the risk of bleeding in people taking blood-thinning medicines like aspirin or warfarin.

- You are taking any other medicines that may affect your blood levels.

- Your doctor tells you to.

- You have any other health problems.

If you are pregnant or trying to become pregnant, your doctor will advise you not to take Oxcabazepine film-coated Tablets.

- Your doctor tells you to.

If you are breastfeeding, your doctor may advise you not to take this medicine.

- Your doctor tells you to.

- You are taking any other medicines that may affect breastfeeding.

3. How to take Oxcabazepine film-coated Tablets.

Always take Oxcabazepine film-coated Tablets exactly as your doctor has told you. Do not take more than prescribed.

- Your doctor tells you to.

- You are taking any other medicines that may affect bleeding.

- Your doctor tells you to.

- You have any other health problems.

4. Possible side effects.

Some of the common side effects of Oxcabazepine film-coated Tablets include:

- Feeling tired
- Headache
- Dizziness
- Nausea
- Vomiting
- Abdominal pain
- Constipation
- Diarrhea
- Stomach upset
- Loss of appetite
- Anemia
- Bleeding

- Your doctor tells you to.

- You are taking any other medicines that may affect bleeding.

- Your doctor tells you to.

- You have any other health problems.

5. How to store Oxcabazepine film-coated Tablets.

Keep your medicine in the original package until it is time to take it.

- Your doctor tells you to.

- You are taking any other medicines that may affect bleeding.

- Your doctor tells you to.

- You have any other health problems.

6. Further information.

This leaflet contains some general information about this medicine and may cause allergic reactions.
to the hospital or doctor so that they know which tablets were consumed.

In overdose can cause unconsciousness, dizziness, nausea, vomiting, abnormal muscle and body activity, convulsions, movement and involuntary eye movements.

If you forget to take Oxcarbazepine

If you forget to take a dose, take one as soon as you remember. Remember it is simple for you to take your next dose. Like your next dose as usual. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Oxcarbazepine

Do not stop taking Oxcarbazepine; unless your doctor tells you to, as stopping it could cause adverse reactions. Your doctor will decide when and how to stop your treatment.

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

4 POSSIBLE SIDE EFFECTS

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

Contact your doctor or go to the nearest casualty department if any of the following occur:

A severe skin reaction such as:

- A severe rash reaction with thickened, red, spotted like a pink, pus-filled lump or raised skin patches, or
- A sudden, severe allergic reaction with hives and swelling of mouth and nose may be fatal.

This side effect is very rare and occurs in fewer than 1 in 10,000 patients, but may require medical attention.

If any of these types of skin reactions occur while you are on Oxcarbazepine, you must not use Oxcarbazepine again.

Stop taking your tablet and get medical advice if:

- The skin colour of the face (such as warning of the start of a severe reaction), or
- The skin is very itchy or swollen and you are unable to sleep.

This may occur in very rare cases and may cause a red rash, fever or pain in the joints.

This side effect is very rare and occurs in fewer than 1 in 10,000 patients.

Contact your doctor immediately if any of the following occur:

- A severe skin reaction such as:
- Your skin, neck, or face becomes itchy or swollen.

This side effect is very rare and occurs in fewer than 1 in 10,000 patients, but may require medical attention.

- Faintness, dizziness, fatigue, or weakness.

This side effect is very rare and occurs in fewer than 1 in 10,000 patients, but may require medical attention.

- In case of symptoms suggestive of blood disorders such as tiredness, dizziness, bruising during exercise, bleeding gums, haemorrhage, disturbance of the urine, or abnormal bleeding such as unusual bruising and bleeding.

This side effect is very rare and occurs in fewer than 1 in 10,000 patients, but may require medical attention.

Other side effects may occur:

Very common (affecting more than 1 in 10):

- Appetite, thirst, or sleep, headache, dizziness, feeling or being sick.

Common (affecting 1 in 10 to 1 in 100):

- Nasal congestion, tiredness, fever, sweating, increased salivation, trouble sleeping, constipation, diarrhoea, or stomach pain.

Less common (affecting 1 in 100 to 1 in 1000):

- Nausea, diarrhoea, loss of concentration, muscle cramps, eye pain, unusual tiredness or weakness, loss of appetite, weight loss, or agitation, or nervousness.

Uncommon (affecting 1 in 1000 to 1 in 10000):

- Headache, confusion, hallucinations, depression, agitation, anxiety, or other mood disturbances.

