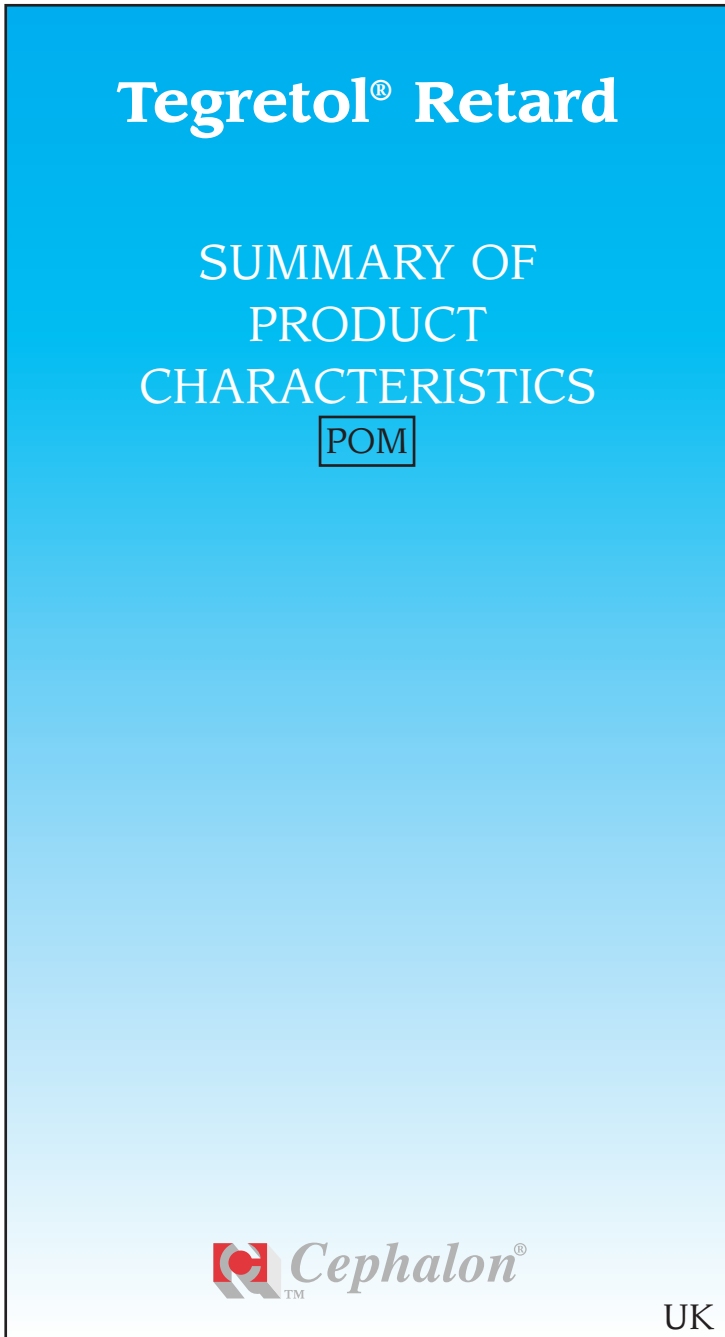


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405 Sep 2001



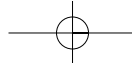
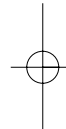
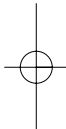
Tegretol[®] Retard

SUMMARY OF PRODUCT CHARACTERISTICS

POM



UK



**1.
Trade Name of the
Medicinal Product**

Tegretol® Retard Tablets 200 mg and 400 mg

**2.
Qualitative and
Quantitative Composition**

The active ingredient is 5-Carbamoyl-5-H-dibenz(b,f)azepine.

Each coated tablet contains 200 mg or 400 mg carbamazepine Ph.Eur.

**3.
Pharmaceutical Form**

The 200 mg tablets are beige-orange, oval, slightly biconvex, coated tablets with a score on each side. One side bears the imprint "H/C", the other "C/G".

The 400 mg tablets are brownish-orange, oval, slightly biconvex coated tablets with a score on each site. One side bears the imprint "ENE/ENE", the other "C/G".

**4.
Clinical Particulars****4.1
Therapeutic Indications**

Epilepsy - generalised tonic-clonic and partial seizures. Tegretol Retard is indicated in newly diagnosed patients with epilepsy and in those patients who are uncontrolled or unable to tolerate their current anti-convulsant therapy.

