IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PPA0465/201/003
Case No: 2071497

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

PCO Manufacturing Limited

Unit 10, Ashbourne Business Park, **Rath**, **Ashbourne**, **Co. Meath**, **Ireland**

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

Tegretol Retard 400mg Gastro-resistant 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 **21/05/2010**.

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

Tegretol Retard 400mg Gastro-resistant Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One Tegretol Retard 400mg Gastro-resistant Tablet contains 400mg carbamazepine

Excipients: Each tablet contains Polyethoxylated castor oil

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant Tablet

Product imported from Poland
Brownish-orange, oval, slightly biconvex, film-coated, gastro-resistant tablets with a score on each side, imprinted with 'ENE/ENE' on one side and 'CG/CG' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. As an anticonvulsant in the management of epilepsy (generalised tonic – clonic and partial seizure types).

2. The paroxysmal pain of trigeminal neuralgia and the lancinating component of other forms of differentiation pain, for example glossopharyngeal neuralgia, peripheral diabetic neuropathy, tabetic lightning pain, superior laryngeal neuralgia, stump pain, phantom limb pain and post herpetic neuralgia.

3. Management of alcohol withdrawal symptoms.

4. Treatment of mania and prophylaxis of manic-depressive illness, especially in patients unresponsive to lithium.

4.2 Posology and method of administration

Tegretol is given orally, usually in two to four divided doses.

Tegretol may be taken during, after or between meals. The tablets should be taken with a little liquid, e.g. a glass of water.

1. **Epilepsy**

It is advised that with a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient. It may be helpful to monitor the plasma concentration of carbamazepine to establish the optimum dose (see section 4.4 special warnings and precautions for use).
Wherever possible, anti-epileptic agents should be prescribed as the sole anti-epileptic agent but if used in polytherapy, the same incremental dosage pattern is advised (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Adults:
Tegretol should be taken in a number of divided doses. The initial dosages should be 100-200mg once or twice daily followed by a slow increase until the best response is obtained, often 800-1200mg daily. In some instances, 1600mg or even 2000mg daily may be necessary.

Elderly:
Due to the potential for drug interactions, the dosage of Tegretol should be selected with caution in elderly patients.

Paediatric Patients:
Usual dosage 10-20mg/kg bodyweight daily in several divided doses.

Age up to 1 year: The usual total daily dose is 100 mg to 200 mg in divided doses.

1-5 years: The usual total daily dose is 200 mg to 400 mg in divided doses.

5-10 years: The usual total daily dose is 400mg to 600mg in divided doses.

10-15 years: The usual total daily dose is 600mg to1000mg in divided doses.

Tegretol tablets are not recommended for children aged 5 years and under.

2. Trigeminal neuralgia and other forms of differentiation pain.

The individual dosage requirements of Tegretol may vary considerably, depending on the age and weight of the patient. It is recommended that the initial dose be small but in some patients a high dose early in treatment may be required. In elderly patients, an initial dose of 100mg twice daily is recommended.

The usual dose is 200 mg 3 to 4 times daily but the dose may be increased gradually until a satisfactory clinical response is obtained, which in some instances necessitates 1600mg Tegretol daily. When the pain goes into remission the dose may be gradually reduced and Tegretol discontinued in the absence of recurrence.

3. **Alcohol withdrawal symptoms**

The dose should be adjusted to suit the needs of the individual patient.
Usually doses of 600-800 mg daily are sufficient but 1200 to 1600mg daily may be required in delirium tremens with subsequent reductions.

4. **Treatment of mania and prophylaxis of manic-depressive illness**

Initial starting dose of 100-200mg daily, in divided doses, increasing gradually until symptoms are controlled or a total of 1600mg given in divided doses is reached. The usual dosage range is 400-600mg daily, given in divided doses.

4.3 Contraindications

- Known hypersensitivity to carbamazepine or structurally related drugs (e.g. tricyclic antidepressants) or any other component of the formulation
- Patients with atrioventricular coduction defects
- Patients with a history of bone-marrow depression
- Patients with a history of hepatic porphyrias (e.g. acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda)
- The use of Tegretol is not recommended in combination with monoamine-oxidase inhibitors (MAOIs) (see section 4.5 Interaction with other medicinal products and other forms of interaction).
- Herbal preparations containing St John's wort (Hypericum perforatum) must not be used while taking Tegretol due to the risk of decreased plasma concentrations and reduced clinical effects of Tegretol (see section 4.5 Interactions with other medicinal products and other forms of Interaction).

