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Epival*

divalproex sodium

THERAPEUTIC CLASSIFICATION Anticonvulsant.

INDICATIONS AND CLINICAL USE Sole or adjunctive therapy in the treatment of simple or complex absence seizures, including petit mal; useful in primary generalized seizures with tonic-clonic manifestations. May also be used adjunctively in patients with multiple seizure types which include either absence or tonic-clonic seizures.

In accordance with the International Classification of Seizures, simple absence is defined as a very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds) accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICTIONS Should not be administered to patients with hepatic disease or significant dysfunction. Contraindicated in patients with known hypersensitivity to the drug.

WARNINGS Hepatic failures resulting in fatalities have occurred in patients receiving valproic acid and its derivatives. These incidences usually have occurred during the first six months of treatment with valproic acid. A recent survey study of valproate use in the United States in nearly 400,000 patients between 1978 and 1984, has shown that children under two years of age who received the drug as part of multiple anticonvulsant therapy were at greatest risk (nearly 20-fold increase) of developing fatal hepatotoxicity. These patients typically had other medical conditions such as congenital metabolic disorders, mental retardation or organic brain disease, in addition to severe seizure disorders. The risk in this age group decreased considerably in patients receiving valproate as monotherapy. Similarly, patients aged 3 to 10 years were at somewhat greater risk if they received multiple anticonvulsants than those who received only valproate. Risk generally declined with increasing age. No deaths have been reported in patients over 10 years of age who received valproate alone.

If Epival is to be used in children two years old or younger, it should be used with extreme caution and as a sole agent. The benefits of seizure control should be weighed against the risk.

Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, anorexia, and vomiting. Patients and parents should be instructed to report such symptoms. Because of the non-specific nature of some of the early signs, hepatotoxicity should be suspected in patients who become unwell, other than through obvious cause, while taking Epival (divalproex sodium).

Liver function tests should be performed prior to therapy and at frequent intervals thereafter especially during the first 6 months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed in patients with a prior history of hepatic disease. Patients with various unusual congenital disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk.

In high-risk patients, it might also be useful to monitor serum fibrinogen and albumin for decrease in concentrations and serum ammonia for increases in concentration. If changes occur, the drug should be discontinued. Dosage should be titrated to and maintained at the lowest dose consistent with optimal seizure control.

The drug should be discontinued immmediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of the drug. The frequency of adverse effects, particularly elevated liver enzymes, may increase with increasing dose. Therefore, the benefit gained by improved seizure control by increasing the dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher dosages.

Use in Pregnancy: According to recent reports in the medical literature, valproic acid may produce teratogenicity in the offspring of women receiving the drug during pregnancy. The incidence of neural tube defects in the fetus may be increased in mothers receiving valproic acid during the first trimester of pregnancy. Based upon a single report, it was estimated that the risk of valproic acid exposed women having children with spina bifida is approximately 1.2%. This risk is similar to that which applies to non-epileptic women who have had children with neural tube defects (anencephaly and spina bifida). Animal studies have demonstrated valproic acid induced teratogenicity, and studies in human females have demonstrated placental transfer of the drug.

Multiple reports in the clinical literature indicate an association between the use of anti-epileptic drugs and an increased incidence of birth defects in children born to epileptic women taking such medication during pregnancy. The incidence of congenital malformations in the general population is regarded to be approximately 2%; in children of treated epileptic women, this incidence may be increased 2-to 3-fold. The increase is largely due to specific defects, e.g. congenital malformations of the heart, cleft lip or palate, and neural tube defects. Nevertheless, the great majority of mothers receiving anti-epileptic medications deliver normal infants.

Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these drugs are also the most commonly prescribed anti-epileptics. Some reports indicate a possible similar association with the use of other anti-epileptic drugs, including trimethadione, paramethadione, and valproic acid. However, the possibility also exists that other factors, e.g. genetic predisposition or the epileptic condition itself may contribute to or may be mainly responsible for the higher incidence of birth defects.

Anti-epileptic drugs should not be discontinued in patients to whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risks to both the mother and the unborn child. With regard to drugs given for minor seizures, the risks of discontinuing medication prior to or during pregnancy should be weighed against the risk of congenital defects in the particular case and with the particular family history.

Epileptic women of child-bearing age should be encouraged to seek the counsel of their physician and should report the onset of pregnancy promptly to him. Where the necessity for continued use of anti-epileptic medication is in doubt, appropriate consultation is indicated.

Nursing Mothers: Valproic acid is excreted in breast milk. Concentrations in breast milk have been reported to be 1 to 10% of serum concentrations. As a general rule, nursing should not be undertaken while a patient is receiving Epival (divalproex sodium).

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses of valproic acid greater than 200 mg/kg/day in rats and 90 mg/kg/day in dogs. Segment 1 fertility studies in rats have shown that doses up to 350 mg/kg/day for 60 days have no effect on fertility. The effect of divalproex sodium and valproic acid on the development of the testes and on sperm production and fertility in humans is unknown.

LONG-TERM TOXICITY STUDIES IN RATS AND MICE INDICATED A POTENTIAL CARCINOGENIC RISK.

PRECAUTIONS Hepatic dysfunction: See CONTRAINDICATIONS and WARNINGS.

General: Because of reports of thrombocytopenia and inhibition of platelet aggregation, platelet counts and bleeding-time determination are recommended before instituting therapy and at periodic intervals. It is recommended that patients be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of dosage or withdrawal of therapy pending investigation.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests; if elevation occurs the drug should be discontinued.

Because Epival (divalproex sodium) may interact with other anti-epileptic drugs, periodic serum level determinations of concurrently administered anti-epileptics are recommended during the early part of therapy. (See DRUG INTERACTIONS.) There have been reports of breakthrough seizures occurring with the combination of valproic acid and phenytoin.

Epival (divalproex sodium) is partially eliminated in the urine as a ketone-containing metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproic acid; the clinical significance of these is unknown.

Driving and Hazardous Occupations: May produce CNS depression, especially when combined with another CNS depressant, such as alcohol. Therefore, patients should be advised not to engage in hazardous occupations, such as driving a car or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: May potentiate the CNS depressant action of alcohol.

There is evidence that valproic acid may cause an increase in serum phenobarbital levels, by impairment of non-renal clearance. This phenomenon can result in severe CNS depression. The combination of valproic acid and phenobarbital has also been reported to produce CNS depression without significant elevations of barbiturate or valproic acid serum levels. Patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate drug levels should be obtained, if possible, and the barbiturate dosage decreased, if indicated.

Primidone is metabolized into a barbiturate, and therefore, may also be involved in a similar or identical interaction.

There is conflicting evidence regarding the interaction of valproic acid with phenytoin (See PRECAUTIONS – General). It is not known if there is a change in unbound (free) phenytoin serum levels. The dosage of phenytoin should be adjusted as required by the clinical situation.

The concomitant use of valproic acid and clonazepam may produce absence status.

ADVERSE REACTIONS The most commonly reported adverse reactions are nausea, vomiting and indigestion. Since valproic acid has usually been used with other anti-epileptics, it is not possible in most cases to determine whether the adverse reactions mentioned in this section are due to valproic acid alone or to the combination of drugs.

Gastrointestinal: Nausea, vomiting and indigestion are the most commonly reported side effects at the initiation of therapy. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have also been reported. Anorexia with some weight loss and increased appetite with some weight gain have also been seen.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients on combination therapy. Sedation usually disappears upon reduction of other anti-epileptic medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before the eyes", tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been reported in patients receiving valproic acid alone or in conjunction with phenobarbital.

Dermatologic: Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Endocrine: There have been reports of irregular menses and secondary amenorrhea in patients receiving valproic acid.

Abnormal thyroid function tests have been reported (See PRECAUTIONS).

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioural deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematopoietic: Thrombocytopenia has been reported. Valproic acid inhibits the second phase of platelet aggregation (See PRECAUTIONS). This may be reflected in altered bleeding time. Bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported. Anemia and bone marrow suppression have been reported.

Hepatic: Minor elevations of transaminases (eg. SGOT and SGPT) and LDH are frequent and appear to be dose related. Occasionally, laboratory tests also show increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (See WARNINGS).

