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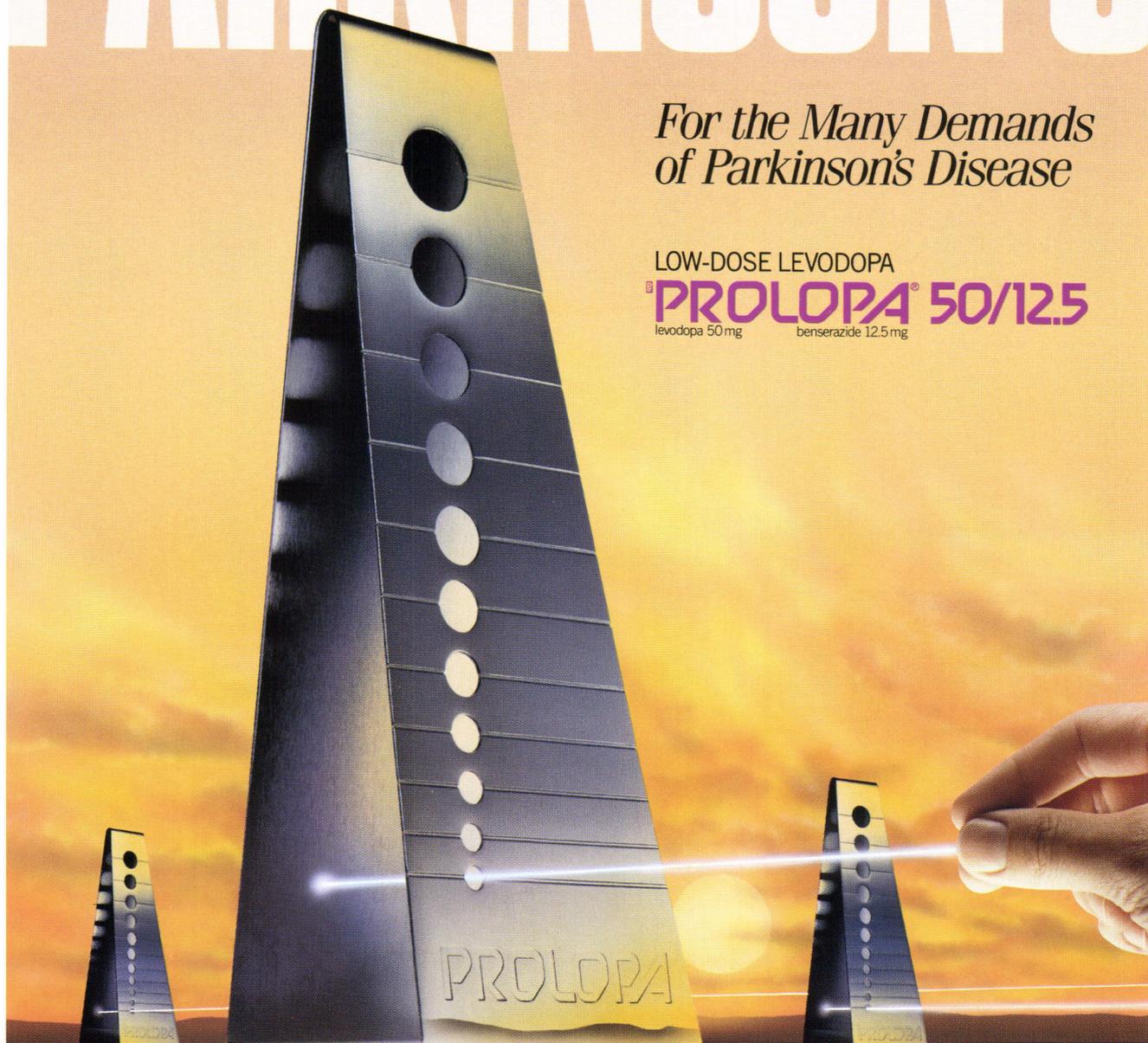
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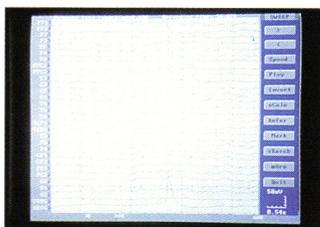
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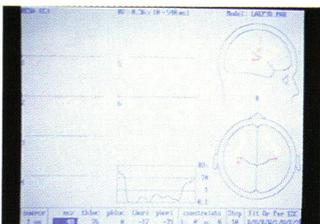
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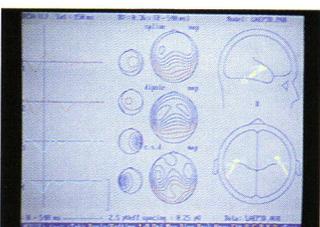
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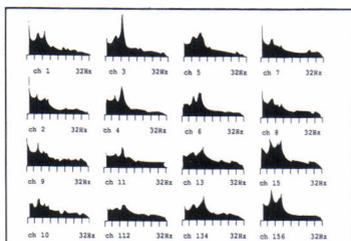
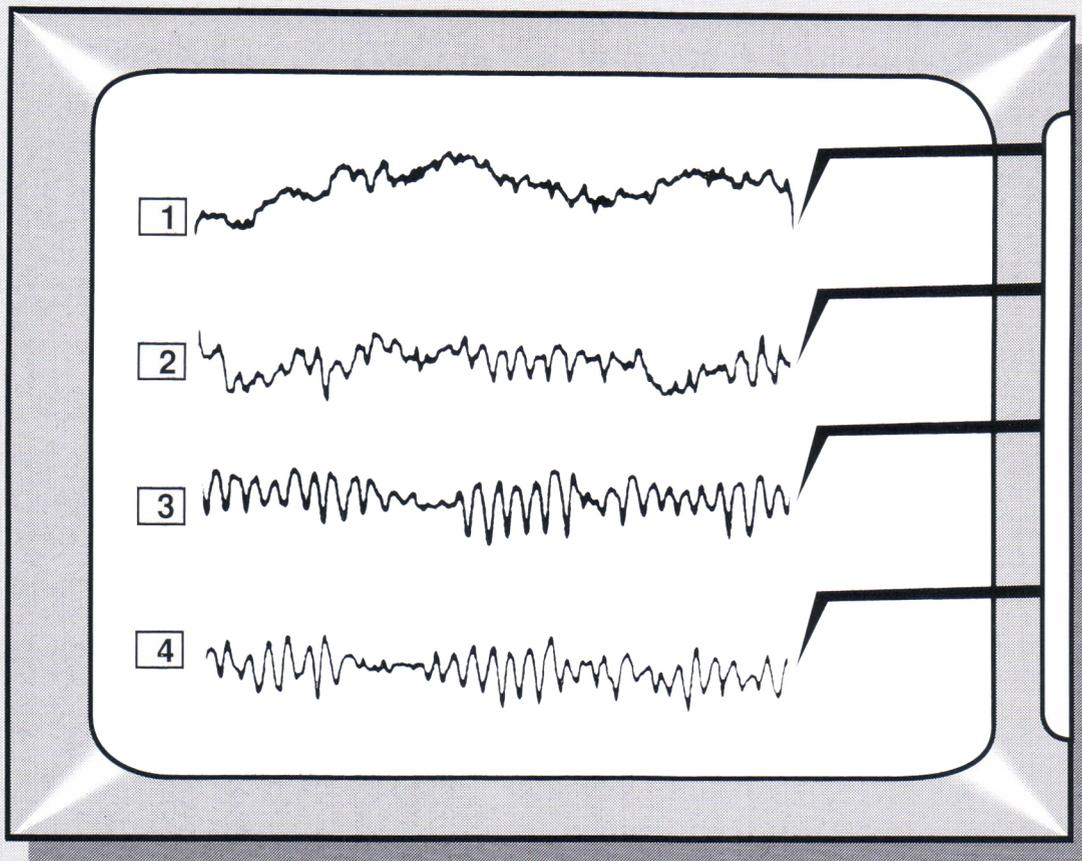
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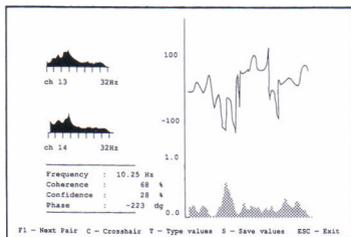
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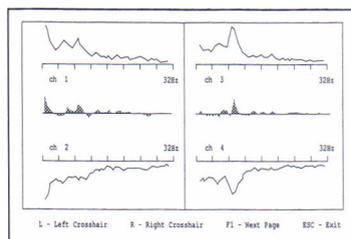
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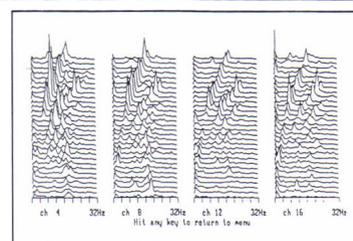
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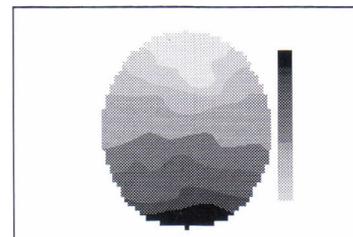
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ACTIONS ParloDel (bromocriptine mesylate) is a dopaminomimetic ergot derivative with D₂ type dopamine receptor agonist activity, and has also D₁ dopamine receptor antagonist properties. The dopaminomimetic activity of bromocriptine in the striatum 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 Turkali, 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 antitumorogenic 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, paresthesia, 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.



