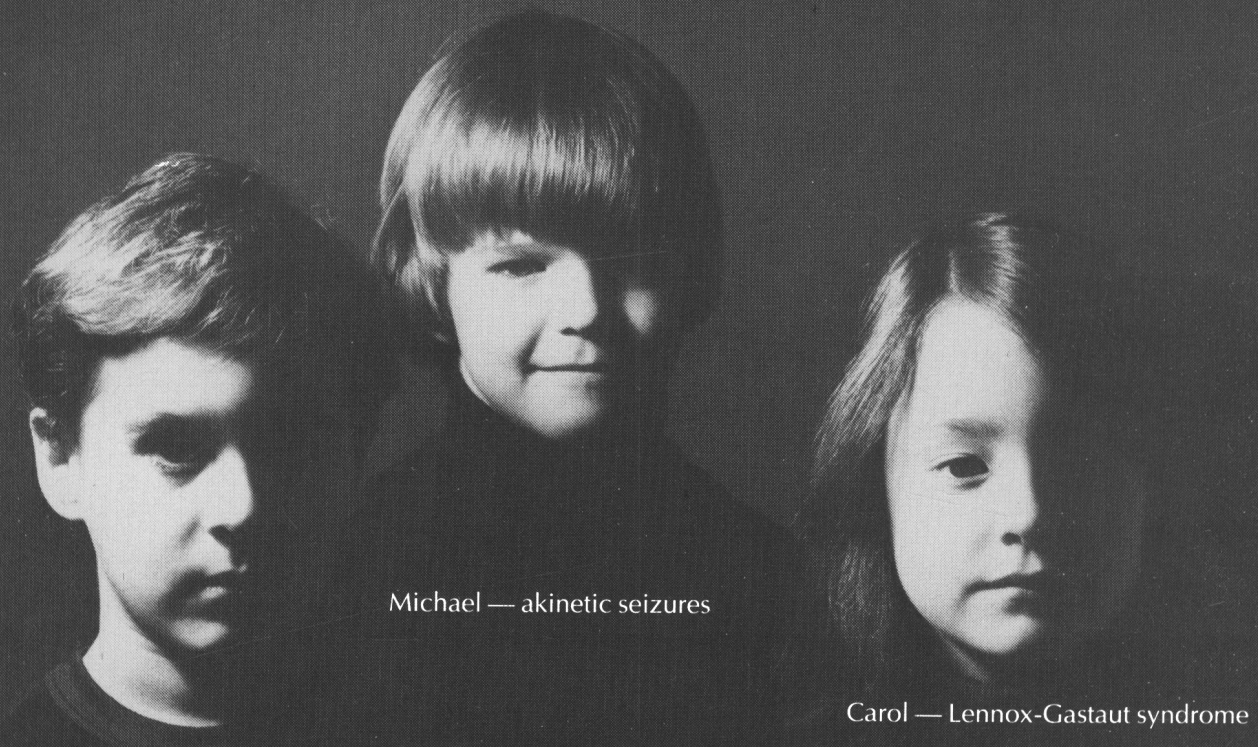
These minors are victims



Jean — myoclonic seizures

Michael — akinetic seizures

Carol — Lennox-Gastaut syndrome

These children, victims of minor motor seizures, may benefit from the many advantages offered by 'Rivotril'.

- Effective in reducing the frequency and/or severity of a variety of epileptic seizures
  - — akinetic seizures
  - — myoclonic seizures
  - — Lennox-Gastaut syndrome (petit mal variant)
  - — absence seizures (where succinimide therapy has failed)
- flexible dosage regimen encourages patient compliance
- no reports of incompatibility with a ketogenic diet
- economical, for long-term therapy
- may be used concomitantly with most other anticonvulsants

'Rivotril' has not been associated with the severe side effects seen with some other anticonvulsant medications.

- No reports of serious side effects, such as hepatotoxicity.
- Very low incidence of nausea and G.I. upsets.[1]
- No serious problems of drug interaction. (eg. ASA)
- Proven safety record in long-term administration.
- Drowsiness, which may occur, is generally dose-related and may be well controlled with proper dosage adjustment.[2,3]

ROCHE®

For Rx Summary, see page xii

Rivotril® for the victims of minor motor seizures

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Brief Prescribing Information
Tegretol® 200 mg carbamazepine

Indications and Clinical Use

A. *Trigeminal Neuralgia:*
Tegretol is indicated for the symptomatic relief of pain of trigeminal neuralgia only during periods of exacerbation of true or primary trigeminal neuralgia (tic douleureux). It should not be used preventively during periods of remission. In some patients, Tegretol has relieved glossopharyngeal neuralgia. For patients who fail to respond to Tegretol, or who are sensitive to the drug, recourse to other accepted measures must be considered.
Tegretol is not a simple analgesic and should not be used to relieve trivial facial pains or headaches.