4.4 Special warnings and precautions for use

Tegretol should be given only under medical supervision. Tegretol should be prescribed only after a critical benefit-risk appraisal and under close monitoring in patients with a history of cardiac, hepatic, or renal damage, adverse haematological reactions to other drugs, or interrupted courses of therapy with Tegretol .

Haematological effects

Agranulocytosis and aplastic anaemia have been associated with Tegretol; however, due to the very low incidence of these diseases, meaningful risk estimates for Tegretol are difficult to obtain. The overall risk in the general untreated population has been estimated at 4.7 persons per million per year for agranulocytosis and 2.0 persons per million per year for aplastic anaemia.

Decreased platelet or white blood cell counts occur occasionally to frequently in association with the use of Tegretol. Nonetheless, complete pre-treatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline.

If the white blood cell or platelet count is definitely low or decreased during treatment, the patient and the complete blood count should be closely monitored (see section 4.8 “Undesirable Effects”). However, treatment with Tegretol should be discontinued if the patient develops leucopenia, which is severe, progressive or accompanied by clinical manifestations, e.g. fever or sore throat. Tegretol should be discontinued if any evidence of significant bone marrow depression appears.

Patients and their relatives should be made aware of early toxic signs and symptoms indicative of a potential haematological problem, as well as symptoms of dermatological or hepatic reactions. If reactions such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric haemorrhage appear, the patient should be advised to consult his physician immediately.

Serious dermatologic reactions

Serious dermatologic reactions, including toxic epidermal necrolysis (TEN; also known as Lyell’s syndrome) and Stevens-Johnson syndrome (SJS), have been reported very rarely with Tegretol. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and may be fatal. Most of the SJS/TEN cases appear in the first few months of treatment with Tegretol. If signs and symptoms suggestive of severe skin reactions (e.g. SJS, Lyell’s syndrome/TEN) appear, Tegretol should be withdrawn at once and alternative therapy should be considered.

Retrospective studies in patients of Han Chinese and Thai ancestry found a strong correlation between the risk of developing SJS/TEN skin reactions associated with carbamazepine and the presence in these patients of the Human Leukocyte Antigen (HLA)-B*1502 allele. Higher reporting rates of SJS (rare rather than very rare) are reported in some countries in Asia (e.g. Taiwan, Malaysia and the Philippines) in which there is a higher prevalence of the HLA-B*1502 allele in the population. The prevalence of carriers of this allele in Asian populations is above 15% in the Philippines, Thailand, Hong Kong and Malaysia, around 10% in Taiwan, around 4% in North China, around 2 to 4% in South Asia including Indians, and less than 1% in Japan and Korea. It is not definitely known whether all individuals of south east-Asian ancestry are at risk due to lack of data. The prevalence of the HLA-B*1502 allele is negligible in Caucasian, African, indigenous peoples of the Americas, and Hispanic populations sampled. The allele HLA-B*1502 has been shown not to be associated to SJS in the Caucasian population.

Whenever possible, screening for the presence of HLA-B*1502 allele should be carried out in patients with ancestry in genetically at-risk populations, prior to initiating treatment with carbamazepeine. (If testing for the presence of the HLA-B*1502 allele should be performed, high-resolution “HLA-B*1502 genotyping” is recommended. The test is positive if either one or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected). If these individuals test positive, carbamazepeine should not be started unless there is no other therapeutic option. Tested patients who are found to be negative for HLA-B*1502 have a low risk of SJS, although the reactions may still very rarely occur.

HLA-B*1502 may be a risk factor for the development of SJS/TEN in Chinese patients taking other anti-epileptic drugs (AED) associated with SJS/TEN. Consideration should therefore be given to avoiding use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable. Screening is not generally recommended in patients from populations in which the prevalence of HLA-B*1502 is low. Screening is generally not recommended for any current Tegretol users, as the risk of SJS/TEN is largely confined to the first few months of therapy, regardless of HLA-B*1502 status.