Metabolic: Hyperammonemia (See PRECAUTIONS). Hyperglycinemia has been reported and associated with a fatal outcome in a patient with pre-existing non-ketotic hyperglycinemia.

Pancreatic: There have been reports of acute pancreatitis occurring in association with therapy with valproic acid.

Other: Edema of the extremities has been reported.

DOSAGE AND ADMINISTRATION The recommended initial dosage is 15/mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases.

The maximal recommended dosage is 60 mg/kg/day. When the total daily dose exceeds 125 mg, it should be given in a divided regimen (See Table).

The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by improving seizure control must be weighed against the increased incidence of adverse effects.

As the dosage is raised, blood levels of phenobarbital or phenytoin may be affected (See PRECAUTIONS).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by a progressive increase of the dose from an initial low level. **The tablets should be swallowed without chewing.**

AVAILABILITY Epival (divalproex sodium) enteric-coated tablets are available as salmon-pink coloured tablets of 125 mg; peach-coloured tablets of 250 mg; lavender-coloured tablets of 500 mg. Supplied in bottles of 100 tablets.

Table of Initial Doses by Weight (based on 15 mg/kg/day)

Weight		Total daily dose (mg)	Dosage (mg) Equivalent to valproic acid		
kg	lb		Dose 1	Dose 2	Dose 3
10-24.9	22-54.9	250	125	0	125
25-39.9	55-87.9	500	250	0	250
40-59.9	88-131.9	750	250	250	250
60-74.9	132-164.9	1,000	250	250	500
75-89.9	165-197.9	1,250	500	250	500

Product monograph available on request.

REFERENCES:

1. Wilder BJ. Epilepsia 1987;28(suppl. 2):S1-S7.
2. Chadwick DW. Epilepsia 1987;28(suppl. 2):S12-S17.
3. Callaghan N et al. Dev Med and Child Neurol 1982;24: 830-836.
4. Callaghan N, Kenry RA, O'Neill B et al. J Neurol Neurosurg Psychiatry 1985;48:639-644.
5. Dreifuss FE, Langer DH. Am J Med 1988;84(suppl. 1A): 34-41.
6. Study F80-118, Abbott Laboratories, Limited.
7. Vining EPG. Epilepsia 1987;28(suppl. 2):S18-S22.
8. A Textbook for the Clinical Application of Therapeutic Drug Monitoring. Section 4: Antiepileptic drugs, W Taylor, D Caviness, eds. Abbott Diagnostics, Abbott Park, Ill, 1987.
9. Drug Interaction Facts. JB Lippincott, St. Louis, MO, 1990.

PAAB MEMBER

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PARLODEL®
(bromocriptine mesylate)

Because quality of life is the issue

ACTIONS Parlodel (bromocriptine mesylate) is a dopaminomimetic ergot derivate with D_2 type dopamine receptor agonist activity, and has also D_1 dopamine receptor antagonist properties. The dopaminomimetic activity of bromocriptine in the striatum is considered responsible for the clinical benefits seen in selected patients with Parkinson's disease, when low doses of the drug are gradually added to levodopa therapy in patients on long-term treatment who develop late side effects of levodopa or no longer respond to the medication. Excessive dopaminomimetic drive may, however, provoke psychotic and other adverse reactions.

The extreme variability in G.I. tract absorption and the extensive and individually variable first-pass metabolism are responsible for the broad variability in plasma concentrations of bromocriptine and, in part, for the variability in dose response.

INDICATIONS* Parkinson's Disease: Parlodel (bromocriptine mesylate) has been found to be clinically useful as an adjunct to levodopa (usually with a decarboxylase inhibitor), in the symptomatic management of selected patients with Parkinson's disease who experience prominent dyskinesia or wearing off reactions on long-term levodopa therapy.

Patients on long-term treatment who are beginning to deteriorate on levodopa therapy may be controlled by reducing the dose of levodopa and adjusting the frequency and schedule of drug administration. Patients maintained on optimal dosages of levodopa who still experience prominent dyskinesia and/or end-of-dose failure may benefit from the concomitant use of Parlodel, by decreasing the occurrence and/or severity of these manifestations. Since rapid escalation of bromocriptine doses causes severe adverse reactions, it is recommended to combine a slow increase of Parlodel, usually with a concomitant, gradual and limited reduction of levodopa dosage. Continued efficacy of bromocriptine for more than two years has not been established and there is some evidence that its efficacy tends to wane. Evidence available indicates that there is no consistent benefit from bromocriptine in patients who have not responded previously to levodopa, and studies have shown significantly more adverse reactions in bromocriptine-treated patients than in patients treated with levodopa. Parlodel is not recommended in the treatment of newly diagnosed patients or as the sole medication in Parkinson's disease.

CONTRAINDICATIONS Other than sensitivity to ergot alkaloids, no absolute contraindications to treatment with Parlodel (bromocriptine mesylate) are known. For procedure during pregnancy see "Use in Pregnancy" under Precautions.

WARNINGS Long-term treatment (6-36 months) with Parlodel in doses of 20 to 100 mg/day has been associated with pulmonary infiltrates, pleural effusion and thickening of the pleura in a few patients. Where Parlodel was discontinued, these changes slowly reverted to normal.

PRECAUTIONS Parlodel (bromocriptine mesylate) may cause hypotension, primarily postural; periodic monitoring of the blood pressure, particularly during the first days of therapy, is advisable. In some patients dizziness (vertigo) may occur with Parlodel; patients should therefore be cautioned against activities requiring rapid and precise responses, such as driving an automobile or operating dangerous machinery, until their response has been determined.

Care should be exercised when administering Parlodel concomitantly with phenothiazines or antihypertensive agents. Due to drug interaction at the receptor site, dosage should be adjusted accordingly.

Alcohol should be avoided during treatment with Parlodel. In some patients, the concomitant use of Parlodel and alcohol has given rise to alcohol intolerance and an increase in the severity and incidence of Parlodel's possible adverse reactions.

Parlodel should always be taken with food. In cases where severe adverse effects, such as nausea, vomiting, vertigo or headaches are severe or persisting, the therapeutic dosage of Parlodel should be reduced to half of one tablet daily (1.25 mg) and increased gradually to that recommended. The dopamine antagonist domperidone may be useful in the control of severe gastrointestinal side effects in parkinsonian patients receiving Parlodel (see Drug Interactions).

As with all medication, Parlodel should be kept safely out of the reach of children.

Use in Pregnancy: If the patient wishes to become pregnant, Parlodel (bromocriptine mesylate) should be stopped as soon as possible after conception is suspected. In this event immunological confirmation should be done immediately. When pregnancy is confirmed, Parlodel, like all other drugs, should be discontinued unless, in the opinion of the treating physician, the possible benefit to the patient outweighs the potential risk to the fetus.

In human studies with Parlodel (reviewed by Turkalj, I.), there were 1410 reported pregnancies, which yielded 1236 live and 5 stillborn infants from women who took Parlodel (bromocriptine mesylate) during early pregnancy. Among the 1241 infants, 43 cases (31 minor and 12 major) of congenital anomalies were reported. The incidence (3.46%) and type of congenital malformations and the incidence of spontaneous abortions (11.13%) in this group of pregnancies does not exceed that generally reported for such occurrences in the population at large.

Use in Parkinson's Disease: Use of Parlodel (bromocriptine mesylate), particularly in high doses, may be associated with mental confusion and mental disturbances. Since patients with Parkinson's disease may manifest varying degrees of dementia, caution should be exercised when treating such patients with Parlodel.

Parlodel administered alone or concomitantly with levodopa may cause visual or auditory hallucinations. These usually resolve with dosage reduction, but discontinuation of Parlodel may be required in some cases. Rarely, after high doses, hallucinations have persisted for several weeks following discontinuation of Parlodel. Caution should be exercised when administering Parlodel to patients with a history of myocardial infarction, particularly if they have a residual atrial, nodal or ventricular arrhythmia.

