Because quality of life is the issue

**Parlodel**
(bromocriptine mesylate)

**Actions**
Parlodel (bromocriptine mesylate) is a dopaminergic ergot derivative with D2 type dopamine receptor antagonist activity, and has also D, dopamine receptor antagonist properties. The dopaminergic 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 dopaminergic drive may, however, provoke psychotic and other adverse reactions.

The extreme variability in G.1. 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**
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%) of 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 anti hypertensive 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, lethargy, and fatigue, and may be produced 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 dopamine antagonist phenomena may increase. The most common newly appearing adverse reactions in combination therapy were: nausea, abdominal involuntary movements, hallucinations, confusion, "on-off" phenomenon, dizziness, drowsiness, fainting, vomiting, asthma, abdominal discomfort, visual disturbance, ataxia, insomnia, depression, hypotension, shortness of breath, constipation and vertigo. Less common adverse reactions include anorexia, nausea, vomiting, diarrhea and constipation, fatigue, headache, leathargy, motility of skin, nasal stuffi­ness, nervousness, nightmares, paraesthesia, 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 or life threatening complications have occurred. The most common 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 suppress 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 an additive 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 dosage titration it is recommended that the dosage of levodopa 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.*
SINEMET® CR should be administered cautiously to patients with a history of seizure activity. It is recommended that baseline and periodic laboratory studies be made to ensure adequate renal function in all patients during treatment with SINEMET® CR. The dose of SINEMET® CR should be reduced if renal impairment occurs while the patient is receiving SINEMET® CR, and should be discontinued if there is a marked decrease in renal function.

Special Senses
- blurred vision
- conjunctivitis

System
- body aches
- chest pain
- diaphoresis
- dyspnea
- fatigue
- headache
- hyperesthesia
- hypotension
- insomnia
- nausea
- nervousness
- palpitation
- perspiration
- postural hypotension
- pyrexia
- respiratory depression
- respiratory infections
- respiratory symptoms
- rhinitis
- sinusitis
- throat pain
- tinnitus
- urine urgency
- urticaria
- xerostomia

Other adverse reactions that were reported frequently were: nausea (0.5%), vomiting (0.3%), constipation (0.5%), anorexia (0.3%), weight loss (0.3%), and headache (0.3%).

Adverse Reactions:
- The adverse reaction most frequently reported was dyskinesia (12.8%).
- Occasionally, prolonged and severe adverse reactions may occur (less than 2% of patients).
- Other adverse reactions that were reported frequently were: nausea (0.5%), vomiting (0.3%), constipation (0.5%), anorexia (0.3%), weight loss (0.3%), and headache (0.3%).

Precautions:
- General: Periodic evaluations of hepatic, hematopoietic, cardiovascular and renal function are recommended during extended therapy (see ADVERSE REACTIONS).
- Patients with chronic liver disease may be at increased risk of developing hepatic dysfunction. Patients with liver disease should be monitored carefully for complications of liver disease.
- Patients with chronic kidney disease may be at increased risk of developing renal dysfunction. Patients with kidney disease should be monitored carefully for complications of kidney disease.

Drug Interactions:
- Other concomitant drugs, in clinical trials of SINEMET® CR patients were included in the study. The effects of these other concomitant drugs on the pharmacokinetics of levodopa or SINEMET® CR have not been studied. However, it is recommended that concomitant therapy with SINEMET® CR be avoided, if possible.

Other Reactions:
- Cardiovascular effects: Palpitations, orthostatic hypotension, hypertension, and hypotension may occur.
- Gastrointestinal effects: Nausea, vomiting, constipation, diarrhea, and dyspepsia may occur.
- Neurologic effects: Dyskinesias, akathisia, and tremors may occur.
- Renal effects: Nephrolithiasis may occur.
- Respiratory effects: Respiratory infections and respiratory depression may occur.
- Other effects: Other adverse reactions that were reported frequently were: nausea (0.5%), vomiting (0.3%), constipation (0.5%), anorexia (0.3%), weight loss (0.3%), and headache (0.3%).

Other Contraindications:
- Patients with a history of drug dependence may be at increased risk of developing drug dependence. Patients with a history of drug dependence should be monitored carefully for complications of drug dependence.
- Other concomitant drugs, in clinical trials of SINEMET® CR patients were included in the study. The effects of these other concomitant drugs on the pharmacokinetics of levodopa or SINEMET® CR have not been studied. However, it is recommended that concomitant therapy with SINEMET® CR be avoided, if possible.