Genetic screening results must never substitute for appropriate clinical vigilance and patient management. Many Asian patients positive for HLA-B*1502 and treated with Tegretol will not develop SJS/TEN and patients negative for HLA-B*1502 of any ethnicity can still develop SJS/TEN. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as AED dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

Other dermatologic reactions

Mild skin reactions e.g. isolated macular or maculopapular exanthemata, can also occur and are mostly transient and not hazardous, and they usually disappear within a few days or weeks, either during the continued course of treatment or following a decrease in dosage. However, since it may be difficult to differentiate the early signs of more serious skin reactions from mild transient reactions, the patient should be kept under close surveillance with consideration given to immediately withdrawing the drug should the reaction worsen with continued use.

The HLA-B*1502 allele has not been found to predict risk of less severe adverse cutaneous reactions from carbamazepine, such as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular eruption).

Hypersensitivity

Tegretol may trigger hypersensitivity reactions, including multi-organ hypersensitivity reactions, which can affect the skin, liver (including intrahepatic bile ducts), haematopoietic organs and lymphatic system or other organs, either individually or together in the context of a systemic reaction (see section 4.8 Undesirable effects) .
Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25 to 30 % of these patients may experience hypersensitivity reactions with oxcarbazepine (Trileptal®). Cross-hypersensitivity can occur between carbamazepine and phenytoin .
In general, if signs and symptoms suggestive of hypersensitivity reactions occur, Tegretol should be withdrawn immediately .

Seizures

Tegretol should be used with caution in patients with mixed seizures, which include absences, either typical or atypical. In all these conditions, Tegretol may exacerbate seizures. In case of exacerbation of seizures, Tegretol should be discontinued.

An increase in seizure frequency may occur during switchover from an oral formulation to suppositories.

Abrupt withdrawal of Tegretol may precipitate seizures.

Hepatic function

Liver function tests should also be performed before commencing treatment and periodically thereafter, particularly in patients with a history of liver disease and in elderly patients. The drug should be withdrawn immediately in cases of aggravated liver dysfunction or acute liver disease.

Some liver function tests in patients receiving carbamazepine may be found to be abnormal, particularly gamma glutamyl transferase. This is probably due to hepatic enzyme induction. Enzyme induction may also produce modest elevations in alkaline phosphatase. These enhancements of hepatic metabolising capacity are not an indication of the withdrawal of carbamazepine.

Severe hepatic reactions to carbamazepine occur very rarely. The development of signs and symptoms of liver dysfunction or active liver disease should be urgently evaluated and treatment with Tegretol suspended pending the outcome of the evaluation.

Gastrointestinal function:

The polyethoxylated castor oil present in this formulation may cause stomach upset and diarrhoea.

Renal function

Baseline and periodic complete urinalysis and BUN determinations are recommended.

Anticholinergic effects

Tegretol has shown mild anticholinergic activity; patients with glaucoma should therefore be warned and advised regarding possible hazards.

Psychiatric effects

The possibility of activation of a latent psychosis, and in elderly patients the possibility of agitation or confusion, especially when high doses of Tegretol are administered should be borne in mind.

Suicidal ideation and behaviour

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 drugs 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 carbamazepine. 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.

Endocrinology

The induction of hepatic enzymes by carbamazepine may reduce the activity of the hormones contained in the combined oral-contraceptive pill. This may appear clinically as breakthrough bleeding or spotting. Breakthrough bleeding has been reported in women taking Tegretol while using hormonal contraceptives; the reliability of oral contraceptives may be adversely affected by Tegretol and women of childbearing age should be advised to consider using alternative forms of birth control while taking Tegretol. Due to enzyme induction Tegretol may cause failure of the therapeutic effect of drugs containing oestrogen and/or progesterone containing drugs (e.g. failure of contraception).

Monitoring plasma levels

Although correlations between dosage and plasma levels of carbamazepine and between plasma levels and clinical efficacy or tolerability are rather tenuous, monitoring of the plasma levels may be useful in the following situations : dramatic increase in seizure frequency; during pregnancy; when treating children or adolescents; in suspected absorption disorders; for verification of compliance; in suspected toxicity where more than one drug is being used (see section 4.5 Interaction with other Medicaments and other Forms of Interaction).

Dose reduction and withdrawal

Abrupt withdrawal of Tegretol may precipitate seizures. If treatment with Tegretol has to be withdrawn abruptly, the switch to another anti-epileptic drug should if necessary be effected under the cover of a suitable drug e.g. i.v. or rectal benzodiazepines, or i.v. phenytoin.