B. *Tegretol has been found useful:*
1) in the management of psychomotor (temporal lobe) epilepsy and,
2) as an adjunct, in some patients with secondary or partial epilepsy with complex symptomatology or secondarily generalized seizures, when administered in combination with other antiepileptic medication.
3) as an alternative medication in patients with generalized tonic-clonic seizures who are experiencing marked side effects or fail to respond to other anticonvulsant drugs.
Tegretol is essentially ineffective in controlling petit mal, minor motor, myoclonic and predominantly unilateral seizures, and does not prevent the generalization of epileptic discharge.

Contraindications
Tegretol should not be administered to patients with a history of hepatic disease or serious blood disorder.
Tegretol should not be administered immediately before, in conjunction with, or immediately after a monoamine oxidase inhibitor. When it seems desirable to administer Tegretol to a patient who has been receiving an MAO inhibitor, there should be as long a drug-free interval as the clinical condition allows, but in no case should this be less than 14 days. Then the dosage of Tegretol should be low initially, and increased very gradually.
Tegretol should not be administered to patients presenting atrioventricular heart block.
Safe use in pregnancy has not been established. Therefore, Tegretol should not be administered during the first three months of pregnancy. Tegretol should not be given to women of childbearing potential unless, in the opinion of the physician, the expected benefits to the patient outweigh the possible risk to the foetus (See Reproductive Studies). Because of demonstrated toxicity in nursing animals, Tegretol should not be administered to nursing mothers.
Because of the similarity of chemical structure, Tegretol should not be administered to patients with known hypersensitivity to any of the tricyclic compounds, such as amitriptyline, trimipramine, imipramine, or their analogues or metabolites.

Warnings
Although reported infrequently, serious adverse effects have been observed during the use of Tegretol. Agranulocytosis and aplastic anemia have occurred in a few instances with a fatal outcome. Leucopenia, thrombocytopenia and hepatocellular and cholestatic jaundice have also been reported. It is, therefore, important that Tegretol should be used carefully and close clinical and frequent laboratory supervision should be maintained throughout treatment in order to detect as early as possible signs and symptoms of a possible blood dyscrasia.
Long-term toxicity studies in rats indicated a potential carcinogenic risk. Therefore, the possible risk of drug use must be weighed against the potential benefits before prescribing carbamazepine to individual patients.

Precautions
Monitoring of Haematological and Other Adverse Reactions: Complete blood studies, including platelet counts, and evaluation of hepatic and renal function and urinalysis should be carried out before treatment is instituted. Careful clinical and laboratory supervision should be maintained throughout treatment, including frequent performance of complete blood counts, in order to detect any early signs or symptoms of blood dyscrasia. Should any signs or symptoms or abnormal laboratory findings suggestive of blood dyscrasia or liver disorder occur, Tegretol should be immediately discontinued until the case is carefully reassessed.
Urinary Retention and Increased Intraocular Pressure: Because of its anticholinergic action, Tegretol should be given cautiously, if at all, to patients with increased intraocular pressure or urinary retention. Such patients should be followed closely while taking the drug.
Occurrence of Behavioural Disorders: Because it is closely related to the other tricyclic drugs, there is some possibility that Tegretol might activate a latent psychosis, or, in elderly patients, produce agitation or confusion, especially when combined with other drugs. Caution should also be exercised in alcoholics.
Use in Patients with Cardiovascular Disorders: Tegretol should be used cautiously in patients with a history of coronary artery disease, organic heart disease, or congestive failure. If a defective conductive system is suspected, an E.K.G. should be performed before administering Tegretol, in order to exclude patients with atrioventricular block.
Use in Patients taking Oral Contraceptives: In women under treatment with Tegretol, the reliability of oral contraceptives may be adversely affected; such patients should accordingly be advised to use some alternative, non-hormonal method of contraception.
Driving and operating Hazardous Machinery: Because dizziness and drowsiness are possible side effects of Tegretol, patients shoud be warned about the possible hazards of operating machinery or driving automobiles.