Other Reactions:
- Cardiovascular effects: Palpitations, orthostatic hypotension, hypertension, and hypotension may occur.
- Gastrointestinal effects: Nausea, vomiting, constipation, diarrhea, and dyspepsia may occur.
- Neurologic effects: Dyskinesias, akathisia, and tremors may occur.
- Renal effects: Nephrolithiasis may occur.
- Respiratory effects: Respiratory infections and respiratory depression may occur.
- Other effects: Other adverse reactions that were reported frequently were: nausea (0.5%), vomiting (0.3%), constipation (0.5%), anorexia (0.3%), weight loss (0.3%), and headache (0.3%).
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Send your donation to the Canadian Paraplegic Association, Ontario Division, 520 Sutherland Drive, Toronto, Ontario M4G 3V9. (416) 422-5640.

Maintenance: Because Parkinson’s disease is progressive, periodic clinical evaluations are recommended and adjustment of the dosage regimen of SINEMET® CR may be required.

Addition of Other Antiparkinson Medications: Anticholinergic agents, dopamine agonists, amantadine and lower doses of selective MAO-B inhibitors can be given with SINEMET® CR. When combining therapies, dosage adjustments may be necessary.

Interruption of Therapy: Patients should be observed carefully if abrupt reduction or discontinuation of SINEMET® CR is required, especially if the patient is receiving neuroleptics (see PRECAUTIONS). If general anesthetics are required, SINEMET® CR may be continued as long as the patient is permitted to take oral medication. If therapy is interrupted temporarily, the usual dosage should be administered as soon as the patient is able to take oral medication.

Availability of Dosage Forms: No. 2041 - SINEMET® CR is peach-colored, oval-shaped, biconvex, scored compressed tablet, engraved SINEMET CR on one side and 32/32 on the other. Available in bottles of 100.


Product Monograph Available on Request

(352-a.5.91) 06-90-SCR-91-CDM-0002-JA
Ticlopidine hydrochloride (Ticlid) 250 mg Tablets

**INDICATIONS AND CLINICAL USE**

Ticlopidine hydrochloride is an inhibitor of platelet function. The effect is not correlated with age, sex, alcohol use, or diabetes.

**Clinical Pharmacology**

Absorption: Ticlopidine hydrochloride is absorbed from the gastrointestinal tract and is extensively metabolized by the liver.

Distribution: Ticlopidine hydrochloride binds reversibly (98%) to plasma proteins, mainly to serum albumin and lipoproteins in plasma.

Metabolism: Ticlopidine hydrochloride is metabolized extensively by the liver; no intact ticlopidine hydrochloride is detected in the urine.

Elimination: Ticlopidine hydrochloride is excreted in the urine and feces. Ticlopidine hydrochloride is a minor component in plasma after a single dose, but at steady state, ticlopidine hydrochloride is the major component.

Therapeutic Trials: Ticlopidine hydrochloride was tested in over 2000 patients with cerebrovascular disease who were treated with ticlopidine for an average of 5.8 years.

**Neutropenia and Thrombocytopenia:**

Neutropenia and thrombocytopenia have been associated with ticlopidine hydrochloride therapy. The incidence of severe neutropenia (ANC < 0.5 x 10^9/L) was 0.8%. Severe neutropenia occurs during the first 3-12 weeks of therapy, and the incidence is about 25% less in patients treated for longer than 12 weeks. The thrombocytopenia may occur as an isolated finding or in combination with neutropenia.

**Hematological:**

Neutropenia and thrombocytopenia have been associated with ticlopidine hydrochloride therapy. Maximal decreases of platelet counts usually occur within 3 weeks of initiation of therapy.

**Laboratory Findings:**

Hematological: Neutropenia and rarely thrombocytopenia have been associated with ticlopidine hydrochloride therapy. Thiopurine methyltransferase activity is reduced in patients treated with ticlopidine hydrochloride.

**Gastrointestinal:**

There have been rare reports of more severe rashes.

**Erectile Dysfunction:**

An association between ticlopidine hydrochloride and erectile dysfunction has not been established.