There have been a few cases of neonatal seizures and / or respiratory depression associated with maternal Tegretol and other concomitant anticonvulsant drug use. A few cases of neonatal vomiting, diarrhoea and / or decreased feeding have also been reported in association with maternal Tegretol use. These reactions may represent a neonatal withdrawal syndrome.

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P4503A4 (CYP3A4) is the main enzyme catalysing formulation of the active metabolite carbamazepine 10, 11 epoxide. Co-administration of inhibitors of CYP3A4 may result in increased carbamazrpine plasma concentrations, which could induce adverse reactions. Coadministration of CYP3A4 inducers might increase the rate of Tegretol metabolism, thus leading to a potential decreases in the carbamazepine serum level and potential decrease in the therapeutic effect. Similarly, discontinuation of a CYP3A4 inducer may decrease the rate of metabolism of carbamazepine, leading to an increase in carbazepine plasma levels.

Carbamazepine is a potent inducer of CYP3A4 and other phase I and phase II enzyme systems in the liver, and may therefore reduce plasma concentrations of comedications mainly metabolized by CYP3A4 by induction of their metabolism.

Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11 epoxide [301]. Co-administration of inhibitors of human microsomal epoxide hydrolase may result in increased carbamazepine-10,11 epoxide plasma concentrations [301].

Agents that may raise carbamazepine plasma levels:

Agents that may raise carbamazepine and/or carbamazepine -10,11-epoxide plasma levels:

Since raised plasma carbamazepine levels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of Tegretol should be adjusted accordingly and /or the plasma levels monitored when used concomitantly with the substance s described below:

Analgesics: anti-inflammatory drugs: dextropropoxyphene, ibuprofen.
Androgens: danazol.
Antibiotics: macrolide antibiotics (e.g. erythromycin, , clarithromycin).
Antidepressants:, fluoxetine, fluvoxamine, nefazodone, paroxetine ,trazodone, viloxazine [303, 304].
Antiepileptics: stiripentol , vigabatrin .
Antifungals: azoles (e.g. itraconazole, ketoconazole, fluconazole, voriconazole).
Antihistamines: loratadine, terfenadine.
Antipsychotics: olanzapine
Antituberculosis: isoniazid.
Antivirals: protease inhibitors for HIV treatment (e.g. ritonavir).
Carbonic anhydrase inhibitors: acetazolamide.
Cardiovascular drugs: diltiazem, verapamil.
Gastrointestinal drugs: possibly cimetidine,omeprazole.
Muscle relaxants: oxybutynin, dantrolene.
Platelet aggregation inhibitors: ticlopidine.
Other interactions: grapefruit juice, nicotinamide (in adults, only in high dosage).

Agents that may raise the active metabolite carbamazepine 10, 11-epoxide plasma levels:

Since raised plasma carbamazepine-10, 11-epoxide levels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of Tegretol should be adjusted accordingly and /or the plasma levels monitored when used concomitantly with the substances described below:
Loxapine, quetiapine, primidone, progabide, valproic acid, valnoctamide and valpromide.

Agents that may decrease carbamazepine plasma levels:

The dose of Tegretol may have to be adjusted when used concomitantly with the substances described below.
Antiepileptics:, oxcarbazepine, phenobarbitone, phenytoin and fosphenytoin, primidone, , and, although the data are partly contradictory, possibly also clonazepam.
Antineoplasics: cisplatin or doxorubicin.
Antimalarials: mefloquine, may antagonised the anticonvulsant effect of carbamazepine
Antituberculosis: rifampicin.
Bronchodilatators or anti-asthma drugs: theophylline,aminophylline.
Dermatological drugs: isotretinoin has been reported to alter the bioavailability and/or clearance of carbamazepine and carbamazepine 10, 11 epoxide.Carbamazepine levels should be monitored.
Other interactions: herbal preparations containing St John's wort (Hypericum perforatum)

Effect of Carbamazepine on plasma levels of concomitant agents:

Plasma or whole blood concentrations of carbamazepine can be reduced by concomitant use of the herbal preparation St John's wort (Hypericum perforatum). This is due to induction of drug metabolising enzymes by St John's wort. Herbal preparations containing St John's wort should therefore not be combined with Tegretol. The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John's wort. If a patient is already taking St John's wort check carbamazepine blood levels and stop St John's wort. Carbamazepine levels may increase on stopping St John's wort. The dose of carbamazepine may need adjusting.