Note: Carbamazepine is not usually effective in absences (petit mal) and myoclonic seizures. Moreover, anecdotal evidence suggests that seizure exacerbation may occur in patients with atypical absences.

The paroxysmal pain of trigeminal neuralgia.

For the prophylaxis of manic-depressive psychoses in patients unresponsive to lithium therapy.

**4.2
Posology and Method
of Administration**

Tegretol Retard is given orally, generally in the same total daily dose as conventional Tegretol dosage forms but usually in two divided doses. In a few patients when changing from other oral dosage forms of Tegretol to Tegretol Retard the total daily dose may need to be increased, particularly when it is used in polytherapy. When starting treatment with Tegretol Retard in monotherapy, 100-200 mg once or twice daily is recommended. This may be followed by a slow increase in dosage until the best response is obtained, often 800-1200 mg daily. In some instances, 1600 mg or even 2000 mg daily may be necessary.

Tegretol Retard (either the whole or half divisible tablet as prescribed), should not be chewed but should be swallowed with a little liquid, before, during or between meals. The divisible tablet presentation enables flexibility of dosing to be achieved.

Epilepsy:

Adults: It is advised that with all formulations of Tegretol, 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 **Pharmacokinetics, Precautions and Interactions**).

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

Children: It is advised that with all formulations of Tegretol, 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 **Pharmacokinetics, Precautions and Interactions**).

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

Age:	up to 5 years:	Tegretol Retard Tablets are not recommended
	5-10 years:	400-600 mg daily
	10-15 years:	600-1000 mg

Wherever possible, Tegretol Retard should be used as the sole drug anti-epileptic agent but, if used in polytherapy, the same incremental dosage pattern is advised.

When Tegretol is added to existing antiepileptic therapy, this should be done gradually while maintaining or, if necessary, adapting the dosage of the other antiepileptic(s) (see 4.5 **Interaction with other Medicaments and other forms of Interaction**).

Trigeminal neuralgia:

Slowly raise the initial dosage of 200-400 mg daily (100 mg twice daily in elderly patients) until freedom from pain is achieved (normally at 200 mg 3-4 times daily). In the majority of patients a dosage of 200 mg 3 or 4 times a day is sufficient to maintain a pain free state. In some

instances, doses of 1600 mg Tegretol daily may be needed. However, once the pain is in remission, the dosage should be gradually reduced to the lowest possible maintenance level.

For the prophylaxis of manic depressive psychosis in patients unresponsive to lithium therapy:

Initial starting dose of 400 mg daily, in divided doses, increasing gradually until symptoms are controlled or a total of 1600 mg given in divided doses is reached. The usual dosage range is 400-600 mg 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 block, a history of bone marrow depression or a history of acute intermittent porphyria.

Because it is structurally related to tricyclic antidepressants, 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.

4.4 Special Warnings and Precautions for Use

4.4.1 Warnings

Agranulocytosis and aplastic anaemia have been associated with Tegretol; however, due to the very low incidence of these conditions, 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, and periodically thereafter.

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.

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.

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 for 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.

Mild skin reactions e.g. isolated macular or maculopapular exanthemata, 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, the patient should be kept under close surveillance and a worsening rash or accompanying symptoms are an indication for the immediate withdrawal of Tegretol.

If signs and symptoms suggestive of severe skin reactions (e.g. Stevens-Johnson syndrome, Lyell's syndrome) appear, Tegretol should be withdrawn at once.

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:

If treatment with Tegretol has to be withdrawn abruptly, the changeover to another anti-epileptic drug should, if necessary, be effected under the cover of a suitable drug (e.g. diazepam i.v., rectal; or phenytoin i.v.).

Isolated reports of impaired male fertility and/or abnormal spermatogenesis are on file. A causal relationship has not been established.

Tegretol and oral contraception:

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. Patients taking Tegretol and requiring oral contraception should receive a preparation containing not less than 50 mcg oestrogen or use of some alternative non-hormonal method of contraception should be considered.

Although correlations between dosages 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 conditions: dramatic increase in seizure frequency/verification of patient compliance; during pregnancy; when treating children or adolescents; in suspected absorption disorders; in suspected toxicity when more than one drug is being used (see 4.5 **Interaction with other Medicaments and other forms of Interaction**).