Adverse Reactions
The reactions which have been most frequently reported with Tegretol are drowsiness, unsteadiness on the feet, vertigo, dizziness, gastrointestinal disturbances, and nausea. These reactions usually occur only during the initial phase of therapy. They have rarely necessitated discontinuing Tegretol therapy, and can be minimized by initiating treatment at a low dosage. The more serious adverse reactions observed are the haematologic, hepatic, cardiovascular and dermatologic reactions, which require discontinuation of therapy.
The following adverse reactions have been reported:
Haematological reactions: Transitory leucopenia, eosinophilia, leucocytosis, thrombocytopenic purpura, agranulocytosis, macrocytic anemia and aplastic anemia. In a few instances, deaths have occurred.
Hepatic disturbances: During the long-term administration of Tegretol, abnormalities in liver function tests and cholestatic or hepatocellular jaundice have been observed.
Dermatological reactions: The following reactions occurred during treatment with Tegretol: skin sensitivity reactions and rashes, erythematous rashes, pruritic eruptions, urticaria, photosensitivity, pigmentary changes, neurodermatitis and in rare cases Stevens-Johnson syndrome, exfoliative dermatitis, alopecia, diaphoresis, erythema multiforme, erythema nodosum, and aggravation of disseminated lupus erythematosus.
Neurological reactions: The reactions reported as occurring during treatment with Tegretol include vertigo, somnolence, disturbances of coordination, confusion, headache, fatigue, blurred vision, transient diplopia and oculomotor disturbances, speech disturbances, abnormal involuntary movements and increase in motor seizures. In addition, peripheral neuritis and paresthesia, depression with agitation, talkativeness, nystagmus, and tinnitus have been reported but only very rarely. There have been some reports of paralysis and other symptoms of cerebral arterial insufficiency but no conclusive relationship to the administration of Tegretol could be established.
Cardiovascular systems: Recurrence of thrombophlebitis in patients with a prior history of thrombophlebitis, congestive heart failure, aggravation of hypertension, Stokes-Adams in patients with AV block, hypotension, syncope and collapse, edema, aggravation of coronary artery disease. Some of these complications (including myocardial infarction and arrhythmia) have been associated with other tricyclic compounds.
Genitourinary reactions: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, and impotence. Elevation of BUN, albuminuria and glycosuria also have been observed.
Digestive tract: Disturbances associated with Tegretol therapy have included nausea, vomiting, gastric or abdominal discomfort, diarrhoea, anorexia and dryness of the mouth and throat, glossitis and stomatitis.
Eyes: There is no conclusive evidence that Tegretol produces pathological changes in the cornea, lens or retina. However, it should be recognized that many phenothiazines and related drugs have been shown to cause eye changes. By analogy, periodic eye examinations, including slitlamp fundoscopy and tonometry, are recommended.
Other reactions reported during treatment with Tegretol include fever and chills, lymphadenopathy, aching joints and muscles, leg cramps and conjunctivitis.

Dosage and Administration
Use in Epilepsy (see Indications): A low initial daily dosage with a gradual increase in dosage is advised. Dosage should be adjusted to the needs of the individual patient.
Adults and Children over 12 years of age: Initially, 100 to 200 mg once or twice a day depending on the severity of the case and previous therapeutic history. The initial dosage is progressively increased, until the best response is obtained, up to 600 mg daily. The usual optimal dosage is 600 mg daily, but occasionally dosages up to 800 to 1000 mg have been used for short periods. As soon as disappearance of seizures has been obtained and maintained, dosage should be reduced very gradually until a minimum effective dose in reached.
Use in-trigeminal neuralgia: The initial daily dosage should be small; 200 mg, taken in two doses of 100 mg each is recommended. The total daily dosage can be increased by 200 mg per day until relief of pain is obtained. This is usually achieved at a dosage between 200 and 800 mg daily, but occasionally up to 1200 mg per day may be necessary. As soon as relief of pain has been obtained and maintained, progressive reduction in dosage should be attempted until a minimum effective dosage is reached. Because trigeminal neuralgia is characterized by periods of remission, attempts should be made to reduce or discontinue the use of Tegretol at intervals of not more than 3 months, depending upon the individual clinical course.
Prophylactic use of the drug in trigeminal neuralgia is not recommeded.
Tegretol should be taken in two or three divided doses daily, with meals whenever possible.

Dosage Forms
Tegretol is available as a 200 mg white, round, flat, bevelled-edged, double-scored tablet, imprinted with the GEIGY monogram.

Availability
Bottles of 50 and 500 tablets. Protect from heat and humidity.

Full information available on request.

See outside back cover.