Rare (affecting less than 1 in 100,000):

- Jaundice, blood transfusion, or an increased number of white blood cells and increased liver enzymes.

Very rare (less than one case per 10,000):
Module 4
Labelling

Carton-Oxcarbazepine 150mg Film Coated Tablets (50 tablets)

Blister foil- Oxcarbazepine 150mg Film Coated Tablets (50 tablets)
PAR Oxcarbazepine 150mg, 300mg & 600mg Film-Coated Tablets

Carton-Oxcarbazepine 600mg Film Coated Tablets (50 tablets)

Blister foil-Oxcarbazepine 600mg Film Coated Tablets (50 tablets)
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data and the Applicant’s response to the questions raised by RMS and CMSs on quality, safety and efficacy, the RMS considers that the application for Oxcarbazepine 150mg, 300mg and 600mg film-coated tablets for the treatment of: partial seizures with or without secondarily generalised tonic-clonic seizures and as monotherapy or adjunctive therapy in adults and in children of 6 years of age and above, is approvable.

These applications are made under Article 10.1 of 2001/83 EC, as amended. Oxcarbazepine 150mg, 300mg and 600mg Film Coated Tablets, have been shown to be generic products of Trileptal Film-coated Tablets, PL 00101/0581-3 which were granted to Novartis Pharmaceuticals UK Ltd on 7th January 2000 and first granted marketing authorisations by the Danish Authorities on 8th June 1990, over 10 years ago.

Oxcarbazepine is an antiepileptic drug (AED) (ATC code: N03A F02) and is indicated for the treatment of partial seizures with or without secondarily generalised tonic-clonic seizures. It is indicated for use as monotherapy or adjunctive therapy in adults and in children of 6 years of age and above.

The test product and the reference product have the same qualitative and quantitative composition of the active substance (oxcarbazepine), the same pharmaceutical form (film-coated tablets), the same strengths (150mg, 300mg and 600mg) and the same route of administration (oral).

No new preclinical or clinical studies were conducted and none are required for an application of this type. These applications for generic products refer to Trileptal Film-coated Tablets, PL 00101/0581-3, which has been licensed within the EEA for over 10 years. The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, batch release and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS has been reassured that the submitted studies have been carried out in accordance with GCP, and agreed ethical principles.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised,
easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Oxcarbazepine 150/300/600 mg Film-coated Tablets |
| Name(s) of the active substance(s) (INN) | Oxcarbazepine |
| Pharmacotherapeutic classification (ATC code) | Nervous System - Antiepileptics - Carboxamide derivatives (N03AF02) |
| Pharmaceutical form and strength(s) | Film-coated Tablets, 150 / 300 / 600 mg |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1304/01-3/DC |
| Reference Member State | United Kingdom |
| Member States concerned | Austria, Bulgaria, Cyprus, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Lithuania, Latvia, Malta, The Netherlands, Norway, Poland, Sweden. |
| Marketing Authorisation Number(s) | PL 00289/1084-1086 |
| Name and address of the authorisation holder | TEVA UK Limited |
| | Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, UK |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

Nomenclature:
INN: Oxcarbazepine

Chemical name: 10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide

Structure:

Molecular formula
C_{15}H_{12}N_{2}O_{2}

Molecular weight
252.28

General Properties
A yellowish to faintly orange crystalline powder.

Solubility
Practically insoluble in water. Slightly soluble in alcohol and chloroform.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

The active substance oxcarbazepine is not the subject of BP or Ph.Eur monographs. An appropriate specification is provided for the active substance oxcarbazepine.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active oxcarbazepine is stored in appropriate packaging that comply with Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs. Specifications and certificates of analysis have been provided.

Batch analysis data are provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for standards used by the active substance manufacturer during validation studies.

Appropriate stability data have been generated for drug substance stored in the same immediate packaging as the commercial packaging. The data demonstrates the stability of the drug substance and supports an appropriate retest period when stored in the proposed packaging.
P. **Medicinal Product**

**Other Ingredients**

Other ingredients consist of pharmaceutical excipients namely lactose monohydrate, maize starch, crospovidone, povidone (K-30), microcrystalline cellulose, sodium starch glycolate (Type A), colloidal anhydrous silica and magnesium stearate. All ingredients within the tablet core comply with relevant Ph.Eur monographs.

The tablet film coating (Opadry 02G32878 Yellow) contains: Hypromellose, Macrogol 6000, Macrogol 400, Titanium dioxide (E171), Iron oxide, yellow (E172), and Sunset yellow aluminium lake (E110). The ingredients within the tablet film coating comply with in-house specifications and are satisfactory.