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See ifc

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.

CONTRAINDICATIONS 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 immediately 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.

Hematologic: 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.

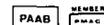
Table of Initial Doses by Weight (based on 15 mg/kg/day)

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.

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EPI/18A01-Jan, 1991 *TM - Abbott Laboratories, Limited

ABBOTT LABORATORIES, LIMITED
P.O. BOX 6150 STATION A
MONTREAL, QUEBEC H3C 3K6

LIORESAL®

(baclofen)
Muscle relaxant
Antispastic agent

INDICATIONS AND CLINICAL USES

Alleviation of signs and symptoms of spasticity resulting from multiple sclerosis. Spinal 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:

- Cartledge, 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).
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See page v

Geigy

Mississauga, Ontario
LSN 2W5

PAAB
CCPP

PROLOPA® 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 paradoxa) 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 levodopa dosage. During maintenance, reduce dosage slowly, if possible, to maximum of 600 mg levodopa 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 levodopa and 25 mg benserazide.

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

Bottles of 100.

Product Monograph available on request.

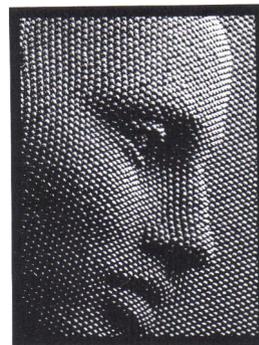
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Roche

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Etiobicoke, Ontario M9C 5J4

DEPRENYL
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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 1: Pharmacokinetic parameters of flunarizine in healthy volunteers

No. of Doses	Dose (mg)	C _{max} (ng/mL)	T _{max} (h)	AUC (ng/mL·h)	t _{1/2α} (h)	Cl _p (mL/min)	t _{1/2β} (mean days) [range]
Single Dose Studies	5	30.5	2-4	133 ^a	2.4	443.7	4 [2-8]
	10	81.5		615 ^d	2.8		
	20	117.0	1091 ^d	3.6			
	30	81.6	1169 ^a	5			
Multiple Dose Studies	14	18.1 ^b	2-6	1264 ^c	301.2	[4-19]	
	14	10					38.8 ^b
	14	15					68.4 ^b
	57	10					114.5

a Area under curve 0 to 8 hours
c Area under curve 0 to 168 hours

b Plasma concentrations at 2 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 asthenia 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

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JANSSEN
PHARMACEUTICA
Mississauga Ontario
*Trademark



once-a-day
SIBELIUM
flunarizine

See pages vi, vii

Intermediate Prescribing Information

Tegretol[®] (carbamazepine)

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

Indications

Symptomatic relief of pain of true or primary trigeminal neuralgia. Not for prophylactic use. Glossopharyngeal neuralgia has been relieved in some patients.

Management of psychomotor (temporal lobe) epilepsy. As an adjunct in some patients with secondary or partial epilepsy with complex symptomatology or secondarily generalized seizures, when combined with other antiepileptic agents.

As an alternative in patients with generalized tonic-clonic seizures and marked side effects or who fail to respond to other anticonvulsant drugs.

Ineffective for controlling petit mal, minor motor, myoclonic and predominantly unilateral seizures, and does not prevent generalization of epileptic discharge. Exacerbation of seizures may occur in patients with atypical absences.

Contraindications

History of hepatic disease or serious blood disorder, in patients with AV heart block (see *Precautions*), hypersensitivity to carbamazepine or to tricyclic compounds.

Do not give with, or within 2 weeks of treatment with monoamine oxidase inhibitors.

Safe use in pregnancy has not been established. Do not administer in first 3 months of pregnancy. Do not give to women of child-bearing potential unless benefits outweigh possible risks to the fetus. Avoid nursing while on TEGRETOL.

Warnings

Although infrequent, serious adverse effects have occurred during TEGRETOL use. Agranulocytosis and aplastic anemia have occurred in a few instances with fatal outcome. Leucopenia, thrombocytopenia, hepatocellular and cholestatic jaundice, and hepatitis have occurred. Use TEGRETOL carefully with close clinical and laboratory supervision during treatment in order to detect signs and symptoms of blood dyscrasias.