Carbamazepine may lower the plasma level, or diminish - or even abolish - the activity of certain drugs. The dosage of the following drugs may have to be adjusted to clinical requirements:
Analgesics, anti-inflammatory agents: methadone, paracetamol, phenazone (antipyrine), tramadol.
Antibiotics: doxycycline.
Anticoagulants: oral anticoagulants (e.g. warfarin, and acenocoumarol).
Antidepressants: bupropion, citalopram, nefazodone [301], trazodone, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortriptyline, clomipramine).The use of Tegretol is not recommended in combination with monoamine-oxidase inhibitors (MAOIs); before administering Tegretol MAOIs should be discontinued for a minimum of 2 weeks, or longer if the clinical situation permits (see section 4.3 Contraindications).
Antiepileptics: clobazam, clonazepam, ethosuximide, lamotrigine, oxcarbazepine, primidone, tiagabine, topiramate, valproic acid,. Plasma phenytoin levels have been reported both to be raised and to be lowered by carbamazepine, and there have been rare reports of an increase in plasma mephenytoin levels.
Antifungals: itraconazole.
Antihelmintics: praziquantel.
Antineoplasics: imatinib.
Antipsychotics: clozapine, haloperidol and bromperidol, olanzapine, quetiapine, risperidone, ziprasidone.
Antivirals: protease inhibitors for HIV treatment (e.g. indinavir, ritonavir, saquinavir).
Anxiolytics: alprazolam, midazolam.
Bronchodilatators or anti-asthma drugs: theophylline.
Contraceptives: hormonal contraceptives (alternative contraceptive methods should be considered).
Cardiovascular drugs: digoxin, calcium channel blockers (dihydropyridine group) e.g. felodipine,isradipine
Corticosteroids: corticosteroids (e.g. prednisolone, dexamethasone).
Immunosuppressants: ciclosporin, everolimus
Thyroid agents: levothyroxine.

Other drug interactions: products containing oestrogens and/or progesterones (gestrinone, tribolone, toremifene)

Plasma phenytoin levels have been reported both to be raised and to be lowered by carbamazpine, and plasma mephenytoin levels have been reported in rare instances to increase.

Combinations to be taken into consideration:

Co- administration of carbamazepine and paracetamol may reduce the bioavailability paracetamol/acetaminophen.

Concomitant use of carbamazepine and isoniazid has been reported to increase isoniazid epatotoxicity.

Combined use of carbamazepine and lithium or metoclopramide on the one hand, and carbamazepine and neuroleptics (haloperidol, thioridazine) on the other, may lead to increased neurological adverse reactions (with the latter combination even in the presence of 'therapeutic plasma levels').
Concomitant medication with Tegretol and some diuretics (hydrochlorothiazide, frusemide) may lead to symptomatic hyponatraemia.

Carbamazepine may antagonise the effects of non- polarising muscle relaxants (e.g. pancuronium); their dosage should be raised and patients monitored closely for a more rapid recovery from neuromuscular blockade than expected.
Carbamazepine, like other psychoactive drugs, may reduce alcohol tolerance; it is therefore advisable for the patient to abstain from alcohol.

4.6 Pregnancy and lactation

Pregnancy

In animals (mice, rats and rabbits) oral administration of carbamazepine during organogenesis led to increased embryonic mortality at daily doses which caused maternal toxicity (above 200mg/kg b.w.) daily i.e. 20 times the usual human dosage**.** In the rat there was also some evidence of abortion at 300mg/kg body weight daily. Near term rat foetuses showed growth retardation, again at maternally toxic doses. No evidence of a teratogenic effect was observed in the three species studied but in one study using mice carbamazepine (40 to 240 mg/kg b.w. daily orally) caused defects in 4.7% of exposed foetuses compared with 1.3% in controls.