**INTERACTION STUDIES**

Ticlopidine hydrochloride is extensively metabolized in the liver and is not metabolized by the cytochrome P450 system. Ticlopidine hydrochloride is a weak inhibitor of CYP3A4 and CYP2C9, and a weak inducer of CYP1A2, CYP2D6, and CYP2C19.

**Clinical Trials:**

In clinical trials of 1 to 5 years duration, discontinuation of Ticlid (ticlopidine hydrochloride) due to one or more adverse effects was required in 20.9% of patients. In these same trials, ASA and placebo led to a significantly higher discontinuation rate (24.2% and 20.6%, respectively).

**PERCENT OF PATIENTS IN CONTROLLED STUDIES**

<table>
<thead>
<tr>
<th>Event</th>
<th>Ticlid</th>
<th>ASA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>2.2(0.2)</td>
<td>1.6(0.1)</td>
<td>0.0(0.0)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1.3(0.8)</td>
<td>0.3(0.1)</td>
<td>0.0(0.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7.0(2.4)</td>
<td>6.2(1.9)</td>
<td>1.7(0.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.9(1.4)</td>
<td>1.4(0.9)</td>
<td>0.9(0.4)</td>
</tr>
<tr>
<td>Melena</td>
<td>1.0(0.4)</td>
<td>0.5(0.4)</td>
<td>0.0(0.0)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.0(0.4)</td>
<td>0.5(0.4)</td>
<td>0.0(0.0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0.8(0.1)</td>
<td>0.1(0.0)</td>
<td>0.0(0.0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0.5(0.4)</td>
<td>0.2(0.1)</td>
<td>0.0(0.0)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>5.6(2.7)</td>
<td>3.7(1.9)</td>
<td>1.3(0.4)</td>
</tr>
</tbody>
</table>

**REFERENCES**

1. Ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients.

**ADVERSE REACTIONS**

**CONTRAINDICATIONS**

Hypersensitivity to ticlopidine hydrochloride or its excipients. Patients with a history of ulcerative lesions of the mouth, nose, or throat, ulcerations in oral cavity, should be cautioned.

**Allergic Reactions:**

The majority of rashes occur within 3 months of initiation of therapy. The incidence of severe neutropenia (ANC < 0.5 x 10^9/L) has been observed in 0.4% of ticlopidine hydrochloride recipients. Maximal decreases of platelet counts usually occur within 3 weeks of initiation of therapy.

**Cardiovascular:**

Hypertension, arrhythmias, and ischemic heart disease have been reported.

**Gastrointestinal:**

Diarrhea and nausea. The majority of cases are mild and transient in nature and occur within 3 months of initiation of therapy.

**Hematological:**

Neutropenia and rarely thrombocytopenia have been associated with ticlopidine hydrochloride therapy. Thiopurine methyltransferase activity is reduced in patients treated with ticlopidine hydrochloride.

**Neurological:**

Seizures and tremors have been reported.

**Respiratory:**

Respiratory symptoms, bronchospasm, and dyspnea have been reported.

**Skin:**

Rash usually occurs within 3 months of initiation of therapy, with a mean time to onset of 11 days. If drug is discontinued, recovery should occur within several days. Many rashes do not recur on drug rechallenge. There have been rare reports of more severe skin reactions.

**Carcinogenicity:**

Ticlopidine hydrochloride was tested for carcinogenic potential in rats and mice with and without metabolic activation. A single 600 mg dose of Ticlid (equivalent to 24 standard mg tablets) of ticlopidine hydrochloride was administered to rats orally daily for 2 years. There were no increases in neoplastic lesions observed in rats treated with ticlopidine hydrochloride. The results in mice were equivocal. The effect is not correlated with age, sex, alcohol use, or diabetes.

**TOLERABILITY OVERDOSE**

There have been rare reports of more severe skin reactions.

**Pharmacological evaluation:**

Drug substance: Ticlopidine hydrochloride is a white crystalline solid. It is freely soluble in water and self-buffered to a pH of 3.6. It also dissolves freely in methanol, sparingly soluble in buffer solutions pH 6.8, methanol and ethanol, and is slightly soluble in acetic acid.

Ticlopidine hydrochloride is a basic quinoline compound, is anionic at pH 7.4, and has an absorption maximum at 291 nm. The sodium salt of ticlopidine hydrochloride is the acid base salt of ticlopidine and is neutral at pH 7.4. The sodium salt of ticlopidine hydrochloride is slightly soluble in acetic acid, is not soluble in methanol, ethanol, and is slightly soluble in water.