Long-term toxicity studies in rats showed potential carcinogenic risk. Weigh possible risk of drug use against potential benefits before prescribing carbamazepine.

Precautions

Perform complete blood studies, including platelet counts, and evaluate hepatic and renal function and urinalysis before starting treatment. Maintain close clinical and laboratory supervision during treatment, including frequent complete blood counts. Discontinue TEGRETOL if signs or symptoms or abnormal laboratory findings suggestive of blood dyscrasia or liver disorder occur until case is reassessed.

Non-progressive or fluctuating asymptomatic leucopenia may occur and does not generally require TEGRETOL withdrawal. Discontinue TEGRETOL if the patient develops leucopenia which is progressive or accompanied by clinical symptoms.

Give TEGRETOL cautiously, if at all, to patients with increased intraocular pressure or urinary retention. Monitor closely.

TEGRETOL may activate latent psychosis, or cause agitation or confusion, especially when used with other drugs. Use caution in alcoholic patients.

Use cautiously in patients with history of coronary artery disease, organic heart disease, or congestive failure. If a defective conductive system is suspected, perform an ECG to exclude patients with AV block.

Warn patients of possible hazards of operating machinery or driving automobiles due to possible dizziness and drowsiness with therapy.

Drug Interactions:

Hepatic enzyme induction by TEGRETOL may diminish activity of drugs metabolized in the liver.

Combined use of TEGRETOL with verapamil, diltiazem, erythromycin, toleandomycin, cimetidine, propoxyphene or isoniazid, can result in elevated plasma carbamazepine levels. Adapt carbamazepine dosage and monitor blood levels.

Concomitant use of carbamazepine and lithium may increase neurotoxic side effect risk.

Adapt dosage of anticoagulants to clinical needs whenever TEGRETOL is initiated or withdrawn.

TEGRETOL may decrease reliability of oral contraceptives. Advise patients to use alternative, non-hormonal method of contraception.

TEGRETOL may reduce alcohol tolerance; avoid alcohol during treatment.

Do not administer TEGRETOL in conjunction with MAO inhibitors. (See *Contraindications*.)

Adverse Reactions

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

Hepatic - During long-term use, abnormal liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Dermatologic - Skin sensitivity reactions and rashes, erythematous rashes, pruritic eruptions, urticaria, photosensitivity, pigmentary changes, neurodermatitis. In rare cases Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, alopecia, diaphoresis, erythema multiforme, erythema nodosum, aggravation of disseminated lupus erythematosus.

Neurologic - Vertigo, somnolence, ataxia, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia and oculomotor disturbances, speech disturbances, abnormal involuntary movements, increase in motor seizures. In rare

cases, peripheral neuritis and paresthesia, depression with agitation, talkativeness, nystagmus, hyperacusis, and tinnitus. There have been reports of paralysis and other symptoms of cerebral arterial insufficiency but no conclusive relationship to TEGRETOL could be established.

Cardiovascular - Thromboembolism, recurrence of thrombophlebitis in patients with 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 effects (including myocardial infarction and arrhythmia) have been associated with other tricyclic agents.

Genitourinary - Urinary frequency, acute urinary retention, oliguria with elevated BP, azotemia, renal failure, impotence, elevation of BUN, albuminuria, glycosuria.

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

Gastrointestinal - Nausea, vomiting, gastric or abdominal discomfort, diarrhea or constipation, anorexia, dryness of the mouth and throat, glossitis, stomatitis.

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

Other: fever and chills, aching joints and muscles, leg cramps, conjunctivitis, adenopathy or lymphadenopathy.

Dosage and Administration

Epilepsy:

Take TEGRETOL tablets and CHEWTABS in 2-4 divided doses daily, with meals whenever possible.

Swallow TEGRETOL CR tablets (either whole or, if so prescribed, only half a tablet) unchewed with some liquid during or after meals. These should be prescribed as a twice-daily dosage. If needed, 3 divided doses may be prescribed.

Adults and Children Over 12 Years of Age:

Initially, 100-200 mg 1-2 times/day depending on severity of case and previous therapeutic history. Increase dose progressively, in divided doses, until best response obtained. Usual optimal dosage is 800-1200 mg/day. Rarely, some adults have received 1600 mg. Once seizures disappear and remain controlled, reduce dose very gradually until minimum effective dose is reached.

Children 6-12 Years of Age:

Initially, 100 mg in divided doses on Day 1. Increase gradually by 100 mg/day until best response is obtained. Do not exceed 1000 mg/day. Once seizures disappear and remain controlled, reduce dose very gradually until minimum effective dose is reached.