Symptomatic hypotension can occur and, therefore, caution should be exercised when administering Parlodel, particularly in patients receiving antihypertensive medication. Periodic evaluation of hepatic, hematopoietic, cardiovascular and renal function is recommended.

Drug Interactions: The concomitant use of erythromycin may increase bromocriptine plasma levels.

Domperidone, a dopamine antagonist, may cause increases in serum prolactin. In so doing, domperidone may antagonise the therapeutically relevant prolactin lowering effect of Parlodel. It is possible that the antitumorigenic effect of Parlodel in patients with prolactinomas may be partially blocked by domperidone administration.

ADVERSE REACTIONS The most frequently observed adverse reactions are nausea, vomiting, headache and gastrointestinal side effects such as abdominal pain, diarrhea and constipation. All these effects may be minimized or even prevented by giving small initial doses of bromocriptine and by taking it with food.

Postural hypotension which can, on rare occasions, lead to fainting and "shock-like" syndromes has been reported in sensitive patients. This is most likely to occur during the first few days of Parlodel treatment.

When bromocriptine is added to levodopa therapy, the incidence of adverse reactions may increase. The most common newly appearing adverse reactions in combination therapy were: nausea, abnormal involuntary movements, hallucinations, confusion, "on-off" phenomenon, dizziness, drowsiness, faintness, fainting, vomiting, asthenia, abdominal discomfort, visual disturbance, ataxia, insomnia, depression, hypotension, shortness of breath, constipation and vertigo.

Less common adverse reactions include anorexia, anxiety, blepharospasm, dry mouth, dysphagia, edema of the feet and ankles, erythromelalgia, epileptiform seizures, fatigue, headache, lethargia, mottling of skin, nasal stuffiness, nervousness, nightmares, parethesia, skin rash, urinary frequency, urinary incontinence, urinary retention and rarely signs or symptoms of ergotism such as tingling of fingers, cold feet, numbness, muscle cramps of feet and legs or exacerbation of Raynaud's syndrome.

Abnormalities in laboratory tests may include elevation of blood urea nitrogen, SGOT, SGPT, GGPT, CPK, alkaline phosphatase and uric acid, which are usually transient and not of clinical significance.

The occurrence of adverse reactions may be lessened by temporarily reducing dosage to one-half tablet two or three times daily.

SYMPTOMS AND TREATMENT OF OVERDOSE There have been several reports of acute overdosage with Parlodel (bromocriptine mesylate) in children and adults. No life threatening reactions have occurred. Symptoms reported included nausea, vomiting, dizziness, drowsiness, hypotension, sweating and hallucinations. Management is largely symptomatic; the cardiovascular system should be monitored. Metoclopramide can be used to antagonize the emesis and hallucinations in patients who have taken high doses.

DOSAGE AND ADMINISTRATION Parlodel (bromocriptine mesylate) should always be taken with food.

Although Parlodel (bromocriptine mesylate) has been found clinically useful in decreasing the severity and frequency of "on-off" fluctuations of late levodopa therapy, the decision to use bromocriptine as adjunctive treatment and the selection of dosage must be individualized in each case. A low dose is recommended. The initial dose of Parlodel is one half of a 2.5 mg tablet (1.25 mg) at bedtime with food to establish initial tolerance. Thereafter, the recommended dosage is 2.5 mg daily in two divided doses, with meals, (half a 2.5 mg tablet twice daily). The dosage may be increased very gradually, if necessary, by adding an additional 2.5 mg per day, once every 2 to 4 weeks, to be taken always in divided doses with meals. Increments should usually not exceed 2.5 mg. Clinical assessments are recommended at two week intervals or less during dosage titration, to ensure that the lowest effective dosage is not exceeded. The usual dosage range is from a few milligrams to 40 mg daily in two or three divided doses with meals. The median dose varies with the experience of individual investigators, but can be around 10 mg daily or higher. During initial titration it is recommended that the dosage of levodopa should be maintained, if possible. Subsequently, it might be desirable to combine a slow increase of bromocriptine with a concomitant, limited and gradual reduction of levodopa.

AVAILABILITY

TABLETS each containing 2.5 mg bromocriptine, as mesylate, available in bottles of 100.
CAPSULES each containing 5 mg bromocriptine, as mesylate, available in bottles of 100.

**For information on other approved indications, please consult the Parlodel product monograph, available to physicians and pharmacists on request.*

SANDOZ

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Brief Prescribing Information

P Tegretol® (carbamazepine)

TEGRETOL® 200 mg
TEGRETOL® CHEWTABS™ 100 mg and 200 mg
TEGRETOL® CR 200 mg and 400 mg

Action

TEGRETOL (carbamazepine) has anticonvulsant properties which have been found useful in the treatment of psychomotor epilepsy and, as an adjunct in the treatment of partial epilepsies, when administered in conjunction with other anticonvulsant drugs to prevent the possible generalization of the epileptic discharge. A mild psychotropic effect has been observed in some patients, which seems related to the effect of the carbamazepine in psychomotor or temporal lobe epilepsy.

TEGRETOL relieves or diminishes the pain associated with trigeminal neuralgia often within 24 to 48 hours.

Like other tricyclic compounds, TEGRETOL has a moderate anticholinergic action which is responsible for some of its side effects. A tolerance may develop to the action of TEGRETOL after a few months of treatment and should be watched for.

TEGRETOL may suppress ventricular automaticity due to its membrane-depressant effect similar to that of quinidine and procainamide, associated with suppression of phase 4 depolarization of the heart muscle fibre. A number of investigators have reported a deterioration of EEG abnormalities with regard to focal alterations and a higher incidence of records with nil beta activity, during carbamazepine-combined treatment.

The absorption of carbamazepine in man is relatively slow. When taken in a single oral dose, TEGRETOL (carbamazepine tablets) and TEGRETOL CHEWTABS (carbamazepine chewable tablets) yield peak plasma concentrations of unchanged carbamazepine within 4-24 hours. With respect to the quantity of carbamazepine absorbed, there is no clinically relevant difference between the various dosage forms. When TEGRETOL CR (carbamazepine controlled release tablets) are administered repeatedly, they yield a lower average maximal concentration of carbamazepine in the plasma, without a reduction in the average minimal concentration. This tends to result in a lower incidence of intermittent concentration-dependent adverse drug reactions. It also ensures that the plasma concentrations remain largely stable throughout the day, thereby making it possible to manage with a twice-daily dosage.

Carbamazepine becomes bound to serum proteins to the extent of 70-80%. The concentration of unchanged substance in the saliva reflects the non-protein-bound portion present in the serum (20-30%).

The elimination half-life of unchanged carbamazepine in the plasma averages approximately 36 hours following a single oral dose, whereas after repeated administration, which leads to autoinduction of hepatic enzymes, it averages only 16-24 hours, depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme-inducing anti-epileptic agents, half-life values averaging 9-10 hours have been found.

Only 2-3% of the dose, whether given singly or repeatedly, is excreted in the urine in unchanged form. The primary metabolite is the pharmacologically active 10, 11-epoxide.

In man, the main urinary metabolite of carbamazepine is the trans-diol derivative originating from the 10, 11-epoxide; a small portion of the epoxide is converted into 9-hydroxymethyl-10-carbamoyl-acridan. Other important biotransformation products are various monohydroxylated compounds, as well as the N-glucuronide of carbamazepine.

The therapeutic range for the steady-state plasma concentration of carbamazepine generally lies between 4-10 mcg/ml.

Indications and Clinical Use

A. Trigeminal Neuralgia:

TEGRETOL (carbamazepine) is indicated for the symptomatic relief of pain of trigeminal neuralgia only during periods of exacerbation of true or primary trigeminal neuralgia (tic douloureux). It should not be used preventively during periods of remission. In some patients, TEGRETOL has relieved glossopharyngeal neuralgia. For patients who fail to respond to TEGRETOL, or who are sensitive to the drug, recourse to other accepted measures must be considered.

TEGRETOL is not a simple analgesic and should not be used to relieve trivial facial pains or headaches.