**REFERENCES:**


**SAFETY STUDIES**

Clinical trials included in the evaluations of ticlopidine hydrochloride were 1-year old male dogs and a single 600 mg dose of Ticld (equivalent to 24 standard mg tablets) of ticlopidine hydrochloride was administered to rats orally daily for 2 years. There were no increases in neoplastic lesions observed in rats treated with ticlopidine hydrochloride. The results in mice were equivocal. The effect is not correlated with age, sex, alcohol use, or diabetes.

**REFERENCES:**

INDICATIONS AND CLINICAL USES

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

WARNINGs

Abrupt Drug Withdrawal: Except for serious adverse reactions, the drug 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.

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.

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, diziness, weakness and fatigue. Others reported:

- Neurological: Headache, insomnia, euphoria, excitement, depression, confusion, hallucinations, paresthesia, muscle pain, tinnitus, slurred speech, coordination disorder, tremor, rigidity, dystonia, ataxia, blurred vision, nystagmus, strabismus, myosis, 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.

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

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.

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 tablets: 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.

References:


See page x

Canadian  $64.20  $74.90  $37.45
US & Foreign  $70  $80  $40
(US $63) (US $72) (US $36)

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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; use for ophthalmoplegic hemi­neuritis has been relieved in some patients.

Management of psychomotor (temporal lobe) epilepsy. As an adjunct in some patients with secondary or partial epilepsy in complex symptomatology or secondarily generalized seizures, when combined with other anticonvulsants. As an alternative in patients with generalized tonic-clonic seizures and mania and where 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 fits. 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 (with or without Bloom's syndrome) or 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 childbearing potential unless benefits outweigh possible risks to the fetus. Avoid nursing white on TEGRETOL.

Warnings

Although serious, adverse serious adverse effects have occurred during TEGRETOL use. Agranulocytosis and aplastic anemia have occurred in a few instances with fatal outcome. Leukopenia, thrombocytopenia, hematopoietic and cholestatic jaundice, and hepatic abscess 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. Weak 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 during treatment. If a 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 intracranial pressure or urinary retention. Monitor closely. TEGRETOL, or cause aplasia or confusion, especially when used with other drugs. Use caution in alcoholics.

Use cautiously in patients with history of coronary artery disease, organic heart disease, or congestive failure. If a definite 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, ticlopidine, phenothiazines, and related drugs may result in elevated plasma carbamazepine levels. Adapt carbamazepine therapy and carefully monitor blood levels. Concomitant use of carbamazepine and lithium may increase neurotoxic side effect risk. Adapt dosage of antidepressants 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, hypoproteinemia, 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, urticaria, urticarial papules and plaques, pigmented changes, neurodermatitis. In rare cases Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, ephelides, discoid, drug eruptions, erythema multiforme, erythema nodosum, aggravated of disseminated lupus erythematosus.

Neurologic - Vertigo, somnolence, ataxia, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia and ocular disturbances, speech disturbances, abnormal involuntary movements, increase in motor seizures. In rare cases, peripheral neuropathy and parasthesia, depression with agitation, talkativeness, nystagmus, hyperacousis, and tinnitus. There have been reports of paralysis and other symptoms of central nervous system insufficiency but no conclusive relationship to TEGRETOL could be established. Cardiovascular - Thromboembolism, occurrence of thromboembolic in patients with prior history of thrombopelities, primary thrombopelities, congestive heart failure, aggravation of hypertension, Stokes-Adams in patients with AV block, hypoten sion, syncope and collapse, edema, aggravation of coronary artery disease. Some of these effects (including myocardial infarction and death) have been associated with other tricyclic agents. Gastrointestinal - Urinary frequency, acute urinary retention, colitis with elevated BP, azotemia, renal failure, impotence, elevation of BUN, albuminuria, glycosuria.

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

Gynaecology - Amenorrhoea, disordered menstruation.