Trigeminal Neuralgia:

Initially, 200 mg in 2 doses of 100 mg. Increase total daily dosage by 200 mg/day until pain relief is obtained. This usually occurs at 200-800 mg/day, but 1200 mg/day may be needed. Reduce dose progressively once pain relief is obtained and maintained, until minimal effective dosage is reached. Because trigeminal neuralgia is characterized by periods of remission, attempt to reduce or discontinue TEGRETOL at intervals of not more than 3 months, depending upon clinical course.

Not for prophylactic use.

Availability

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

Protect from heat and humidity.

Product Monograph available on request.

REFERENCES:

- Smith DB, et al: Results of a nationwide Veterans Administration cooperative study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone. *Epilepsia* 1987; 28(Suppl 3):550-558.
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Epival - xii, xx

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Lioresal - v, xxi

Tegretol - x, xxiii, obc

Deprenyl

Eldepryl - viii, ix

Prolopa - xv, xxi

Dupont

Sinemet - xiii

Hoescht

Frisium - xxvii, xxviii, ibc

Janssen

Sibelium - vi, vii, xxii

Nicolet Instruments - xi, xiv

Nihon Kohden - iii

Neuroscan - xvi

Ohio Medical - iv

PS Medical - xvii

Sandoz Canada

Parlodol - ifc, xix

Stellate Systems - xviii

STT Medical - 271, xxiv

Transplantation - xxv

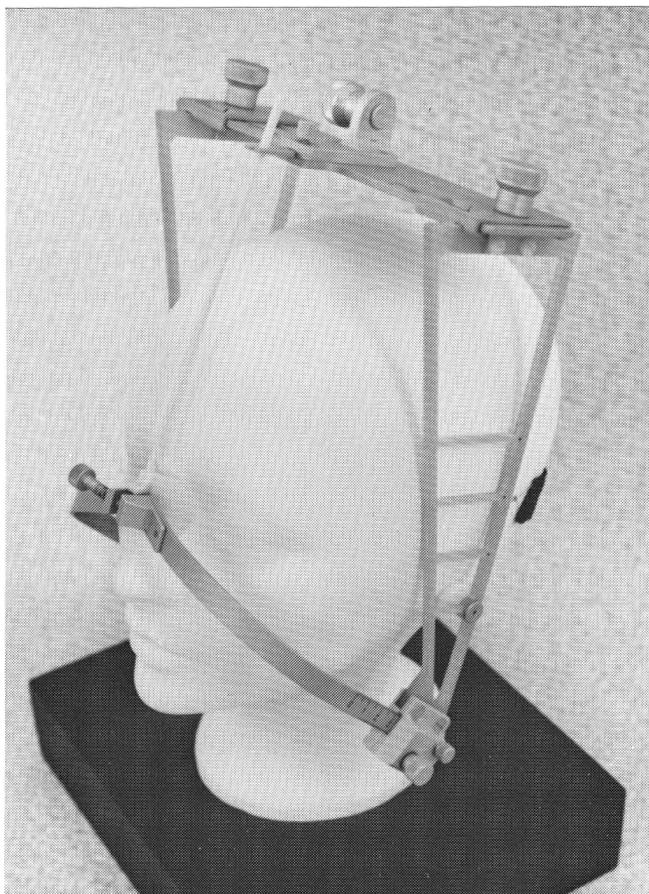
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Frisium (clobazam) Tablets, 10 mg
THERAPEUTIC CLASSIFICATION Anticonvulsant for adjunctive therapy.
ACTIONS Frisium (clobazam) is a 1,5-benzodiazepine with anti-convulsant properties. In general, the mode of anti-epileptic action of clobazam is probably largely analogous to that of the 1,4-benzodiazepines. The differences between clobazam (a 1,5-benzodiazepine) and the 1,4-benzodiazepines in terms of therapeutic efficacy and neuro-toxicity are possibly due to the variation in degree of the agonist action at the high affinity benzodiazepine receptor or to differing relative action at the high and low affinity benzodiazepine receptors. Regarding the mechanism of action, it is likely that modifications to the function of gamma-aminobutyric acid (GABA) as an important inhibitory neurotransmitter underlie the pharmacological effects of the benzodiazepines. Electro-physiological studies have shown that benzodiazepines potentiate GABA-ergic transmission at all levels of the neuroaxis, including the spinal cord, hypothalamus, hippocampus, substantia nigra, cerebellar cortex and cerebral cortex. The changes induced by the interaction of GABA with its receptors is enhanced by benzodiazepines, resulting in a decrease in the firing rate of critical neurons in many regions of the brain. The oral absorption of clobazam, like that of all benzodiazepines, is fast and complete. The time to peak concentration ranges from 1 to 4 hours. The administration of food with the drug has variable effects on the rate of absorption. The drug is highly lipophilic and is rapidly distributed in fat and cerebral gray matter. Within 1 to 4 hours of administration it has accumulated in white matter and is then redistributed widely. The volume of distribution is large. Clobazam is extensively metabolized and is not excreted in unchanged form by any species