Offspring of epileptic mothers are known to be more prone to developmental disorders, including malformations. The possibility that carbamazepine, like all major antiepileptic drugs, increases this risk has been reported, although conclusive evidence from controlled studies with carbamazepine monotherapy is lacking. However developmental disorders and malformations, including spina bifida and also other congenital anomalies, e.g. craniofacial defects, cardiovascular malformations, hypospadias and anomalies involving various body systems, have been reported in association with Tegretol. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

Taking these data into consideration:

- Pregnant women with epilepsy should be treated with special care .
- If women receiving Tegretol become pregnant or plan to become pregnant, or if the problem of initiating treatment with Tegretol arises during pregnancy, the drug's potential benefits must be carefully weighed against its possible hazards, particularly in the first 3 months of pregnancy.
- In women of childbearing age Tegretol should, wherever possible, be prescribed as monotherapy, because the incidence of congenital abnormalities in the offspring of women treated with a combination of antiepileptic drugs is greater than in those of mothers receiving the individual drugs as monotherapy.
- Minimum effective doses should be given and monitoring of plasma levels is recommended.
- 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 treatment must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Monitoring and prevention

Folic acid deficiency is known to occur in pregnancy. Antiepileptic drugs have been reported to aggravate deficiency. This deficiency may contribute to the increased incidence of birth defects in the offspring of treated epileptic women. Folic acid supplementation is recommended before and during pregnancy.

In the neonate

In order to prevent bleeding disorders in the offspring, it has also been recommended that vitamin K1 be given to the mother during the last weeks of pregnancy as well as to the neonate.

There have been a few cases of neonatal seizures and/or respiratory depression associated with maternal Tegretol and other concomitant anticonvulsant drug use. A few cases of neonatal vomiting, diarrhoea and/or decreased feeding have also been reported in association with maternal Tegretol use. These reactions may represent a neonatal withdrawal syndrome.

Lactation

Although carbamazepine passes into the breast milk in concentrations of about 25-60% of the plasma level, this is not believed to present a significant hazard to the infant, which is likely to receive at most 10% of an appropriate therapeutic dose of carbamazepine for an infant with epilepsy. As with all drugs, the benefits of breast-feeding should be weighed against the remote possibility of an adverse effect occurring in the infant.

Fertility

There have been very rare reports of impaired male fertility and/or abnormal spermatogenesis.

4.7 Effects on ability to drive and use machines

The patients ability to react may be impaired by dizziness and drowsiness caused by Tegretol, especially in the early stages of treatment. Patients should therefore exercise due caution when driving a vehicle or operating machinery.

4.8 Undesirable effects

Particularly at the start of treatment with Tegretol, or if the initial dosage is too high or when treating elderly patients, certain types of adverse reaction occur very commonly or commonly, e.g. CNS adverse reactions (dizziness, headache, ataxia, drowsiness, fatigue, diplopia); gastrointestinal disturbances nausea, vomiting) and allergic skin reactions.

The dose – related adverse reactions usually abate within a few days, either spontaneously or after a transient dosage reduction. The occurrence of CNS adverse reactions may be a manifestation of relative overdosage or significant fluctuation in plasma levels. In such cases it is advisable to monitor the plasma levels and divide the daily dosage into smaller (i.e. 3-4) fractional doses.

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10 000, < 1/1000); very rare (< 1/10 000), including isolated reports.

Table 1

Blood and lymphatic system disorders		
	Very common:	leukopenia.
	Common:	thrombocytopenia, eosinophilia.
	Rare:	leukocytosis, lymphadenopathy, folic acid deficiency .
	Very rare:	agranulocytosis, aplastic anaemia, pancytopenia, pure red cell aplasia, anaemia, megaloblastic anaemia, acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda, reticulocytosis, and possibly haemolytic anaemia.

Immune system disorders		
	Rare:	a delayed multiorgan hypersensitivity disorder (of serum sickness type) with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly and abnormal liver function tests, occurring in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon). Treatment must be discontinued immediately if such hyprsensitivity reactions occur.
	Very rare:	aseptic meningitis, with myoclonus and peripheral eosinophilia; anaphylactic reaction, angioneurotic oedema.
Endocrine disorders		
	Common:	oedema, fluid retention, weight increase, hyponatraemia and blood osmolarity decreased due to an antidiuretic hormone (ADH)-like effect leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, confusional state, neurological disorders.
	Very rare:	Blood prolactin increased with or without clinical manifestations such as galactorrhoea, gynecomastia, abnormal thyroid function tests: decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations, bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol), leading to osteomalacia/osteoporosis, increased blood cholesterol, including HDL cholesterol, and triglycerides.
Psychiatric disorders		
	Rare:	hallucinations (visual or auditory), depression, anorexia, restlessness, aggression, agitation, confusional state.
	Very rare:	activation of psychosis.
Nervous system disorders		
	Very common:	dizziness, ataxia, drowsiness, fatigue.
	Common:	headache, diplopia, accommodation disorders (e.g. blurred vision).
	Uncommon:	abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics); nystagmus.
	Rare:	orofacial dyskinesia, eye movement disturbances, speech disorders (e.g. dysarthria, slurred speech), choreoathetosis, neuropathy peripheral, paraesthesia, and paresis.
	Very rare:	taste disturbances, neuroleptic malignant syndrome.
Eye disorders		
	Very rare:	lenticular opacities, conjunctivitis, intraocular pressure increased.
Ear and labyrinth disorders		
	Very rare:	hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception.