Ophthalmologic - No there is conclusive evidence that TEGRETOL produces pathological changes in the eye. However, many phonophores 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, achy 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 daily on an empty stomach or immediately before the evening meal, depending on severity of case and previous therapeutic history. Increase dose progressively, until 3-4 divided doses or least amount attained. Usually 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 daily until best response is obtained. Do not exceed 1500 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 1500 mg may be required. Reduce gradually over a period of several weeks since progression 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 G-E 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. G-E depressed 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 biocovers with distinct red spots. G-EY depressed on one side and PL 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 convex tablet, engraved CGG on one side and QC/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: Brown-orange, capsule-shaped, slightly convex tablet, engraved CGG on one side and EN/ 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.

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THE CANADIAN SOCIETY OF CLINICAL NEUROPHYSIOLOGISTS
EXAMINATION IN ELECTROENCEPHALOGRAPHY

The Examining Committee is pleased to announce the names of successful candidates in the first CSCN EEG Examination held in June 1991:

Dr. Betty Koo
Dr. Hiroshi Otsubo
Dr. Lyle Weston

SCHEDULE FOR 1992 EXAMINATIONS

Multiple-choice written in home city:
Saturday, May 23, 1992

Oral examination for successful written candidates:
June 1992 in association with Canadian Congress of Neurological Sciences at Winnipeg

DEVELOPMENTAL NEUROBIOLOGY

Sudden Infant Death Syndrome

The Hospital For Sick Children Research Institute, one of the largest and most active of its kind in the world, is seeking an outstanding young scientist with a Ph.D. to carry out research in developmental neurobiology as related to Sudden Infant Death Syndrome (SIDS). The appointee will be expected to collaborate closely with an established group studying SIDS and will also develop his/her own research programme. Expertise in neurotransmitter receptor localization, receptor gene expression, and growth factor regulation is preferred. The position is for an initial three-year period, with the possibility of renewal for a further three years. Send curriculum vitae, a brief description of research interests, and the names of three references before December 31, 1991.

Please forward replies to: Dr. L. Becker, Division of Pathology, The Hospital For Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8.

BEHAVIOURAL NEUROLOGY FELLOWSHIP

The Behavioural Neurology Program at Baycrest Hospital invites applications for a one or two year fellowship beginning July 1, 1992.

The fellowship will offer clinical and research training in the cognitive neurology of degenerative disease, stroke and neuropsychiatric disorders.

For further information, please contact: Morris Freedman, M.D., Director, Behavioural Neurology Program, Baycrest Hospital, Room 4W36, 3560 Bathurst Street, Toronto, Ontario M6A 2E1

Baycrest Centre for Geriatric Care

We sincerely appreciate the interest of all applicants however, only those selected for an interview will be contacted.

SCOTT & WHITE

The Division of Neurological Surgery of Scott & White Clinic and Texas A&M University College of Medicine is seeking a Neurosurgeon to fill a clinical/faculty position as Director of the Division of Neurological Surgery.

Scott & White is located in Temple, Texas, approximately 60 miles north of Austin and 120 miles south of Dallas/Ft. Worth. Temple is a family oriented city of 50,000 with numerous nearby lakes and outdoor activities.

Scott & White provides an exceptionally attractive salary and benefits package to include 4 weeks vacation and 3 weeks C.M.E.

For more information, please call Barry Harper at 1-800-725-3627 or send curriculum vitae to:

Dennis J. Lynch, M.D.
Chairman, Department of Surgery
Scott & White Clinic, Texas A&M University College of Medicine
2401 South 31st Street
Temple, TX 76508

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The incidence of neural tube defects in the fetus may be sometimes seen at higher dosages. Anti-epileptic drugs should not be discontinued in patients to whom the drug is administered to prevent major seizures, because this may precipitate status epilepticus with attendant hypoxia and risks to both the mother and the unborn child. With regard to drugs given for minor seizures, premature discontinuation of the drug or during pregnancy should be weighted against the risk of convulsive seizures 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 physicians and should be kept informed of the onset of pregnancy promptly to him. Where the necessity for continued use of anti-epileptic medication is in doubt, appropriate counseling is indicated.

Nursing Mothers: Valproic acid is excreted in breast milk. Concentrations in breast milk have been reported to be 1 to 2% 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. Segment fertility studies in rats have shown that doses up to 50 mg/kg/day for 60 days have no effect on fertility. The effect of valproates on spermatogenesis in rodents 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 initiating therapy and at intervals thereafter. It is recommended that patients be monitored for platelet count prior to planned surgical procedures. Clinical evidence of aplastic anemia or hemorrhage/coagulation is an indication for reduction of dosage or withdrawal of therapy pending investigation.