studied. Clobazam forms a number of metabolites with N-desmethyloclobazam being the most important. The half-life of N-desmethyloclobazam is much longer (mean 42 hours; range 36-46 hours) than for clobazam (mean 18 hours; range 10-30 hours). N-desmethyloclobazam reaches higher serum levels, especially with long term administration of clobazam. The half-life increases with the patient's age. The drug is about 85% protein-bound; hepatic disease may alter both the metabolism of the drug and its protein binding thus affecting plasma clobazam levels. There have been no studies that have demonstrated a clear-cut correlation between serum levels of clobazam or of N-desmethyloclobazam to clobazam efficacy. Most reports indicate there is no, or only a very weak, correlation between the clobazam dose, or blood levels, and its clinical effects. Therapeutic blood levels for clobazam are in the range of 50ng - 300ng/mL with the corresponding range for N-desmethyloclobazam being from 1000 - 4000ng/mL. The serum levels at which anti-convulsant effects can be expected are not yet known but it can be assumed that the therapeutic range lies in the order of the figures given above. Since N-desmethyloclobazam blood levels are 10-20 times higher than those for clobazam, and this metabolite also has anti-epileptic effects, it may be more important to the anti-epileptic efficacy of clobazam than the parent compound itself. After oral administration of ¹⁴C-labelled clobazam to man, approximately 90% of the radioactivity was recovered in urine. Seven double-blind studies have been reported in which clobazam was given as adjunctive therapy versus placebo within an established anti-epileptic regimen; clobazam was shown to be significantly superior to placebo.
INDICATIONS Frisium (clobazam) has been found to be of value as adjunctive therapy in patients with epilepsy who are not adequately stabilized with their current anti-convulsant therapy. **CONTRA-INDICATIONS** Hypersensitivity to clobazam, severe muscle weakness (myasthenia gravis) and narrow angle glaucoma. **WARNINGS** Use in the elderly: Frisium (clobazam) should be used with caution in elderly and debilitated patients, and those with organic brain disorders, with treatment initiated at the lowest possible dose. [See Precautions]. **Potentiation of drug effects:** Patients should be cautioned about the possibility of additive effects when Frisium is combined with alcohol or other drugs with central nervous system depressant effects. Patients should be advised against consumption of alcohol during treatment with Frisium. [See Precautions]. **Physical and psychological dependence:** Physical and psychological dependence are known to occur in persons taking benzodiazepines. Caution must be exercised if it is at all necessary to administer Frisium to individuals with a history of drug misuse or those who may increase the dose on their own initiative. Such patients must be placed under careful surveillance. Signs and symptoms of withdrawal may follow discontinuation of use of Frisium; thus it should not be abruptly discontinued after prolonged use. [See Precautions]. **Use in pregnancy:** Frisium should not be used in the first trimester of pregnancy and thereafter only if strictly indicated. Nursing mothers in whom therapy with Frisium is indicated should cease breast-