Cardiac disorders		
	Rare:	cardiac conduction disorders; hypertension or hypotension.
	Very rare:	bradycardia, arrhythmia, atrioventricular block with syncope, circulatory collapse, congestive heart failure, aggravation of coronary artery disease, thrombophlebitis, thromboembolism (e.g. pulmonary embolism).
Respiratory, thoracic and mediastinal disorders		
	Very rare:	pulmonary hypersensitivity characterized e.g. by fever, dyspnoea, pneumonitis or pneumonia.
Gastrointestinal disorders		
	Very common:	nausea, vomiting.
	Common:	dry mouth; with suppositories, rectal irritation may occur.
	Uncommon:	diarrhoea, constipation.
	Rare:	abdominal pain.
	Very rare:	glossitis, stomatitis, pancreatitis.
Hepatobiliary disorders		
	Very common:	increased gamma-GT (due to hepatic enzyme induction), usually not clinically relevant.
	Common:	increased blood alkaline phosphatase.
	Uncommon:	increased transaminases.
	Rare:	hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, jaundice.
	Very rare:	granulomatous hepatitis, hepatic failure.
Skin and subcutaneous tissue disorders		
	Very common:	dermatitis allergic, urticaria which may be severe .
	Uncommon:	exfoliative dermatitis and erythroderma.
	Rare:	systemic lupus erythematosus, pruritus.
	Very rare:	Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity reaction, erythema multiforme and nodosum, alterations in skin pigmentation, purpura, acne, hyperhydrosis, hair loss, ; hirsutism [301]
Musculoskeletal, connective tissue and bone disorders		
	Rare	muscular weakness
	Very rare:	arthralgia, muscle pain, muscle spasms.
Renal and urinary disorders		
	Very rare:	interstitial nephritis, renal failure, renal impairment (e.g. albuminuria, haematuria, oliguria, and blood urea increased/azotemia), urinary frequency, urinary retention.
Reproductive system		
	Very rare:	sexual dysfunction/impotence, spermatogenesis abnormal (with decreased sperm count and/or motility).
Investigations		
	Very Rare:	Hypogammaglobinaemia

*In some Asian countries also reported as rare. See also section 4.4 Special Warnings and precautions for use

4.9 Overdose

Signs and symptoms:
The presenting signs and symptoms of overdosage involve the central nervous, cardiovascular or respiratory systems.

Central nervous system:
CNS depression; disorientation, somnolence, agitation, hallucination, coma; blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyppereflexia, later hyporeflexia; convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis.

Respiratory system:
Respiratory depression, pulmonary oedema.

Cardiovascular system:
Tachycardia, changes in blood pressure (hypotension and at times hypertension), cardiac arrhythmias, conduction disturbance with widening of QRS complex; syncope, in association with cardiac arrest.

Gastrointestinal system:
Vomiting, delayed gastric emptying, reduced bowel motility.

Renal function:
Retention of urine, oliguria or anuria; fluid retention, water intoxication due to ADH-like effect of carbamazepine.

Laboratory findings:
Hyponatraemia, possibly metabolic acidosis, possibly hyperglycaemia, increased muscle creatinine phosphokinase.

Treatment:
There is no specific antidote to Tegretol.
Management according to the patient's clinical condition. Possible admission to hospital. Measurement of the plasma level to confirm carbamazepine poisoning and to ascertain the size of the overdose. Evacuation of the stomach, gastric lavage, and administration of activated charcoal. Supportive medical care in an intensive care unit with cardiac monitoring and careful correction of electrolyte imbalance, if required.

Special recommendations:

Hypotension: administer dopamine or dobutamine i.v.

Disturbances of cardiac rhythm: to be managed on an individual basis.