Hyperammonemia may occur, and hyperammonemia 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 (divalproex sodium) may interact with other agents which increase serum ammonia by some of the mechanisms described above, hepatic impaction should be suspected in patients who become ufeless, or other than obvious cause, while taking Epival or divalproex sodium.

Liver function tests should be performed prior to therapy and at frequent intervals thereafter especially during the first 6 months. However, patients should not rely totally on serum biochemistry since these tests may not be abnormal in all patients. Simultaneous monitoring of the erythrocyte sedimentation rate, intern medical history and physical examination. Caution should be observed in patients with a prior history of hepatic disease. Patients with various unusual con genital 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 increase in fibrinogen concentration, as these tests may occur, the drug should be discontinued. Dosage should be limited to the lowest dose consistent with optimal seizure control.

The drug should be discontinued immediately in the presence of the early signs of hepatic dysfunction suspected, 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 may 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, the incidence of neural tube defects may be increased in mothers receiving valproic acid during the first trimester of pregnancy. Based upon a single report, it was estimated that the incidence of neural tube defects in children with spina bifida is approximately 1.2%. This risk is similar to that which applies to non-epileptic women who have had seizures. Because the neural tube defects (spina bifida, anorectal malformations of the heart, cleft lip or palate, and neural tube defects) occur at essentially the same time in utero, 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 valproic acid and the reaction to the therapy.

Gastrointestinal: Nausea, vomiting and indigestion are the most commonly reported side effects at the initiation of therapy with these drugs. These symptoms are generally 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 been reported.

Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration have been reported.

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

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, hemarthromatosis and frank hemorrhage have been reported. Relative lymphocytosis and hypo fibrinogenemia have also been reported. Anemia and bone marrow suppression have been reported.

Hepatic: Minor elevations of transaminases (e.g. SGOT and SGPT) are frequently observed. Occasionally, laboratory tests also show increases in serum bilirubin and abnormal changes in other liver function tests. These may reflect potentially serious hepatotoxicity (See WARNINGS).

Metabolic: Hyperammonemia (See PRECAUTIONS). Hyperammonemia has been reported in patients with a pre-existing non-ketotic hyperammonemia.

Miscellaneous: 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 intervals of 5 to 10 mg/kg/day till 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). Whenever the possibility of advanced liver toxicity (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 not be affected. It should be carefully noted that patients who have never had a seizure may have a seizure when therapy is initiated, and that some patients with no apparent history of seizures may have a seizure when the drug is discontinued or the dose is reduced.

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

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

Gastrointestinal:

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Total daily dose (mg)</th>
<th>Dosage (mg)</th>
<th>Epival 375 mg</th>
<th>Epival 500 mg</th>
<th>Epival 750 mg</th>
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<tr>
<td>10-24.9</td>
<td>25-49.4</td>
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<td>500-250</td>
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<td>40-59.9</td>
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<td>60-74.9</td>
<td>132-164.5</td>
<td>1320-1645</td>
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<td>1320-250</td>
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<td>75-89.9</td>
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<td>1650-1875</td>
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<td>120-159.9</td>
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<td>5000-250</td>
</tr>
</tbody>
</table>

Product monograph available on request.

REFERENCES:

TRANSPLANTATION

A proven, effective treatment for end-stage organ disease.

Through transplants, hundreds of Canadians have a chance of a normal, productive life.

But many others don't get that chance. They die waiting for donated kidneys, hearts, lungs and livers.

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ROY T.
Kidney Transplant
June 26, 1989
Frisium® (clobazam) Tablets, 10 mg