B. TEGRETOL has been found useful in:

1. the management of psychomotor (temporal lobe) epilepsy and,
2. as an adjunct, in some patients with secondary or partial epilepsy with complex symptomatology or secondarily generalized seizures, when administered in combination with other antiepileptic medication.
3. as an alternative medication in patients with generalized tonic-clonic seizures who are experiencing marked side effects or fail to respond to other anticonvulsant drugs.

TEGRETOL is not effective in controlling petit mal, minor motor, myoclonic and predominantly unilateral seizures, and does not prevent the generalization of epileptic discharge. Moreover, recent information suggests that exacerbation of seizures may occasionally occur in patients with atypical absences.

Contraindications

TEGRETOL (carbamazepine) should not be administered to patients with a history of hepatic disease or serious blood disorder.

TEGRETOL should not be administered immediately before, in conjunction with, or immediately after a monoamine oxidase inhibitor. When it seems desirable to administer TEGRETOL to a patient who has been receiving an MAO inhibitor, there should be as long a drug-free interval as the clinical condition allows, but in no case should this be less than 14 days. Then the dosage of TEGRETOL should be low initially, and increased very gradually.

TEGRETOL should not be administered to patients presenting atrioventricular heart block. *(See Sections on Action and Precautions).*

Safe use in pregnancy has not been established. Therefore, TEGRETOL should not be administered during the first 3 months of pregnancy. TEGRETOL should not be given to women of child-bearing potential unless, in the opinion of the physician, the expected benefits to the patient outweigh the possible risk to the fetus *(See Reproductive Studies).* Because of demonstrated toxicity in nursing animals TEGRETOL should not be administered to nursing mothers.

TEGRETOL should not be administered to patients with known hypersensitivity to carbamazepine or to any of the tricyclic compounds, such as amitriptyline, trimipramine, imipramine, or their analogues or metabolites, because of the similarity in chemical structure.

Warnings

Although reported infrequently, serious adverse effects have been observed during the use of TEGRETOL (carbamazepine). Agranulocytosis and aplastic anemia have occurred in a few instances with a fatal outcome. Leucopenia, thrombocytopenia, hepatocellular and cholestatic jaundice, and hepatitis have also been reported. It is, therefore, important that TEGRETOL should be used carefully and close clinical and frequent laboratory supervision should be maintained throughout treatment in order to detect as early as possible signs and symptoms of a possible blood dyscrasia.

Long-term toxicity studies in rats indicated a potential carcinogenic risk *(See Section on "Toxicology").* Therefore, the possible risk of drug use must be weighed against the potential benefits before prescribing carbamazepine to individual patients.

Precautions

Monitoring of Hematological and Other Adverse Reactions:

Complete blood studies, including platelet counts, and evaluation of hepatic and renal function and urinalysis should be carried out before treatment is instituted. Careful clinical and laboratory supervision should be maintained throughout treatment, including frequent performance of complete blood counts, in order to detect any early signs or symptoms of blood dyscrasia. Should any signs or symptoms or abnormal laboratory findings suggestive of blood dyscrasia or liver disorder occur, TEGRETOL (carbamazepine) should be immediately discontinued until the case is carefully reassessed.

Non-progressive or fluctuating asymptomatic leucopenia, which is encountered, does not generally call for the withdrawal of TEGRETOL. However, treatment with TEGRETOL should be discontinued if the patient develops leucopenia which is progressive or accompanied by clinical manifestations, e.g. fever or sore throat.

Urinary Retention and Increased Intraocular Pressure:

Because of its anticholinergic action, TEGRETOL should be given cautiously, if at all, to patients with increased intraocular pressure or urinary retention. Such patients should be followed closely while taking the drug.

Occurrence of Behavioural Disorders:

Because it is closely related to the other tricyclic drugs, there is some possibility that TEGRETOL might activate a latent psychosis, or, in elderly patients, produce agitation or confusion, especially when combined with other drugs. Caution should also be exercised in alcoholics.

Use in Patients with Cardiovascular Disorders:

TEGRETOL should be used cautiously in patients with a history of coronary artery disease, organic heart disease, or congestive failure. If a defective conductive system is suspected, an ECG should be performed before administering TEGRETOL, in order to exclude patients with atrioventricular block.

Driving and Operating Hazardous Machinery:

Because dizziness and drowsiness are possible side effects of TEGRETOL, patients should be warned about the possible hazards of operating machinery or driving automobiles.

Drug Interactions:

Induction of hepatic enzymes in response to TEGRETOL may have the effect of diminishing the activity of certain drugs that are metabolized in the liver. This should be considered when administering TEGRETOL concomitantly with other anti-epileptic agents and drugs such as theophylline.

Concomitant administration of TEGRETOL with verapamil, diltiazem, erythromycin, troleandomycin, cimetidine, propoxyphene or isoniazid, has been reported to result in elevated plasma levels of carbamazepine. Since an increase in the blood levels of carbamazepine may result in unwanted effects (e.g. dizziness, headache, ataxia, diplopia and nystagmus may occur), the dosage of carbamazepine should be adapted accordingly and blood levels monitored.

The concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

In patients receiving oral anticoagulant medication, the dosage of the anticoagulant should be readapted to clinical requirements whenever treatment with TEGRETOL is initiated or withdrawn.

TEGRETOL, like other anticonvulsants, may adversely affect the reliability of oral contraceptives. Patients should accordingly be advised to use some alternative, non-hormonal method of contraception.

TEGRETOL, like other psycho-active drugs, may reduce the patient's alcohol tolerance; it is therefore advisable to abstain from alcohol consumption during treatment.

TEGRETOL should not be administered in conjunction with an MAO inhibitor. *(See Section on Contraindications).*

Adverse Reactions

The reactions which have been most frequently reported with TEGRETOL (carbamazepine) are drowsiness, unsteadiness on the feet, vertigo, dizziness, gastrointestinal disturbances, and nausea. These reactions usually occur only during the initial phase of therapy. They have rarely necessitated discontinuing TEGRETOL therapy, and can be minimized by initiating treatment at a low dosage.

The more serious adverse reactions observed are the hematologic, hepatic, cardiovascular and dermatologic reactions, which require discontinuation of therapy. If treatment with TEGRETOL has to be withdrawn abruptly, the change-over to another anti-epileptic drug should be effected under cover of diazepam.

The following adverse reactions have been reported:

Hematologic – Transitory leucopenia, eosinophilia, hyponatremia, leucocytosis, thrombocytopenic purpura, agranulocytosis, macrocytic anemia and aplastic anemia. In a few instances, deaths have occurred.

Hepatic – During the long-term administration of TEGRETOL, abnormalities in liver function tests, cholestatic and hepatocellular jaundice, and hepatitis have been reported.

Dermatologic – The following reactions occurred during treatment with TEGRETOL: skin sensitivity reactions and rashes, erythematous rashes, pruritic eruptions, urticaria, photosensitivity, pigmentary changes, neurodermatitis and in rare cases Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, alopecia, diaphoresis, erythema multiforme, erythema nodosum, and aggravation of disseminated lupus erythematosus.

Neurologic – The reactions reported as occurring during treatment with TEGRETOL include vertigo, somnolence, ataxia, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia and oculomotor disturbances, speech disturbances, abnormal involuntary movements and increase in motor seizures. In addition, peripheral neuritis and paresthesia, depression with agitation, talkativeness, nystagmus, hyperacusis, and tinnitus have been reported but only very rarely. There have been some reports of paralysis and other symptoms of cerebral arterial insufficiency but no conclusive relationship to the administration of TEGRETOL could be established.

Cardiovascular – Thromboembolism, recurrence of thrombophlebitis in patients with a prior history of thrombophlebitis, primary thrombophlebitis, congestive heart failure, aggravation of hypertension, Stokes-Adams in patients with AV block, hypotension, syncope and collapse, edema, aggravation of coronary artery disease. Some of these complications (including myocardial infarction and arrhythmia) have been associated with other tricyclic compounds.

Genitourinary – Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Elevation of BUN, albuminuria and glycosuria also have been observed.

Respiratory – Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Gastrointestinal – Disturbances associated with TEGRETOL therapy have included nausea, vomiting, gastric or abdominal discomfort, diarrhea or constipation, anorexia and dryness of the mouth and throat, glossitis and stomatitis.