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.

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.

**4.4.2
Precautions**

Baseline and periodic complete urinalysis and BUN determinations are recommended.

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

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.

4.5 Interactions with other Medicaments and other forms of Interaction

Cytochrome P450 3A4 (CYP 3A4) is the main enzyme catalysing formation of carbamazepine 10, 11-epoxide. Co-administration of inhibitors of CYP 3A4 may result in increased plasma concentrations which could induce adverse reactions. Co-administration of CYP 3A4 inducers might increase the rate of Tegretol metabolism, thus leading to a potential decrease in carbamazepine serum level and potential decrease in the therapeutic effect.

Agents that may raise Tegretol plasma levels:

Isoniazid, verapamil, diltiazem, ritonavir, dextropropoxyphene, viloxazine, fluoxetine, fluvoxamine, possibly cimetidine, acetazolamide, danazol, nicotinamide (in adults, only in high dosage), nefazodone, macrolide antibiotics (e.g. erythromycin, clarithromycin), azoles (e.g. itraconazole, ketoconazole, fluconazole), terfenadine, loratadine. 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.

Agents that may decrease Tegretol plasma levels:

Phenobarbitone, phenytoin, primidone, or theophylline, rifampicin, cisplatin or doxorubicin and, although the data are partly contradictory, possibly also clonazepam or valproic acid. Mefloquine may antagonise the anticonvulsant effect of Tegretol. On the other hand, valproic acid and primidone have been reported to raise the plasma level of the pharmacologically active carbamazepine 10, 11-epoxide metabolite. The dose of Tegretol may consequently have to be adjusted.

Isotretinoin has been reported to alter the bioavailability and/or clearance of carbamazepine and carbamazepine 10, 11-epoxide; carbamazepine plasma concentrations should be monitored.

Serum levels of carbamazepine can be reduced by concomitant use of the herbal remedy St John's wort (*Hypericum perforatum*).

Effect of Tegretol on plasma levels of concomitant agents:

Carbamazepine may lower the plasma level, diminish or even abolish the activity of certain drugs. The dosage of the following drugs may have to be adjusted to clinical requirement: levothyroxine, clobazam, clonazepam, ethosuximide, primidone, valproic acid, alprazolam, corticosteroids, (e.g. prednisolone, dexamethasone); cyclosporin, digoxin, doxycycline, dihydroxyridine derivatives, e.g. felodipine and isradipine; indinavir, saquinavir, ritonavir, haloperidol, imipramine, methadone, tramadol, oral contraceptives (alternative contraceptive methods should be considered) see section 4.4 "Special Warnings and Precautions for Use", gestrinone, tibolone, toremifene, theophylline, oral anticoagulants (warfarin), lamotrigine, tiagabine, topiramate, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortriptyline, clomipramine), clozapine, olanzapine and risperidone

Plasma phenytoin levels have been reported both to be raised and to be lowered by carbamazepine, 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 of paracetamol/acetaminophen.

Concomitant use of carbamazepine and isoniazid has been reported to increase isoniazid-induced hepatotoxicity.

The combination of lithium and carbamazepine may cause enhanced neurotoxicity in spite of lithium plasma concentrations being within the therapeutic range.

Combined use of carbamazepine with metoclopramide or major tranquilisers e.g. haloperidol, thioridazine may also result in an increase in neurological side-effects.

Because it (carbamazepine) is structurally related to tricyclic anti-depressants, 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.

Concomitant medication with Tegretol and some diuretics (hydrochlorothiazide, frusemide) may lead to symptomatic hyponatraemia.

Carbamazepine may antagonise the effects of non-depolarising muscle relaxants (e.g. pancuronium); their dosage should be raised and patients monitored closely for a more rapid recovery from neuromuscular blockade than expected.

Tegretol, like other psychoactive drugs, may reduce alcohol tolerance; it is therefore advisable for the patient to abstain from alcohol.