**THERAPEUTIC CLASSIFICATION**
Anticonvulsant for adjunctive therapy.

**INDICATIONS**
Frisium® possesses a high degree of 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 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 and to differing relative action at the high and low affinity benzodiazepine receptors. Regarding the mechanisms 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 in the nervous system, including the spinal cord, hypothalamus, hippocampus, substantia nigra, cerebellar cortex and cerebral cortex. The changes induced in GABA-ergic transmission have been shown to be due to an increase of the receptors unoccupied benzodiazepines, resulting in a decrease in the firing rate of critical neurons in many regions of the brain. The oral absorption of clobazam, like the other 1,4-benzodiazepines, is bioavailable in 100%. The term of 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 rapidly distributed in fat in the event of an overdose. 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-desmethylclobazam being the most important. The half-life of N-desmethylclobazam is much longer (mean 42 hours; range 36-46 hours) than for clobazam (mean 18 hours; range 10-30 hours). All the metabolites in normal serum levels, even in patients with a long term administration of clobazam. The half-life increases with the patient's age. The drug is about 50% protein-bound; hepatic disease may affect the metabolism and therefore increase the half-life. The posibility of additive effects when Frisium is combined with alcohol or other central nervous system depressants should be suspected. Respirations, pulse and blood pressure are noticed with large overdoses. Patients exhibit some alteration and are more susceptible when the effects of the drug increase. Given the route of excretion, forced diuresis by the usual means or diuresis by the use of benzodiazepines, impairment of consciousness combined with respiratory depressions 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 extent as to impair driving performance or the ability to operate machinery, especially when benzodiazepines are used in conjunction 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 depressive reactions, and rarely of suicidal tendencies. Use in patients with depression or psychosis:

**SYMPTOMS AND TREATMENT OF OVERDOSE SYMPTOMS:**
The clinical manifestations are drowsiness, confusion, reduced reflexes, personality changes, and amnesia. If the patient is on other medications, adverse effects may be additive. Blood pressure is monitored. Patients exhibit some alteration and are more susceptible when the effects of the drug are increased. Given the route of excretion, forced diuresis by the usual means or diuresis through the use of benzodiazepines, impairment of consciousness combined with respiratory depression and/or coma are observed, the presence of other central nervous system depressants should be suspected. Respiration, pulse and blood pressure should be monitored. General supportive measures aimed at maintaining cardiovascular function should be instituted and administration of intravenous fluids started. Hypotension and central nervous system depression may be 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. Adult: 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 (2-16 years), the initial daily dose is 0.5-1 mg/kg/day. The initial dose in children (2-16 years) should be 5 mg, 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. Dosing FORM Composition: Frisium (clobazam) tablets, 10 mg contain clobazam as active ingredient, Povidone, Magnesium Stearate, Calcium Carbonate, Silicon Dioxide, NF, and Magnesium Stearate, NF. Storage Conditions: Frisium tablets should be stored in their original containers at room temperature, protected from light, moisture, and excessive heat. Available as a yellow, or off-white, uncoated, beveled, round tablets of 7 mm diameter, marked with 'BELL' above and below the scorebreak on the obverse and the Hoechst Tower logo on the reverse. Available as a foil blister of 30 (3 X10) tablets.

**Prophylactic use**
Frisium® (clobazam) Tablets, 10 mg

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**Prophylactic use**
NEW FROM INNOVATIVE HOECHST RESEARCH

Frisium® 10 mg (clobazam)
ANTICONVULSANT FOR ADJUNCTIVE THERAPY

EFFICACY
- Frisium is efficacious in all seizure types in both pediatric and adult patients.¹
- Frisium achieves complete control in up to 30% of refractory patients depending on seizure type.¹

SAFETY
- Adverse events are generally mild and transient.²
- Clinically significant drug interactions are uncommon.
- Impairment of alertness is less pronounced with Frisium than with other benzodiazepines.※

DOSAGE
- Daily doses up to 30 mg may be taken as a single dose at bedtime.

IN EPILEPSY

add Frisium® 10 mg (clobazam) TO ACHIEVE SEIZURE CONTROL

For brief prescribing information see page xxvi

※ Please consult precautions statement in product monograph.

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Unfortunately, some antiepileptic drugs can suppress more than seizures.

Some antiepileptic drugs such as phenytoin can impair a patient's cognitive abilities.\textsuperscript{1,2,3,4}

In contrast, Tegretol® CR (controlled release carbamazepine) has little impact on cognitive function while providing excellent seizure control.\textsuperscript{1,2,3,4}

Tegretol CR delivers more consistent blood levels than conventional Tegretol. Therefore, it can reduce the frequency of intermittent side-effects and offers a more stable pattern of cognitive functioning.\textsuperscript{5,6}

When initiating therapy, or switching therapy as medically appropriate, consider Tegretol CR. It comes in easy-to-break 200 mg and 400 mg tablets for dosage flexibility and with a convenient B.I.D. dosing schedule to enhance patient compliance.

Tegretol CR. Because the last thing an antiepileptic drug should affect is potential.