Ophthalmic – There is no conclusive evidence that TEGRETOL produces pathological changes in the cornea, lens or retina. However, it should be recognized that many phenothiazines and related drugs have been shown to cause eye changes. By analogy, periodic eye examinations, including slit-lamp fundoscopy and tonometry, are recommended.

Other reactions reported during treatment with TEGRETOL include fever and chills, aching joints and muscles, leg cramps, conjunctivitis, and adenopathy or lymphadenopathy.

Symptoms and Treatment of Overdosage

Symptoms of Overdosage:

The symptoms of overdosage include dizziness, ataxia, drowsiness, stupor, nausea, vomiting, restlessness, agitation, disorientation; tremor, involuntary movements, opisthotonos, abnormal reflexes (slowed or hyperactive); mydriasis, nystagmus; flushing, cyanosis, and urinary retention. Hypotension or hypertension may develop. Coma may ensue. EEG and ECG changes may occur. The laboratory findings in isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria.

Treatment of Overdosage:

There is no known specific antidote to TEGRETOL (carbamazepine). Experience with accidental TEGRETOL overdosage is limited. Since TEGRETOL is chemically related to the tricyclic antidepressants, reference to treatment of TOFRANIL (imipramine) overdosage is relevant.

It is recommended that emesis be induced, and that gastric lavage be performed. Vital signs should be watched and symptomatic treatment should be administered as required. Hyperirritability may be controlled by the administration of parenteral diazepam or barbiturates. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient, either in overdosage or in recent therapy (within two weeks).

Barbiturates may also induce respiratory depression, particularly in children. It is therefore advisable to have equipment available for artificial ventilation and resuscitation when barbiturates are employed. Paraldehyde may be used to counteract muscular hypertonus without producing respiratory depression.

Shock (circulatory collapse) should be treated with supportive measures, including intravenous fluids, oxygen, and corticosteroids.

It is recommended that the electrocardiogram be monitored, particularly in children, to detect any cardiac arrhythmias or conduction defects.

Dosage and Administration

Use in Epilepsy (See Indications):

A low initial daily dosage of TEGRETOL (carbamazepine) with a gradual increase in dosage is advised. Dosage should be adjusted to the needs of the individual patient.

TEGRETOL tablets and CHEWTABS should be taken in 2 to 4 divided doses daily, with meals whenever possible.

The controlled release characteristics of TEGRETOL CR reduce the daily fluctuations of plasma carbamazepine. TEGRETOL CR tablets (either whole or, if so prescribed, only half a tablet) should be swallowed unchewed with a little liquid during or after a meal. These controlled release tablets should be prescribed as a twice-daily dosage. If necessary, three divided doses may be prescribed.

Adults and Children Over 12 Years of Age:

Initially, 100 to 200 mg once or twice a day depending on the severity of the case and previous therapeutic history. The initial dosage is progressively increased, in divided doses, until the best response is obtained. The usual optimal dosage is 800 to 1200 mg daily. In rare instances some adult patients have received 1600 mg. As soon as disappearance of seizures has been obtained and maintained, dosage should be reduced very gradually until a minimum effective dose is reached.

Children 6-12 Years of Age:

Initially, 100 mg in divided doses on the first day. Increase gradually by adding 100 mg per day until the best response is obtained. Dosage should generally not exceed 1000 mg daily. As soon as disappearance of seizures has been obtained and maintained, dosage should be reduced very gradually until a minimum effective dose is reached.

Use in Trigeminal Neuralgia:

The initial daily dosage should be small; 200 mg taken in 2 doses of 100 mg each is recommended. The total daily dosage can be increased by 200 mg/day until relief of pain is obtained. This is usually achieved at dosages between 200 and 800 mg daily, but occasionally up to 1200 mg/day may be necessary. As soon as relief of pain has been obtained and maintained, progressive reduction in dosage should be attempted until a minimal effective dosage is reached. Because trigeminal neuralgia is characterized by periods of remission, attempts should be made to reduce or discontinue the use of TEGRETOL at intervals of not more than 3 months, depending upon the individual clinical course.

Prophylactic use of the drug in trigeminal neuralgia is not recommended.

Availability

TEGRETOL Tablets 200 mg: Each white, round, flat, bevelled-edge double-scored tablet engraved GEIGY on one side contains 200 mg carbamazepine. Available in bottles of 100 and 500 tablets.

TEGRETOL CHEWTABS 100 mg: Pale pink, round, flat, bevelled-edge tablets with distinct red spots. GEIGY engraved on one side and MR on the other. Fully bisected between the M and R. Each chewable tablet contains 100 mg carbamazepine. Available in bottles of 100 CHEWTABS.

TEGRETOL CHEWTABS 200 mg: Pale pink, oval biconvex tablets with distinct red spots. GEIGY engraved on one side and PU engraved on the other. Fully bisected between the P and U. Each chewable tablet contains 200 mg carbamazepine. Available in bottles of 100 CHEWTABS.

TEGRETOL CR 200 mg: Beige-orange, capsule-shaped, slightly biconvex tablet, engraved CG/CG on one side and HC/HC on the other. Fully bisected on both sides. Each controlled release tablet contains 200 mg carbamazepine. Available in bottles of 100 tablets.

TEGRETOL CR 400 mg: Brownish-orange, capsule-shaped, slightly biconvex tablet, engraved CG/CG on one side and ENE/ENE on the other. Fully bisected on both sides. Each controlled release tablet contains 400 mg carbamazepine. Available in bottles of 100 tablets.

Protect from heat and humidity.

Product Monograph available on request.

References:

1. Data on File – CIBA-GEIGY Canada Ltd.
2. Arvidsson J. Eeg-Olofsson O. The diurnal variation of carbamazepine and carbamazepine-10, 11-Epoxide in plasma and saliva in children with epilepsy using convenient and slow release (CR) formulation of Tegretol. Acta Neurol Scand 1981; Suppl 88:64;1-202.

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December, 1987

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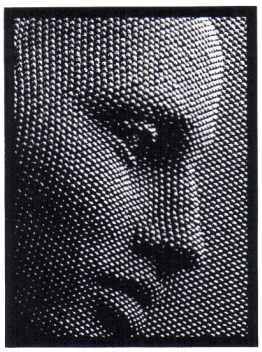

Prescribing Information

ACTION AND CLINICAL PHARMACOLOGY

SIBELIUM* (flunarizine hydrochloride) prevents the deleterious effects of cellular calcium overload by reducing excessive transmembrane fluxes of calcium. Flunarizine does not interfere with normal cellular calcium homeostasis. Flunarizine also has antihistaminic properties.

The effects of flunarizine in the prophylaxis of migraine are most pronounced with regards to the reduction of the frequency of attacks. The severity of migraine attacks improves to a lesser extent, while little or no effect is seen on the duration of migraine episodes.

The pharmacokinetic parameters of orally administered flunarizine are summarized in Table 1.

Flunarizine is well absorbed; peak plasma levels are attained 2 to 4 hours after oral administration in healthy volunteers. Plasma concentrations increase gradually during chronic administration of 10 mg daily, reaching a steady state level after 5 to 6 weeks of drug administration. Steady state plasma levels remain constant during prolonged treatment although there is substantial interindividual variation; plasma levels range between 39 and 115 ng/mL.

In 50 elderly patients (mean age 61 years), with intermittent claudication, long term (median 6 months) treatment with flunarizine, 10 mg per day, yielded fairly constant steady state plasma levels albeit with considerable interindividual differences. While plasma flunarizine levels were between 50 ng/mL and 100 ng/mL in 46% of patients, individual values ranged from less than 20 ng/mL to 580 ng/mL. Flunarizine was devoid of cumulative effects as shown by repeated measurements.

As indicated by the large apparent volume of distribution (mean = 43.2 L/kg; range = 26.7 – 79.9 L/kg) seen after the oral administration of 30 mg in healthy volunteers, flunarizine is extensively distributed to tissues. Drug concentrations in tissues, particularly adipose tissue and skeletal muscle, were several times higher than plasma levels.