4.6 Pregnancy and Lactation

In animals (mice, rats and rabbits) oral administration of carbamazepine during organogenesis led to increased embryo mortality at daily doses which caused maternal toxicity (above 200 mg/kg b.w. daily i.e. 20 times the usual human dosage). In the rat there was also some evidence of abortion at 300 mg/kg b.w. daily. Near-term rat foetuses showed growth retardation, again at maternally toxic doses. There was no evidence of teratogenic potential in the three species tested but, in one study using mice, carbamazepine (40-240 mg/kg b.w. daily orally) caused defects (mainly dilatation of cerebral ventricles in 4.7% of exposed foetuses as compared with 1.3% in controls).

Pregnant women with epilepsy should be treated with special care.

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.

If pregnancy occurs in a woman receiving Tegretol, 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 three months of pregnancy. Minimum effective doses should be given and monitoring of plasma levels is recommended.

Offspring of epileptic mothers with untreated epilepsy are known to be more prone to developmental disorders, including malformations. The possibility that carbamazepine, like all major antiepileptic drugs, increases the risk has been reported, although conclusive evidence from controlled studies with carbamazepine monotherapy is lacking. However, there are reports on developmental disorders and malformations, including spina bifida, in association with Tegretol. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

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.

Vitamin K₁ to be given to the mother during the last weeks of pregnancy as well as to the newborn to prevent bleeding disorders in the offspring, has also been recommended.

Use during lactation:

Carbamazepine passes into the breast milk (about 25-60% of the plasma concentrations). The benefits of breast-feeding should be weighed against the remote possibility of adverse effects occurring in the infant. Mothers may breast-feed their infants, provided the infant is observed for possible adverse reactions (e.g. excessive somnolence, allergic skin reaction).

4.7 Effects on Ability to Drive and Use Machines

The patient's ability to react may be impaired by dizziness and drowsiness caused by Tegretol, especially at the start of treatment or in connection with dose adjustments; 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), as well as 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.

Frequency estimate: very common $\geq 10\%$, common $\geq 1\%$ to $< 10\%$; uncommon $\geq 0.1\%$ to $< 1\%$; rare $\geq 0.01\%$ to $< 0.1\%$; very rare $< 0.01\%$

Central Nervous System:

Neurological:

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, oculomotor disturbances, speech disorders (e.g. dysarthria or slurred speech), choreoathetotic disorders, peripheral neuritis, paraesthesia, muscle weakness, and parietic symptoms.

Cases of neuroleptic malignant syndrome have been reported. The causative role of carbamazepine in inducing or contributing to the development of a neuromalignant syndrome, especially in conjunction with neuroleptics, is unclear.

Psychiatric:**Rare:**

Hallucinations (visual or acoustic), depression, loss of appetite, restlessness, aggressive behaviour, agitation, confusion.

Very rare:

Activation of psychosis.

Skin and appendages:**Very Common:**

Allergic skin reactions, urticaria, which may be severe.

Uncommon:

Exfoliative dermatitis and erythroderma.

Rare:

Lupus erythematosus-like syndrome, pruritus.

Very rare:

Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity, erythema multiforme and nodosum, alterations in skin pigmentation, purpura, acne, sweating, hair loss.

Very rare cases of hirsutism have been reported, but the causal relationship is not clear.

Blood:**Very common:**

Leucopenia.

Common:

Thrombocytopenia, eosinophilia.

Rare:

Leucocytosis, lymphadenopathy, folic acid deficiency.

Very rare:

Agranulocytosis, aplastic anaemia, pure red cell aplasia, megaloblastic anaemia, acute intermittent porphyria, reticulocytosis, and possibly haemolytic anaemia.

Liver:**Very common:**

Elevated gamma-GT (due to hepatic enzyme induction), usually not clinically relevant.

Common:

Elevated alkaline phosphatase.

Uncommon:

Elevated transaminases.

Rare:

Hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, jaundice.

Very rare:

Granulomatous hepatitis.

Gastro-intestinal tract:**Very common:**

Nausea, vomiting.

Common:

Dryness of the mouth. With suppositories rectal irritation may occur.

Uncommon:

Diarrhoea or constipation.

Rare:

Abdominal pain.

Very rare:

Glossitis, stomatitis, pancreatitis.

Hypersensitivity reactions:**Rare:**

A delayed multi-organ hypersensitivity disorder with fever, skin rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leucopenia, eosinophilia, hepato-splenomegaly and abnormal liver function tests, occurring in various combinations. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, colon).

Very rare:

Aseptic meningitis, with myoclonus and peripheral eosinophilia, anaphylactic reaction, angioedema.