Satisfactory certificates of analysis have been provided for all excipients.

With the exception of lactose none of the excipients used contain material derived from animal or human origin. The applicant has provided a declaration that milk used in the production of lactose is sourced from healthy animals under the same conditions as that for human consumption.

**Pharmaceutical development**

The formulation objective was to develop generic film-coated tablets bioequivalent to the reference product, Trileptal 600mg, 300mg & 150mg Tablets.

The objectives of the development programme were to develop a formula and a manufacturing process for Oxcarbazepine 150mg, 300mg & 600mg Film Coated Tablets, to produce tablets with the following:

1) comparable dissolution profile to the brand  
2) bioequivalent to the brand  
3) meet all physical and chemical specifications for the dosage form in general and for this product.

**Bio waiver**

A bio waiver was submitted to extrapolate the results from the bioequivalence study on the 600 mg strength to the 150 mg and 300 mg strengths. The following bio waiver criteria outlined in CPMP/EWP/QWP/1401/98 are fulfilled:

- the same manufacturer uses the same process for all strengths  
- the qualitative composition of the different strengths is the same  
- the different strengths are proportionally formulated  
- dissolution profiles of all strengths are similar under identical conditions.

The brand-leader SmPC states that oxcarbazepine exhibits linear pharmacokinetics over the range 300 – 2400 mg. Individual doses lower than 300 mg may be required in children, hence the need for the 150 mg strength. In the clinical overview, the Applicant has argued that linear pharmacokinetics also includes doses of 150 mg and has been found to be satisfactory.

**Dissolution and impurity profiles**

Dissolution and impurity profiles for all three strengths of drug product were found to be similar to those for the reference products.
**Manufacturing Process**  
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process.

**Finished Product Specification**  
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container-Closure System**  
Oxcarbazepine tablets are packaged in blister packs composed of transparent polyvinyl chloride (PVC)/polyvinylidene chloride (PVdC)/aluminium. Blister pack presentation is available in pack sizes of 1, 30, 50, 56, 100, 200 and 500 film-coated. Not all the pack sizes may be marketed. The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging for assessment before those pack sizes are commercially marketed. All primary product packaging complies with EU legislation regarding contact with food.

**Stability of the product**  
Stability studies have been performed on the two pilot-scale batches of 150mg strength and 600mg strength and a single pilot-scale batch of 300mg strength. All batches are packaged in the proposed commercial packaging. A post approval commitment has been proposed to provide the first three consecutive commercial scale batches of each strength. Stability testing is performed according to the relevant ICH guidelines. Based on the results of the stability studies, the applicant has proposed a shelf life of 3 years, with no specific storage conditions which is acceptable.

**SPC, PIL, Labels**  
The SPC, PIL and Labels are pharmaceutically acceptable. A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Conclusion**  
The grant of marketing authorisations is recommended.

**III.2 PRE-CLINICAL ASPECTS**  
No new preclinical studies were submitted with this application. This is acceptable as oxcarbazepine is a well known active ingredient and no new preclinical issues are considered to arise as a result of its inclusion in the proposed product. The nonclinical overview provides a satisfactory review of the relevant preclinical pharmacological and toxicological literature and has been written by an adequately qualified person.

**III.3 CLINICAL ASPECTS**

**Introduction**  
The precise mechanism by which oxcarbazepine and MHD exert their antiseizure effect is unknown; however, *in vitro* electrophysiological studies indicate that they produce blockade of voltage-sensitive sodium channels, resulting in stabilization of hyperexcited neural
membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may contribute to the anticonvulsant effects of the drug.

**Indications**
In line with the reference product SPC.

**Dose and Dose Regimen**
In line with the reference product SPC.

**Pharmacokinetics**
Following oral administration, oxcarbazepine is completely absorbed and extensively metabolized to its pharmacologically active 10-monohydroxy metabolite (MHD). The half-life of the parent is about two hours, while the half-life of MHD is about nine hours, so that MHD is responsible for most antiepileptic activity.

*Effect of Food:* Food has no effect on the rate and extent of absorption of oxcarbazepine. Therefore, oxcarbazepine tablets can be taken with or without food. Approximately 40% of MHD is bound to *serum proteins*, predominantly to *albumin*. Binding is independent of the serum concentration within the therapeutically relevant range. Oxcarbazepine and MHD do not bind to *alpha-1-acid glycoprotein*.

Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to its 10-monohydroxy metabolite, MHD, which is primarily responsible for the pharmacological effect of oxcarbazepine. MHD is metabolized further by conjugation with glucuronic acid.

Oxcarbazepine is cleared from the body mostly in the form of metabolites which are predominantly excreted by the kidneys. More than 95% of the dose appears in the *urine*, with less than 1% as unchanged oxcarbazepine. Fecal excretion accounts for less than 4% of the administered dose. Approximately 80% of the dose is excreted in the urine either as glucuronides of MHD (49%) or as unchanged MHD (27%); the inactive DHD accounts for approximately 3% and conjugates of MHD and oxcarbazepine account for 13% of the dose.

**Bioequivalence study**
To support the application, the applicant has submitted the report of a single-dose bioequivalence study under fasting conditions.

Adverse events were monitored to ensure the safety of the subjects.

The applicant investigated the active substance (oxcarbazepine) and the active metabolite (10-OH-carbazepine-MHD) which primarily exerts the pharmacological activity of Oxcarbazepine.

It is known that pharmacokinetics are linear over the therapeutic dose range and a single bioequivalence study on the highest tablet strength is considered sufficient to support this application from the clinical assessor’s point of view.

**Study design**
A single-dose, open-label, randomised, 2-way cross-over study, performed under fasting conditions. Subjects were confined to a clinical research facility from at least 10 hours prior to drug administration, until after the 24 hours post-dose blood draw, in each period. The treatment phases were separated by a washout period of 7 days.
Test and reference products

Test Product: Oxcarbazepine 600mg film-coated tablets

Reference product: Trileptal® 600 mg tablets

Population studied:

Subjects were housed in the clinical facility the evening before drug administration until 12 hours after drug administration. Study drug was administered after an overnight fast with 240 ml water. Blood samples were collected prior to study drug administration and up to 72.0 hours post-dose. No serious or significant adverse events were reported during this study. A total of 79 post-dose adverse events were reported by 44 of the 98 subjects who received at least one dose of the study medication. 40 AEs reported by 29 of the 97 subjects who received treatment A and 39 AEs reported by 28 of the 95 subject who received treatment B. The most common adverse event was “somnolence” which is expected by this type of drugs. No significant changes in the subject’s state of health were noticed.

Analytical, pharmacokinetic and statistical methods

Methods used were adequate. Parametric ANOVA on AUC0-t, AUC0-inf, Cmax, T1/2 el and Kel; geometric confidence intervals for AUC0-t, AUC0-inf and Cmax; and non-parametric test (Wilcoxon) for Tmax;

• Covariates in the ANOVA model: group, sequence, sequence*group, subject (sequence*group), period (group), treatment and treatment*group;

• Ln-transformed parameters: AUC0-t, AUC0-inf and Cmax.
Results:
Pharmacokinetics:

**SUMMARY OF RESULTS**

**OXCARBAZEPINE**

\( N = 94 \)

**Pharmacokinetic Parameters**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test (Oxcarbazepine (A))</th>
<th>Reference (Trileptal® (B))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td><strong>AUC(_{0-4})</strong> (ng h/mL)</td>
<td>5714.54</td>
<td>1818.21</td>
</tr>
<tr>
<td><strong>AUC(_{0-inf})</strong> (ng h/mL)</td>
<td>6909.66</td>
<td>1833.47</td>
</tr>
<tr>
<td><strong>C(_{max})</strong> (ng/mL)</td>
<td>2021.62</td>
<td>804.27</td>
</tr>
<tr>
<td>Residual area (%)</td>
<td>2.92</td>
<td>1.47</td>
</tr>
<tr>
<td><strong>T(_{max})</strong> (h)</td>
<td>1.48</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>T(_{1/2,\text{inf}})</strong> (h)</td>
<td>1.33</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>K(_{el})</strong> (h(^{-1}))</td>
<td>0.0415</td>
<td>0.0112</td>
</tr>
<tr>
<td><strong>T(_{1/2,\text{el}})</strong> (h)</td>
<td>11.63</td>
<td>2.13</td>
</tr>
</tbody>
</table>