Flunarizine is 99.1% bound; 90% is bound to plasma proteins and 9% distributed to blood cells, leaving less than 1% present as free drug in the plasma water.

Flunarizine is metabolized principally through N-oxidation and aromatic hydroxylation. During a 48 hour period after a single 30 mg dose, minimal urinary (< 0.2%) and fecal (< 6%) excretion of flunarizine and/or its metabolites was found. This indicates that the drug and its metabolites are excreted very slowly over a prolonged period of time.

Flunarizine has a long elimination half-life of about 19 days.

Table I: Pharmacokinetic parameters of flunarizine in healthy volunteers

	No. of Doses	Dose (mg)	Cmax (ng/mL)	Tmax (h)	AUC (ng/mL*h)	$t_{1/2\alpha}$ (h)	Clp (mL/min)	$t_{1/2\beta}$ (mean days) [range]
Single		5	30.5	2-4	133[a]	2.4		
Dose		10	81.5		615[c]	2.8		
Studies		20	117.0		1091[c]	3.6		
		30	81.6	2-6	1169[c]	5	443.7	4 [2-8]
Multiple	14	5	18.1[b]					
Dose	14	10	38.8[b]					
Studies	14	15	68.4[b]		1264[c]		301.2	[4-19]
	57	10	114.5		1678[d]			19

a Area under curve 0 to 8 hours
b Plasma concentrations at 2 hours
c Area under curve 0 to 168 hours
d Area under curve 0 to 24 hours

INDICATIONS AND CLINICAL USE

SIBELIUM (flunarizine hydrochloride) is indicated in the prophylaxis of classic and common migraine. Flunarizine is not indicated in the treatment of acute migraine attacks.

CONTRAINDICATIONS

SIBELIUM (flunarizine hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

Flunarizine is contraindicated in patients with a history of depression or pre-existing extrapyramidal disorders.

PRECAUTIONS

Since sedation and/or drowsiness occur in some patients during treatment with SIBELIUM (flunarizine hydrochloride) (see ADVERSE REACTIONS), patients should be cautioned against activities which require alertness or rapid, precise responses (e.g. operating machinery or a motor vehicle) until the response to the drug has been determined.

Use in Pregnancy

To date, there are no data to support the use of flunarizine during pregnancy. It should therefore not be administered to pregnant women unless the anticipated benefits outweigh the potential risks.

Use During Lactation

Studies in lactating dogs have shown that flunarizine is excreted in milk. The concentration of flunarizine in milk is much greater than that in plasma. Breast feeding should therefore be discouraged in women taking flunarizine.

Use in the Elderly

The efficacy of flunarizine in the prophylaxis of migraine has not been established in elderly subjects.

Use in Children

The efficacy of flunarizine in the prophylaxis of migraine has not been established in patients younger than 18 years of age.

Use in Patients with Parkinson's Disease

Flunarizine is contraindicated in patients with pre-existing Parkinson's disease or other extrapyramidal disorders (see CONTRAINDICATIONS). Clinical studies indicate that prolonged flunarizine treatment, even at recommended doses, can produce motor disturbances in elderly subjects who did not show previous neurological deficits. The clinical symptoms resemble Parkinson's disease however, they do not improve with antiparkinson medication. Experience to date suggests that in most instances the extrapyramidal symptoms tend to be reversible following discontinuation of flunarizine treatment. It is recommended that patients on flunarizine therapy be followed closely so that extrapyramidal symptoms may be detected early and if necessary, treatment discontinued.

Use in Depressive Patients

Clinical studies indicate that flunarizine can, even at recommended doses, precipitate depression mostly in younger patients (see CONTRAINDICATIONS).

Endocrine Effects

Galactorrhea has been reported in a few female patients, some of whom were also on oral contraceptives, within the first two months of flunarizine treatment. Discontinuation of flunarizine therapy resolved the galactorrhea in most cases. Flunarizine therapy caused a mild but significant elevation of serum prolactin levels while GH, LH, FSH and TSH levels did not show significant variation. Two cases of menstrual irregularities have been reported.

Drug Interactions

Evidence from therapeutic trials in epileptic patients indicates that whereas flunarizine does not affect the kinetics of phenytoin, carbamazepine and valproic acid, it does decrease the plasma levels of mephenytoin. Furthermore, steady state levels of flunarizine are reduced by coadministration of two or more anticonvulsants. This is considered to be a result of enhanced first pass metabolism of flunarizine as a consequence of liver enzyme induction by the anticonvulsant medications.

In other studies, flunarizine was shown not to affect the anticoagulant effect of warfarin sodium or the hypoglycemic effect of glibenclamide and insulin.

Use in Patients with Impaired Hepatic Function

Flunarizine is metabolised by the liver, therefore care should be exercised when flunarizine is given to patients with compromised liver function.

ADVERSE REACTIONS

In clinical trials with SIBELIUM (flunarizine hydrochloride) migraine patients, drowsiness (also described as sedation or fatigue) as well as weight gain (and/or increased appetite occurred fairly frequently, in the order of 20 and 15%, respectively. Of 840 migraine patients, 23 (2.7%) and 9 (1.1%) required withdrawal from flunarizine therapy due to drowsiness and weight gain, respectively.

The most serious side effect encountered in migraineurs during clinical trials was depression. Of 840 migraine patients, 11 (1.3%) were withdrawn due to depression. International post-marketing experience suggests that patients between 20 and 54 years of age with a personal or familial history of depression are particularly at risk (see CONTRAINDICATIONS and PRECAUTIONS).

Clinical experience in other indications and epidemiologic surveys suggest that extrapyramidal symptoms may develop during flunarizine therapy. Elderly patients are particularly at risk (see CONTRAINDICATIONS and PRECAUTIONS).

Other side effects encountered in clinical trials for migraine prophylaxis included the following:

Gastrointestinal:	Heartburn, nausea, emesis, gastralgia;
Central Nervous System:	Insomnia and sleep change, anxiety, dizziness/vertigo;
Miscellaneous:	Dry mouth, asthenia, muscle aches, skin rash

SYMPTOMS AND TREATMENT OF OVERDOSE

There has been no experience to date with overdosage of SIBELIUM (flunarizine hydrochloride). Based on the pharmacological properties of the drug, sedation and asthena may be expected to occur. Treatment should consist of induction of emesis or gastric lavage and supportive measures.

DOSAGE AND ADMINISTRATION

The usual adult dosage of SIBELIUM (flunarizine hydrochloride) 10 mg per day administered in the evening. Patients who experience side effects may be maintained on 5 mg HS.

Duration of Therapy

Clinical experience indicates that the onset of effect of flunarizine is gradual and maximum benefits may not be seen before the patient has completed several weeks of continuous treatment. Therapy therefore should not be discontinued for lack of response before an adequate time period has elapsed, e.g. 6-8 weeks.

DOSAGE FORMS

Composition:	Each red and grey capsule contains 5 mg flunarizine (as hydrochloride).
Availability:	SIBELIUM flunarizine hydrochloride capsules are available in blister packages of 60 capsules.
Storage:	SIBELIUM capsules 5 mg should be stored at or below 25°C, protected from light and moisture.

Product monograph available on request

REFERENCES

1. Sibelium product monograph. 2. Todd PA and Benfield P. Flunarizine. A reappraisal of its pharmacological properties and therapeutic use in neurological disorders. *Drugs* 1989; 38 (4): 481-99. 3. Louis P. A double-blind placebo-controlled prophylactic study of flunarizine (Sibelium) in migraine. *Headache* 1981; 21 (6): 235-9. 4. Amery WK et al. Flunarizine, a calcium entry blocker in migraine prophylaxis. *Headache* 1985; 25 (5): 249-54. 5. Amery WK. Flunarizine, a calcium channel blocker: a new prophylactic drug in migraine. *Headache* 1983; 23: 70-4. 6. Lucking CH et al. Flunarizine vs. propranolol in the prophylaxis of migraine: two double-blind comparative studies in more than 400 patients. *Cephalalgia* 1988; 8 (suppl 8) : 21-6. 7. Vanhoutte PM. The expert committee of the World Health Organization on classification of calcium antagonists: the viewpoint of the raporteur. *Am J Cardiol* 1987; 59: 3A-8A. 8. Centonze V et al. Efficacy and tolerability of flunarizine in the prophylaxis of migraine. *Cephalalgia* 1985; 2:163-8. 9. Martinez-Lage JM. Flunarizine (Sibelium) in the prophylaxis of migraine. An open, long-term, multicenter trial. *Proc 3rd Inter Headache Symp* September, 1987. 10. Sorensen PS et al. A placebo-controlled, double-blind, cross-over trial of flunarizine in common migraine. *Cephalalgia* 1986; 6: 7-14.