Treatment must be discontinued immediately if such hypersensitivity reactions occur.

Cardiovascular system:**Rare:**

Disturbances of cardiac conduction.

Very rare:

Bradycardia, arrhythmias, AV-block with syncope, collapse, congestive heart failure, hypertension or hypotension, aggravation of coronary artery disease, thrombophlebitis, thrombo-embolism.

Endocrine system and metabolism:**Common:**

Oedema, fluid retention, weight increase, hyponatraemia and reduced plasma osmolality due to an antidiuretic hormone (ADH)-like effect, leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, mental confusion, neurological abnormalities.

Very rare:

Increase in prolactin with or without clinical symptoms such as galactorrhoea, gynaecomastia, abnormal thyroid function tests;

4.9 Overdose

decreased L-thyroxine (FT₄, T₄, T₃) and increased TSH, usually without clinical manifestations, disturbances of bone metabolism (decrease in plasma calcium and 25-OH-cholecalciferol), leading to osteomalacia, elevated levels of cholesterol, including HDL cholesterol, and triglycerides.

Urogenital systems:

Very rare:

Interstitial nephritis and renal failure, signs of renal dysfunction including albuminuria, haematuria, oliguria and elevated BUN/azotaemia, urinary frequency, urinary retention, sexual disturbances/impotence.

Sense organs:

Very rare:

Taste disturbances; lens opacities, conjunctivitis, hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception.

Musculoskeletal system:

Very rare:

Arthralgia, muscle pain or cramp.

Respiratory tract:

Very rare:

Pulmonary hypersensitivity characterised e.g. by fever, dyspnoea, pneumonitis or pneumonia.

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 hyperreflexia, later hyporeflexia; convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis.

Respiratory system:

Respiratory depression, pulmonary oedema.

Cardiovascular system:

Tachycardia, hypotension and at times hypertension, conduction disturbance with widening of QRS complex; syncope in association with cardiac arrest.

Gastro-intestinal 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.

Management should initially be guided by the patient's clinical condition; 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. Delay in evacuating the stomach may result in delayed absorption, leading to relapse during recovery from intoxication. Supportive medical care in an intensive care unit with cardiac monitoring and careful correction of electrolyte imbalance.

Special recommendations:

Hypotension:

Administer dopamine or dobutamine i.v.

Disturbances of cardiac rhythm:

To be handled 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

Therapeutic class: Anti-epileptic, neurotropic and psychotropic agent; (ATC Code: N03 AX 1). Dibenzazepine derivative.

As an antiepileptic agent its spectrum of activity embraces: partial seizures (simple and complex) with and without secondary generalisation;

generalised tonic-clonic seizures, as well as combinations of these types of seizures.

The mechanism of action of carbamazepine, the active substance of Tegretol, has only been partially elucidated. Carbamazepine stabilises hyperexcited nerve membranes, inhibits repetitive neuronal discharges, and reduces synaptic propagation of excitatory impulses. It is conceivable that prevention of repetitive firing of sodium-dependent action potentials in depolarised neurons via use- and voltage-dependent blockade of sodium channels may be its main mechanism of action.

Whereas reduction of glutamate release and stabilisation of neuronal membranes may account for the antiepileptic effects, the depressant effect on dopamine and noradrenaline turnover could be responsible for the antimanic properties of carbamazepine.

5.2 Pharmacokinetic Properties

Absorption

Carbamazepine is almost completely absorbed but the rate of absorption from the tablets is slow and may vary amongst the various formulations and between patients. Peak concentrations of active substance in the plasma are attained within 24 hours of administration of single dose of Tegretol Retard Tablets.

The retard formulation shows about 15% lower bioavailability than standard preparations due mainly to the considerable reduction in peak plasma levels occasioned by controlled release of the same dosage of carbamazepine. Plasma concentrations show less fluctuation but auto-induction of carbamazepine occurs as with standard carbamazepine preparations.

The bioavailability of Tegretol in various oral formulations has been shown to lie between 85-100%.

Ingestion of food has no significant influence on the rate and extent of absorption, regardless of the dosage form of Tegretol.

Steady-state plasma concentrations of carbamazepine are attained within about 1-2 weeks, depending individually upon auto-induction by carbamazepine and hetero-induction by other enzyme-inducing drugs, as well as on pre-treatment status, dosage, and duration of treatment.