Convulsions: administer a benzodiazepine (e.g. diazepam) or another anticonvulsant, e.g. phenobarbitone (with caution because of increased respiratory depression), or paraldehyde.

Hyponatraemia (water intoxication): fluid restriction and slow and careful NaCl 0.9% infusion i.v. These measures may be useful in preventing brain damage.

Charcoal haemoperfusion has been recommended. Forced diuresis, haemodialysis, and peritoneal dialysis have been reported not to be effective.

Relapse and aggravation of symptomatology on the 2nd and 3rd day after overdose, due to delayed absorption, should be anticipated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Antiepileptic, neurotropic, and psychotropic agent. (ATC Code: N03 AF01).

Mechanism of action: Carbamazepine is a dibenzazepine derivative with antiepileptic, neurotropic and psychotropic properties. The mechanism of action is uncertain.

5.2 Pharmacokinetic properties

Absorption:
Peak plasma concentrations are attained within 2 hours of dosing. With respect to the amount of active substance absorbed, there is no clinically relevant difference between the oral dosage forms. After a single oral dose of 400mg carbamazepine (tablets) the mean peak concentration of unchanged carbamazepine (CBZ) in the plasma is approximately 4.5µg/ml.

The bioavailability of carbamazepine is almost 100% and is unaffected by food.

The total bioavailability of carbamazepine from suppositories is approximately 25% less than from oral formulations. For doses up to 300mg approximately 75% of the total amount absorbed reaches the general circulation within 6 hours of administration. For these reasons the maximum recommended daily dose is limited to 250mg qd (1000mg per day), the equivalent of 800mg per day orally. Clinical trials have shown that when suppositories are substituted for oral dosage forms plasma levels within the range 5-8µg/ml (19-34µmol/L) are reached. It should be possible, therefore, to maintain therapeutically effective plasma levels in most patients.

Elimination

Elimination half life after a single dose, mean 36 h whereas after repeated administration, which leads to auto-induction of hepatic enzymes, it averages only 16-24 hours: co-medication with other enzyme-inducing drugs (phenytoin, phenobarbitone) : mean 9-10 h. The therapeutic plasma concentration range of carbamazepine at steady state is usually between 4-12µg/ml (17-50µmol/L).

Serum protein binding: 70-80%.

Distribution: Apparent volume of distribution 0.8-1.5 L/kg.

Biotransformation

Carbamazepine is extensively metabolised in the liver mainly by oxidative pathways and the greater part is excreted as the inactive glucuronide with up to 40% as metabolites of which only carbamazepine epoxide is pharmacologically active, (carbamazepine 11,12 epoxide). Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11 epoxide [301].

This may constitute up to 30% of circulating active material originating as carbamazepine, in particular polytherapy is an important factor in augmenting epoxide levels. The inactive 10, 11-diol represents the end product of carbamazepine biotransformation. Only about 3% of pharmacologically active material (unchanged plus epoxide) is excreted.

Other important biotransformation pathways for carbamazepine lead to various monohydroxylated compounds, as well as to the N-glucuronide of carbamazepine produced by UGT2B7.

Patients with hepatic and renal impairment

In advanced hepatic disease carbamazepine metabolism may be impaired.

Elderly
The pharmacokinetics of carbamazepine are unaltered in the elderly but its metabolism may be affected by hepatic dysfunction (see above).

Children
In children the relatively high rate of metabolism of the drug may require higher doses (in mg/kg b. w.) of carbamazepine to maintain therapeutic concentrations

5.3 Preclinical safety data

The incidence of tumours was found to be increased in rats treated with carbamazepine for 2 years. The significance of these findings relative to the use of carbamazepine in humans, is at present unknown. Bacterial and mammalian mutagenicity studies yielded negative results.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Silica, colloidal anhydrous
Ethylcellulose aqueous dispersion
Microcrystalline cellulose
Methacrylic acid copolymer
Magnesium stearate
Carmellose sodium
Talc

Tablet coating:
Hypromellose
Polyethoxylated castor oil
Iron oxide red (E172)
Iron oxide yellow (E172)
Titanium dioxide (E171)
Talc

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from moisture

6.5 Nature and contents of container

Blister packs of 30 tablets in an overlabelled outer carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing Ltd
Unit 10
Ashbourne Business Park
Rath
Ashbourne
Co. Meath
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA465/201/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st May 2010

10 DATE OF REVISION OF THE TEXT