feeding, since clobazam passes into breast milk. Several studies have suggested an increased risk of congenital malformations associated with the use of minor tranquilizers (chloridiazepoxide, diazepam and meprobamate) during the first trimester of pregnancy. If Frisium is prescribed to a woman of child-bearing potential she should be warned to consult her physician regarding the discontinuation of the drug if she intends to become, or suspects she might be, pregnant. **Anterograde amnesia:** Anterograde amnesia is known to occur after administration of benzodiazepines. **Use in patients with depression or psychosis:** Frisium is not recommended for use in patients with depressive disorders or psychosis. **PRECAUTIONS Driving and Hazardous Activities:** Frisium (clobazam) possesses a mild central nervous system depressant effect, therefore patients should be cautioned against driving, operating dangerous machinery or engaging in other hazardous activities, particularly in the dose adjustment period, or until it has been established that they do not become drowsy or dizzy. **Use in the Elderly:** Elderly and debilitated patients, or those with organic brain syndrome, have been found to be prone to the CNS depressant activity of benzodiazepines even after low doses. Manifestations of this CNS depressant activity include ataxia, oversedation and hypotension. Therefore, medication should be administered with caution to these patients, particularly if a drop in blood pressure might lead to cardiac complications. Initial doses should be low and increments should be made gradually, depending on the response of the patient, in order to avoid oversedation, neurological impairment and other possible adverse reactions. **Dependence Liability:** Frisium should not be administered to individuals prone to drug abuse. Caution should be observed in all patients who are considered to have potential for psychological dependence. Withdrawal symptoms have been observed after abrupt discontinuation of benzodiazepines. These include irritability, nervousness, insomnia, agitation, tremors, convulsions, diarrhea, abdominal cramps, vomiting and mental impairment. As with other benzodiazepines, Frisium should be withdrawn gradually. **Tolerance:** Loss of part or all of the anti-convulsant effectiveness of clobazam has been described in patients who have been receiving the drug for some time. There is no absolute or universal definition for the phenomenon and reports vary widely on its development. The reported success of clobazam in intermittent therapy in catamenial epilepsy implies that tolerance may be minimized by intermittent treatment but long-term follow-up is unreported. No studies have identified or predicted which patients are likely to develop tolerance or precisely when this might occur. **Use in Mental and Emotional Disorders:** It should be recognized that suicidal tendencies may be present in patients with emotional disorders; particularly those depressed. Protective measures and appropriate treatment may be necessary and should be instituted without delay. Since excitement and other paradoxical reactions can result from the use of benzodiazepines in psychotic patients, Clobazam should not be used in patients suspected of having psychotic tendencies. **Use in Patients with Impaired Renal or Hepatic Function:** Clobazam requires dealkylation and hydroxylation before conjugation. **Usual precautions should be taken if Frisium is used in patients who may have some impairment of renal or hepatic function.** It is suggested that the dose in such cases be carefully titrated. In patients for whom prolonged therapy with Frisium is indicated, blood counts and liver function should be monitored periodically. **Use in Patients with Acute, Severe Respiratory Insufficiency:** In patients with acute, severe respiratory insufficiency, respiratory function should be monitored. **Laboratory Tests:** If Frisium is administered for repeated cycles of therapy, periodic blood counts and liver and thyroid function tests are advisable. **Drug Interactions:** Most studies of the potential interactions of clobazam with other anti-epileptic agents have failed to demonstrate significant interactions with phenytoin, phenobarbital, or carbamazepine. However, one study noted that the addition of clobazam caused a 25% increase in serum drug levels in 29% of patients taking carbamazepine, 63% of patients taking phenytoin, 13% of those taking valproate and 14% of those on phenobarbital. The contradictory findings in different studies are presumably due to variations in patient susceptibility, and although clinically significant interactions are unusual, they may occur. Alcohol may also significantly increase plasma clobazam levels. **Several of the established anti-epileptic agents:** carbamazepine, diphenhydantoin, phenobarbital, valproic acid, cause the blood levels of clobazam to decrease slightly. Findings are less consistent with regard to N-desmethyloclobazam: serum levels are lower with concurrent valproic acid, but higher with carbamazepine and diphenhydantoin. **Toxicologic Studies:** In mouse, clobazam was associated with hepatomas in high-dose males. In rat, an increased