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Mississauga, Ontario
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once-a-day
℗SIBELIUM*
flunarizine

See pages iv, v

https://doi.org/10.1017/S0317167100031218 Published online by Cambridge University Press

PrLIORESAL®

(baclofen)
Muscle relaxant
Antispastic agent

INDICATIONS AND CLINICAL USES

Alleviation of signs and symptoms of spasticity resulting from multiple sclerosis. Spina cord injuries and other spinal cord diseases.

CONTRAINDICATIONS

Hypersensitivity to LIORESAL.

WARNINGS

Abrupt Drug Withdrawal: Except for serious adverse reactions, the dose should be reduced slowly when the drug is discontinued to prevent visual and auditory hallucinations, confusion, anxiety with tachycardia and sweating, and worsening of spasticity.

Impaired Renal Function: Caution is advised in these patients and reduction in dosage may be necessary.

Stroke: Has not been of benefit and patients have shown poor tolerability to the drug.

Pregnancy and Lactation: Not recommended as safety has not been established. High doses in rats and rabbits are associated with an increase of abdominal hernias and ossification defects in the fetuses.

PRECAUTIONS

Not recommended in children under 12 as safety has not been established.

Because sedation may occur, caution patients regarding the operation of automobiles or dangerous machinery, activities made hazardous by decreased alertness, and use of alcohol and other CNS depressants.

Use with caution in spasticity that is utilized to sustain upright posture and balance in locomotion, or whenever spasticity is utilized to obtain increased function, epilepsy or history of convulsive disorders (clinical state and EEG should be monitored), peptic ulceration, severe psychiatric disorders, elderly patients with cerebrovascular disorders, and patients receiving antihypertensive therapy.

ADVERSE REACTIONS

Most common adverse reactions are transient drowsiness; dizziness, weakness and fatigue. Others reported:

Neuropsychiatric: Headache, insomnia, euphoria, excitement, depression, confusion, hallucinations, paresthesia, muscle pain, tinnitus, slurred speech, coordination disorder, tremor, rigidity, dystonia, ataxia, blurred vision, nystagmus, strabismus, miosis, mydriasis, diplopia, dysarthria, epileptic seizures.

Cardiovascular: Hypotension, dyspnea, palpitation, chest pain, syncope.

Gastrointestinal: Nausea, constipation, dry mouth, anorexia, taste disorder, abdominal pain, vomiting, diarrhea, and positive test for occult blood in stool.

Genitourinary: Urinary frequency, enuresis, urinary retention, dysuria, impotence, inability to ejaculate, nocturia, hematuria.

Other: Rash, pruritus, ankle edema, excessive perspiration, weight gain, nasal congestion.

Some of the CNS and genitourinary symptoms reported may be related to the underlying disease rather than to drug therapy.

The following laboratory tests have been found to be abnormal in a few patients receiving LIORESAL: SGOT, alkaline phosphatase and blood sugar (all elevated).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Signs and Symptoms: Vomiting, muscular hypotonia, hypotension, drowsiness, accommodation disorders, coma, respiratory depression, and seizures.

Co-administration of alcohol, diazepam, tricyclic anti-depressants, etc., may aggravate the symptoms.

Treatment: Treatment is symptomatic. In the alert patient, empty the stomach (induce emesis followed by lavage). In the obtunded patient, secure the airway with a cuffed endotracheal tube before beginning lavage (do not induce emesis).

Maintain adequate respiratory exchange; do not use respiratory stimulants. Muscular hypotonia may involve the respiratory muscles and require assisted respiration. Maintain high urinary output. Dialysis is indicated in severe poisoning associated with renal failure.

DOSAGE AND ADMINISTRATION

Optimal dosage of LIORESAL requires individual titration. Start therapy at a low dosage and increase gradually until optimum effect is achieved (usually 40-80 mg daily).

The following dosage titration schedule is suggested:

5 mg t.i.d. for 3 days
10 mg t.i.d. for 3 days
15 mg t.i.d. for 3 days
20 mg t.i.d. for 3 days

Total daily dose should not exceed a maximum of 20 mg q.i.d.

The lowest dose compatible with an optimal response is recommended. If benefits are not evident after a reasonable trial period, patients should be slowly withdrawn from the drug (see Warnings).

AVAILABILITY

LIORESAL (baclofen) 10 mg tablets: White to off-white flat-faced, oval tablets with GEIGY monogram on one side and the identification code 23 below the monogram. Fully bisected on the reverse side.

LIORESAL D.S. 20 mg tablet: White to off-white capsule-shaped, biconvex tablets. Engraved GEIGY on one side and GW with bisect on the other.

Available in bottles of 100 tablets.

Product Monograph supplied on request.

References:

1. Cartlidge, N.E.F., Hudgson, P., Weightman, D.: A comparison of baclofen and diazepam in the treatment of spasticity. J Neurol. Sci. 23: 17-24 (1974).
2. Young, R., Delwaide, P.: Spasticity. New England Journal of Medicine 304: 28-33 & 96-99 (1981).
3. From, A., Heltberg, A.: A double blind trial with baclofen and diazepam in spasticity due to multiple sclerosis. Acta Neurol. Scandinav. 51: 158-166, (1975).

see obc

Geigy

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PrPROLOPA® 50/12.5

levodopa 50 mg benserazide 12.5 mg

Rx Summary

Antiparkinsonian Agent

Indications

Treatment of Parkinson's syndrome when not drug induced.

Contraindications

Known hypersensitivity to levodopa or benserazide; in patients in whom sympathomimetic amines are contraindicated; concomitantly with, or within 2 weeks of, MAOI administration; uncompensated cardiovascular, endocrine, renal, hepatic, hematologic or pulmonary disease; narrow-angle glaucoma.

Warnings

Discontinue levodopa at least 12 hours before initiating 'Prolopa'. See Dosage section for substitution recommendations.

Not indicated in intention tremor, Huntington's chorea or drug-induced Parkinsonism.

Increase dosage gradually to avoid CNS side effects (involuntary movements). Observe patients for signs of depression with suicidal tendencies or other serious behavioural changes. Caution in patients with history of psychotic disorders or receiving psychotherapeutic agents.

In patients with atrial, nodal or ventricular arrhythmias or history of myocardial infarction initiate treatment cautiously in hospital. Caution in patients with history of melanoma or suspicious undiagnosed skin lesions. Safety in patients under 18 years has not been established. In women who are or may become pregnant, weigh benefits against possible hazards to mother and fetus. Not recommended for nursing mothers.

Precautions

Monitor cardiovascular, hepatic, hematopoietic and renal function during extended therapy. Caution in patients with history of convulsive disorders. Upper gastrointestinal hemorrhage possible in patients with a history of peptic ulcer.

Normal activity should be resumed gradually to avoid risk of injury. Monitor intraocular pressure in patients with chronic wide-angle glaucoma. Pupillary dilation and activation of Horner's syndrome have been reported rarely. Exercise caution and monitor blood pressure in patients on anti-hypertensive medication. 'Prolopa' can be discontinued 12 hours prior to anesthesia. Observe patients on concomitant psychoactive drugs for unusual reactions.

Adverse Reactions

Most common are abnormal involuntary movements, usually dose dependent, which necessitate dosage reduction. Other serious reactions are periodic oscillations in performance (end of dose akinesia, on-off phenomena and akinesia paradoxica) after prolonged therapy, psychiatric disturbances (including paranoia, psychosis, depression, dementia, increased libido, euphoria, sedation and stimulation), and cardiovascular effects (including arrhythmias, orthostatic hypotension, hypertension, ECG changes and angina pectoris).