Different preparations of carbamazepine may vary in bioavailability; to avoid reduced effect or risk of breakthrough seizures or excessive side effects, it may be prudent to avoid changing the

formulation.

Distribution

Carbamazepine is bound to serum proteins to the extent of 70-80%. The concentration of unchanged substance in cerebrospinal fluid and saliva reflects the non-protein bound portion in plasma (20-30%). Concentrations in breast milk were found to be equivalent to 25-60% of the corresponding plasma levels.

Carbamazepine crosses the placental barrier.

Assuming complete absorption of carbamazepine, the apparent volume of distribution ranges from 0.8 to 1.9 L/kg.

Elimination

The elimination half-life of unchanged carbamazepine averages approx. 36 hours following a single oral dose, whereas after repeated administration it averages only 16-24 hours (auto-induction of the hepatic mono-oxygenase system), depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme-inducing drugs (e.g. phenytoin, phenobarbitone), half-life values averaging 9-10 hours have been found.

The mean elimination half-life of the 10, 11-epoxide metabolite in the plasma is about 6 hours following single oral doses of the epoxide itself.

After administration of a single oral dose of 400 mg carbamazepine, 72% is excreted in the urine and 28% in the faeces. In the urine, about 2% of the dose is recovered as unchanged drug and about 1% as the pharmacologically active 10, 11-epoxide metabolite. Carbamazepine is metabolised in the liver, where the epoxide pathway of biotransformation is the most important one, yielding the 10, 11-transdiol derivative and its glucuronide as the main metabolites.

Cytochrome P450 3A4 has been identified as the major isoform responsible for the formation of carbamazepine 10, 11-epoxide from carbamazepine. 9-Hydroxy-methyl-10-carbamoyl acridan is a minor metabolite related to this pathway. After a single oral dose of carbamazepine about 30% appears in the urine as end-products of the epoxide pathway.

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

Characteristics in patients

The steady-state plasma concentrations of

carbamazepine considered as "therapeutic range" vary considerably inter-individually; for the majority of patients a range between 4-12 mcg/ml corresponding to 17-50 mcmol/l has been reported. Concentrations of carbamazepine 10, 11-epoxide (pharmacologically active metabolite): about 30% of carbamazepine levels.

Owing to enhanced carbamazepine elimination, children may require higher doses of carbamazepine (in mg/kg) than adults to maintain therapeutic concentrations.

There is no indication of altered pharmacokinetics of carbamazepine in elderly patients as compared with young adults.

No data are available on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function.

5.3 Preclinical Safety Data

In rats treated with carbamazepine for two years, the incidence of tumours of the liver was found to be increased. 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

Each 200 mg and 400 mg tablet contains colloidal silicon dioxide, ethylcellulose pseudolatex, microcrystalline cellulose, ethyl acrylate/methyl methacrylate copolymer, magnesium stearate, croscarmellose sodium type A, talc, hydroxypropylmethylcellulose, glyceryl polyoxyethylene glycol stearate, red iron oxide (E.172), yellow iron oxide (E.172) and titanium dioxide (E.171).

6.2 Incompatibilities

None known

6.3 Shelf life

Three years

6.4 Special precautions for storage

Store below 25°C and protect from moisture.

6.5 Nature and contents of container

Tegretol Retard Tablets 200 mg and 400 mg come in PVC/PCTFE (PVC 190-270 micron; PCTFE 15-25 micron; aluminium foil 26-34 micron) or PCV/PE/PVdC (PVC 190-270 micron;

PE 20-40 micron; PVdC 32-59 micron; aluminium foil 26-34 micron) blister packs of 56 tablets.

6.6 Instructions for use/handling

None

7. Marketing Authorisation Holder

Novartis Pharmaceuticals UK Limited
Trading as Geigy Pharmaceuticals
Frimley Business Park
Frimley
Camberley
Surrey
GU16 7SR
England.

8. Marketing Authorisation Number

Tegretol Retard Tablets 200 mg: PL 00101/0457
Tegretol Retard Tablets 400 mg: PL 00101/0458

9. Date Of First Authorisation/ Renewal of Authorisation

4 July 1997/26 March 2001

10. Date of (Partial) Revision of the Text

26 March 2001