IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0749/073/002
Case No: 2045306

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Teva Pharma B.V.

Computerweg 10, **3542 DR Utrecht**, **Netherlands**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Oxcarbazepine Teva 300 mg Film-coated Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **19/06/2009** until **18/06/2014**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oxcarbazepine Teva 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-markeing 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_{min} are summarised in the following table.

Summary of antiepileptic medicinal product interactions with oxcarbazepine		
Antiepileptic medicinal product co-administered	Influence of oxcarbazepine on antiepileptic medicinal product concentration	Influence of antiepileptic medicinal product on MHD concentration
Carbamazepine	0-22% decrease (30% increase of carbamazepine epoxide)	40 % decrease
Clobazam	Not studied	No influence
Felbamate	Not studied	No influence
Lamotrigine	Slight decrease*	No influence
Phenobarbital	14-15% increase	30-31% decrease
Phenytoin	0-40% increase	29 – 35% decrease
Valproic acid	No influence	0-18% decrease

* 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).

Blood and lymphatic system disorders	
Uncommon	Leucopenia
Very rare	Thrombocytopenia
Unknown	Bone marrow depression, aplastic anaemia, agranulocytosis, pancytopenia, neutropenia
Immune system disorders	
Very rare	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.
Unknown	Anaphylactic reactions.
Metabolism and nutrition disorders	
Common	Hyponatraemia
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_{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 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
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 Pharma B.V.
Computerweg 10
3542 DR Utrecht
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA749/73/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th June 2009

10 DATE OF REVISION OF THE TEXT