incidence of thyroid adenomas was seen in males. There were three malignancies: two (male and female) in the thyroid and one (female) in the liver. (See Carcinogenicity) The relevance of these findings to man has not been established. **ADVERSE REACTIONS** From 19 published studies of Frisium (clobazam) use in epileptic patients, the overall incidence of side-effects was 33% of which drowsiness, dizziness and fatigue were most frequently reported. Canadian experience provides a similar overall incidence (32%) with drowsiness reported in 17.3% of patients, and 12% of patients terminating treatment because of side-effects. The incidence of side-effects was lower in patients under 16 years of age (23.7%) than the incidence in adults (43.1%); p<0.05, whereas treatment discontinuation incidences were similar across age groups: 10.6% and 13.8% respectively. The following side-effects occurred at incidences of greater than 1% (ataxia [3.9%], weight gain [2.2%], dizziness [1.8%], nervousness [1.6%], behaviour disorder [1.4%], hostility and blurred vision [1.3%]) while other effects occurred at a less than 1% incidence. **Symptoms of tiredness may sometimes appear, especially at the beginning of treatment with Frisium and when higher doses are used.** Also in rare instances and usually only temporarily, the patient may experience dryness of the mouth, constipation, loss of appetite, nausea, dizziness, muscle weakness, disorientation, tiredness, or a fine tremor of the fingers, but also paradoxical reactions, e.g., restlessness and irritability. After prolonged use of benzodiazepines, impairment of consciousness combined with respiratory disorders has been reported in very rare cases, particularly in elderly patients; it sometimes persisted for some length of time. Under experimental conditions, impairment of alertness has been observed to be less pronounced after therapeutic doses of clobazam than after other benzodiazepines. Nevertheless, even when used as directed, the drug may alter reactivity to such an extent as to impair driving performance or the ability to operate machinery, especially when it is taken in conjunction with alcohol. As with other drugs of this type (benzodiazepines), the therapeutic benefit must be balanced against the risk of habituation and dependence during prolonged use. Isolated cases of skin reactions such as rashes or urticaria have been observed. **SYMPTOMS AND TREATMENT OF OVERDOSAGE** Symptoms: The cardinal manifestations are drowsiness, confusion, reduced reflexes, increasing sedation, and coma. Effects on respiration, pulse and blood pressure are noticed with large overdoses. Patients exhibit some jitteriness and overstimulation usually when the effects of the drug begin to wear off. **Treatment:** Immediate gastric lavage may be beneficial if performed soon after ingestion of Frisium (clobazam). Given the route of excretion, [see 'ACTIONS' Section] forced diuresis by short acting 'loop' diuretic may be useful some hours post-ingestion. If respiratory depression and/or coma are observed, the presence of other central nervous system depressants should be suspected. Respirations, pulse and blood pressure should be monitored. General supportive measures aimed at maintaining cardiopulmonary function should be instituted and administration of intravenous fluids started. Hypotension and central nervous system depression are managed by the usual means. **DOSE AND ADMINISTRATION** As with other benzodiazepines, the possibility of a decrease in anticonvulsant efficacy in the course of treatment must be borne in mind. In patients with impaired liver and kidney function, Frisium (clobazam) should be used in reduced dosage. **Adults:** Small doses, 5-15 mg/day, should be used initially, gradually increasing to a maximum daily dose of 80 mg as necessary. **Children:** In infants (<2 years), the initial daily dose is 0.5-1 mg/kg/day. The initial dose in children (2-16 years) should be 5 mg/day, which may be increased at 5-day intervals to a maximum of 40 mg/day. As with all benzodiazepines, abrupt withdrawal may precipitate seizures. It is therefore recommended that Frisium be gradually reduced in dose before treatment is discontinued. **Administration:** If the daily dose is divided, the higher portion should be taken at night. Daily doses up to 30 mg may be taken as a single dose at night. **DOSE FORM Composition:** Frisium (clobazam) tablets, 10 mg contain clobazam as active ingredient; Lactose, USP; Starch (Corn), NF; Talc, USP; Colloidal Silicon Dioxide, NF; and Magnesium Stearate, NF. **Storage Conditions:** Frisium tablets should be stored in their original containers at room temperature, below 25°C. **Availability:** Frisium is available as white, uncoated, bevelled, round tablets of 7 mm diameter, marked with 'BGL' above and below the scorebreak on the obverse and the Hoechst 'Tower and Bridge' logo on the reverse. Frisium 10 mg tablets are packaged in blisters of PVC film and aluminium foil and are distributed in packs of 30 [3x10] tablets.

Product Monograph available on request.

References:

1. Clobazam in the Treatment of Refractory Epilepsy - The Canadian Experience: The Canadian Clobazam Cooperative Group. In press *Epilepsia*, 1991. Data on file Hoechst Canada Inc.
2. Shorvon, S.D.: Benzodiazepines - clobazam. *Antiepileptic Drugs*, 3rd ed., 1989.

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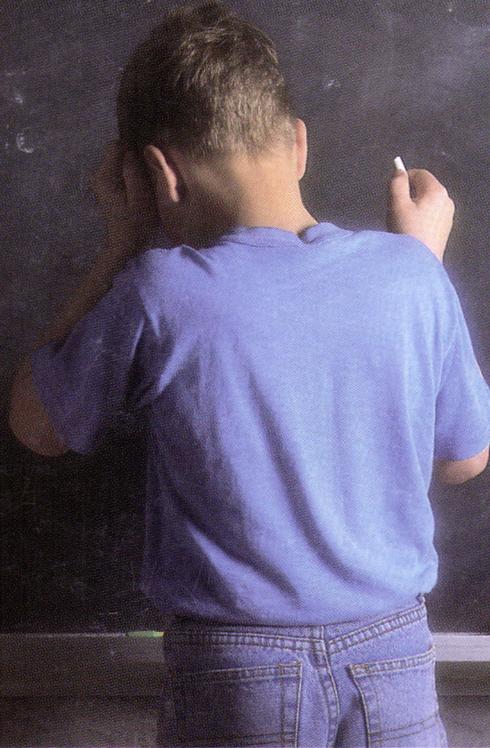
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