Neurologic, intellectual, gastrointestinal, dermatologic, hematologic, musculoskeletal, respiratory, genitourinary and ophthalmologic reactions have also been reported. Consult Product Monograph for complete list.

Dosage

Individualize therapy and titrate in small steps to maximize benefit without dyskinesias. Do not exceed the recommended dosage range.

Initially, one capsule 'Prolopa' 100-25 once or twice daily, increased carefully by one capsule every third or fourth day (slower in post-encephalitic Parkinsonism) until optimum therapeutic effect obtained without dyskinesias. At upper limits of dosage, increment slowly at 2-4 week intervals. Administer with food.

Optimal dosage is usually 4-8 'Prolopa' 100-25 capsules daily, in 4-6 divided doses.

'Prolopa' 200-50 capsules are intended for maintenance therapy once optimal dosage has been determined using 'Prolopa' 100-25 capsules. No patient should receive more than 1000-1200 mg levodopa daily during the first year of treatment. 'Prolopa' 50-12.5 capsules should be used when frequent dosing is required to minimize adverse effects.

For patients previously treated with levodopa, **allow at least 12 hours to elapse** and initiate 'Prolopa' at 15% of previous levopoda dosage. During maintenance, reduce dosage slowly, if possible, to maximum of 600 mg levopoda daily.

Supply

'Prolopa' 50-12.5 capsules containing 50 mg levodopa and 12.5 mg benserazide. Contains mannitol.

'Prolopa' 100-25 capsules containing 100 mg levopoda and 25 mg benserazide.

'Prolopa' 200-50 capsules containing 200 mg levodopa and 50 mg benserazide.

Bottles of 100.

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REFERENCES: Rajput, A.H., Stern, W., and Laverty, W.H., (1984). Chronic low dose levopoda therapy in Parkinson's disease: an argument for delaying levodopa therapy. Neurology, 991-996. **2.** Quinn, N.P., (1990) Levodopa-Based Therapy. Pub: Therapy of Parkinson's Disease by Marcel Decker. 169-184. **3.** Pinder, R.M., et al. (1976). Levodopa and decarboxylase inhibitors: A Review of their Clinical Pharmacology and Use in the Treatment of Parkinsonism. Drugs 11: 329-377. **4.** Mondal, B.K., Mondal, K.N. (1986). Parkinson's Disease in the Elderly: A Long-Term Efficacy Study of Levodopa-Benserazide Combination Therapy. Pharmather., 4(9): 571-576. **5.** Rinne, U.K., Molsa, P. (1979). Levopoda with benserazide or carbidopa in Parkinson's disease. Neurology 29, 1584-1589. **6.** Birkmayer, W. (1983). Deprenyl (selegiline) in the treatment of Parkinson's disease. Acta Neurol Scand (Suppl); 95: 103-5. **7.** Csanda, E., and Tarczy, M. (1987). Selegiline in the early and late phases of Parkinson's disease. J Neural Transm (Suppl); 25: 105-13. **8.** Knoll, J., (1983). Deprenyl (selegiline): the history of its development and pharmacological action. Acta Neurol Scand (Suppl); 95: 57-80 34. **9.** Presthus, J., Berstad, J., and Lien, K. (1987). Selegiline (deprenyl) and low-dose levopoda treatment of Parkinson's disease. A double-blind crossover trial. Acta Neurol Scand Sep 76 (3): 200-3. **10.** Presthus, J., and Hajba, A., (1983). Deprenyl (selegiline) combined with levopoda and a decarboxylase inhibitor in the treatment of Parkinson's disease. Acta Neurol Scand (Suppl); 95: 127-33. **11.** Rinne, U.K. (1987). Deprenyl as an adjuvant to levopoda in the treatment of Parkinson's disease. J Neural Transm (Suppl) 25: 149-55.

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VALPROATE: THE GROWTH OF EXPERIENCE IN PRIMARY GENERALIZED EPILEPSY

For years, valproate has been regarded as an excellent choice for the control of absence seizures.[1,2]

In addition to its proven efficacy in simple and complex absence seizures,[2,3] valproate has been shown to be as effective as previous standards in controlling primary generalized seizures with tonic-clonic manifestations.[4]

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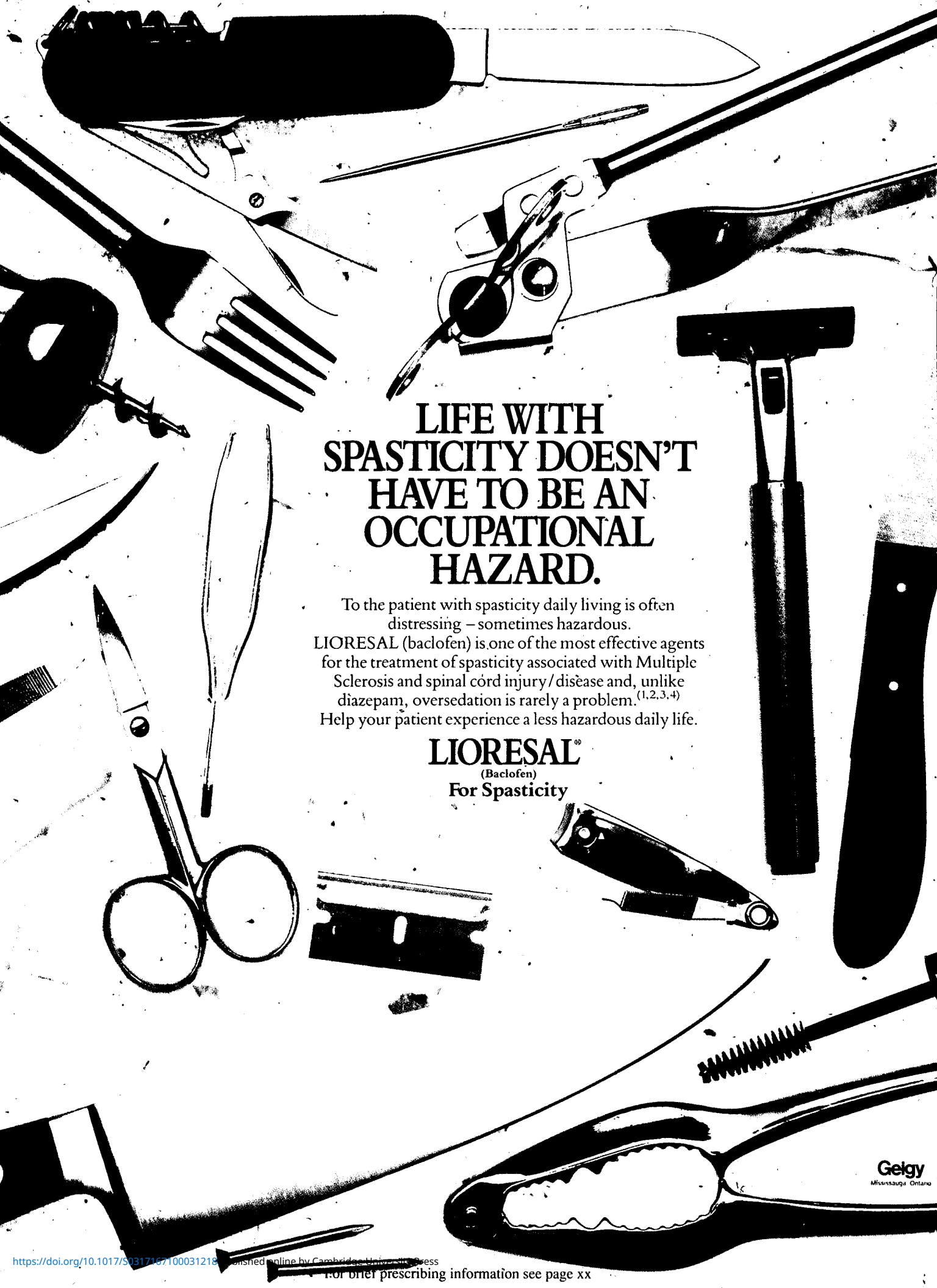

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