*Median and interquartile ranges are presented.*

**Oxcarbazepine (A) vs Trileptal® (B)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test (Oxcarbazepine (A))</th>
<th>Reference (Trileptal® (B))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC(_{0-4})</strong></td>
<td>103.48%</td>
<td>105.18%</td>
</tr>
<tr>
<td><strong>AUC(_{0-inf})</strong></td>
<td>101.61%</td>
<td>100.80%</td>
</tr>
<tr>
<td><strong>C(_{max})</strong></td>
<td>106.00%</td>
<td>105.61%</td>
</tr>
<tr>
<td>Ratio(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90% Geometric C.I.(^2)</td>
<td>101.61% to 106.00%</td>
<td>100.80% to 105.61%</td>
</tr>
<tr>
<td>Intra-Subject CV</td>
<td>9.94 %</td>
<td>9.63 %</td>
</tr>
</tbody>
</table>

\(^1\) Calculated using least-squares means according to the formula: \(e^{(\text{Oxcarbazepine (A)} - \text{Trileptal® (B)}) / X 100}\)

\(^2\) 90% Geometric Confidence Interval using In-transformed data
SUMMARY OF RESULTS
10-OH-CARBAMAZEPINE
N = 94

Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test (Oxcarbazepine (A))</th>
<th>Reference (Trileptal® (B))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD CV(%)</td>
</tr>
<tr>
<td>AUC₀-t</td>
<td>198226.84</td>
<td>37528.13 18.93</td>
</tr>
<tr>
<td>AUC₀-inf</td>
<td>201685.05</td>
<td>38889.49 19.28</td>
</tr>
<tr>
<td>Cₘₘₙ</td>
<td>8321.70</td>
<td>1792.04 21.53</td>
</tr>
<tr>
<td>Residual area (%)</td>
<td>1.64</td>
<td>2.03 123.46</td>
</tr>
<tr>
<td>Tₘₘₙ</td>
<td>4.75</td>
<td>1.65 34.79</td>
</tr>
<tr>
<td>Kₗₗₙ</td>
<td>4.30</td>
<td>1.40 -</td>
</tr>
<tr>
<td>Kₗₗₙ</td>
<td>0.0714</td>
<td>0.0133 18.65</td>
</tr>
<tr>
<td>Tₙₙₙₙ</td>
<td>10.07</td>
<td>2.06 20.47</td>
</tr>
</tbody>
</table>

*Medians and interquartile ranges are presented.

Oxcarbazepine (A) vs Trileptal® (B)

<table>
<thead>
<tr>
<th></th>
<th>AUC₀-t</th>
<th>AUC₀-inf</th>
<th>Cₘₘₙ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio¹</td>
<td>100.43%</td>
<td>100.51%</td>
<td>101.99%</td>
</tr>
<tr>
<td>90% Geometric C.I.²</td>
<td>99.10% to 101.77%</td>
<td>99.18% to 101.85%</td>
<td>99.71% to 104.31%</td>
</tr>
<tr>
<td>Intra-Subject CV</td>
<td>5.46%</td>
<td>5.47%</td>
<td>9.30%</td>
</tr>
</tbody>
</table>

¹ Calculated using least-squares means according to the formula: \( \frac{\text{Oxcarbazepine (A)}}{\text{Trileptal® (B)}} \times 100 \)
²90% Geometric Confidence Interval using ln-transformed data

Assessor’s comments:

A standard BE study was conducted. Study design was adequate to address the BE. The 90% confidence intervals for the test/reference ratios for AUC₀-t, AUC₀-inf and metabolite were within the narrow therapeutic index criteria of 90-110% and Cₘₘₙ for Oxcarbazepine was within conventional bioequivalence criteria. This is acceptable.

Pharmacovigilance system

The RMS considers that the Pharmacovigilance system as described by the Applicant fulfils the requirements and provides adequate evidence that the Applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

The Applicant has provided the statement from the MAH and the QPPV required and is acceptable.
Risk Management Plan
No Risk Management System has been provided since the application concerns a generic with a reference medicinal product for which no additional risk minimisation activities have been identified.

Periodic Safety Update Report (PSUR)
The PSUR submission scheme proposed by the applicant is acceptable.

BENEFIT RISK ASSESSMENT
The benefit-risk ratio is considered favourable.

V OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Oxcarbazepine 150mg, 300mg & 600mg Film Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Oxcarbazepine 600mg Film Coated Tablets and Trileptal® 600 mg tablets (Oxcarbazepine) (Novartis). Given that linear kinetics apply between the 600mg, 300mg and 150mg tablets, that proportional formulae for the tablets have been used and that similar dissolution results have been shown for the three strengths, separate bioequivalence studies using the 300mg and 150mg tablets are not considered necessary.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with oxcarbazepine is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>