PAAB
CCPP

Geigy
Dorval, Qué. H9S 1B1

G-9091

Rivotril®

Rx Summary

Indications
Alone or adjunctively in the management of myoclonic, akinetic and petit mal variant seizures. In petit mal (absence spells) when response to succinimides unsatisfactory.

Contraindications
Hypersensitivity to benzodiazepines. Clinical or biochemical evidence of significant liver disease. Narrow angle glaucoma.

Warnings
Use in pregnancy: in women who are or who may become pregnant when potential benefits warrant possible risks to mother and fetus. Mothers receiving 'Rivotril' should not breastfeed infants. Consider the risk/benefit of long-term use, particularly in children.

Precautions
Use of multiple anticonvulsants may increase CNS depression and dosage of each may need adjustment downward. Avoid abrupt withdrawal and consider substitution with another anticonvulsant during withdrawal.
May cause paradoxical increase in seizure activity or new seizure types. Concomitant use with valproic acid may produce absence status.
Caution patients against engaging in hazardous activities requiring complete mental alertness or physical coordination. Warn against concomitant use of alcohol or other CNS depressant drugs.
Monitor patients who may be prone to increasing the dosage on their own accord.
Administer with caution to patients with impaired renal function. Periodic liver function tests and blood counts may be advisable during long-term therapy.
Institute therapy with caution in patients with chronic respiratory disease because of possible hypersecretion in upper respiratory tract.

Adverse Reactions
Drowsiness has occurred in 50% and ataxia in 30% of patients but these effects have diminished with time. Behavioural problems have been noted in approximately 25% and increased salivation in 7% of patients.
Consult monograph for complete list of reported adverse reactions.

Dosage
Depends upon age and must be determined according to clinical response and tolerance.
Daily requirements should be given in 2 or 3 divided doses and if not equal, the larger dose should be given before retiring.
Children up to 10 years (30 kg): Initial dose should be 0.01 to 0.03 mg/kg/day and should not exceed 0.05 mg/kg/day. Increase dose by 0.25 to 0.5 mg every third day to maintenance dose of 0.1 to 0.2 mg/kg/day providing optimum response.
Adults: Initial dose should not exceed 1.5 mg/day. Increase dose by 0.5 to 1.0 mg every third day to maintenance dose of 8 to 10 mg/day with optimum response. Dosage in excess of 20 mg/day should be administered with caution.
Bear in mind possible increased depressant effects whenever 'Rivotril' is added to an existing anticonvulsant regimen.

Supply
Orange, cylindrical, biplane tablets with RIVOTRIL 0.5 engraved on one face, and single scored on the other with ROCHE above and C below the score, each containing 0.5 mg clonazepam.
White, cylindrical, biplane tablets with RIVOTRIL 2 engraved on one face, and single scored on the other with ROCHE above and C below the score, each containing 2 mg clonazepam.
Bottles of 100.

References
1. Shakir, R.A. et al: *Arch. Neurol.* **36**:302, May 1979.
2. Bruni, J.: *CMAJ* **120**:819, April 7, 1979.
3. Browne, T.R.: *New Eng. J. Med.* (Ed.), **299**:812-816, Oct. 1978.

Product Monograph available on request.
®Reg. Trade Mark

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Hoffmann-La Roche Limited
Vaudreuil, Québec J7V 6B3

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Can. 0048

Original Research in Medicine and Chemistry

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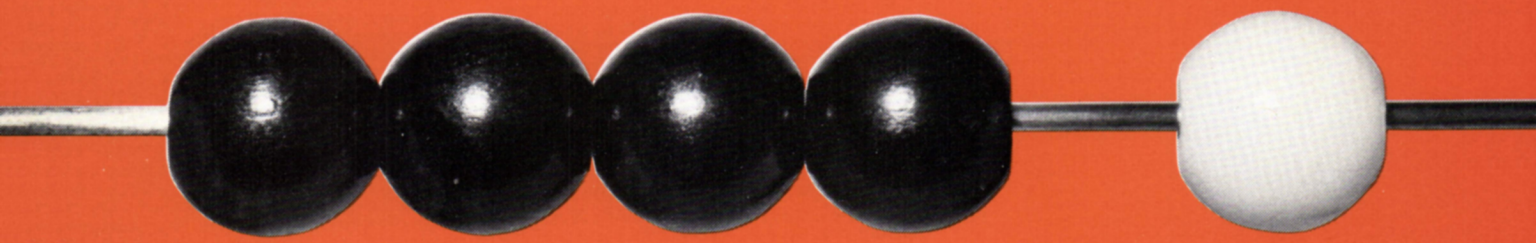
the 4:1 ratio



preferred by Parkinson patients

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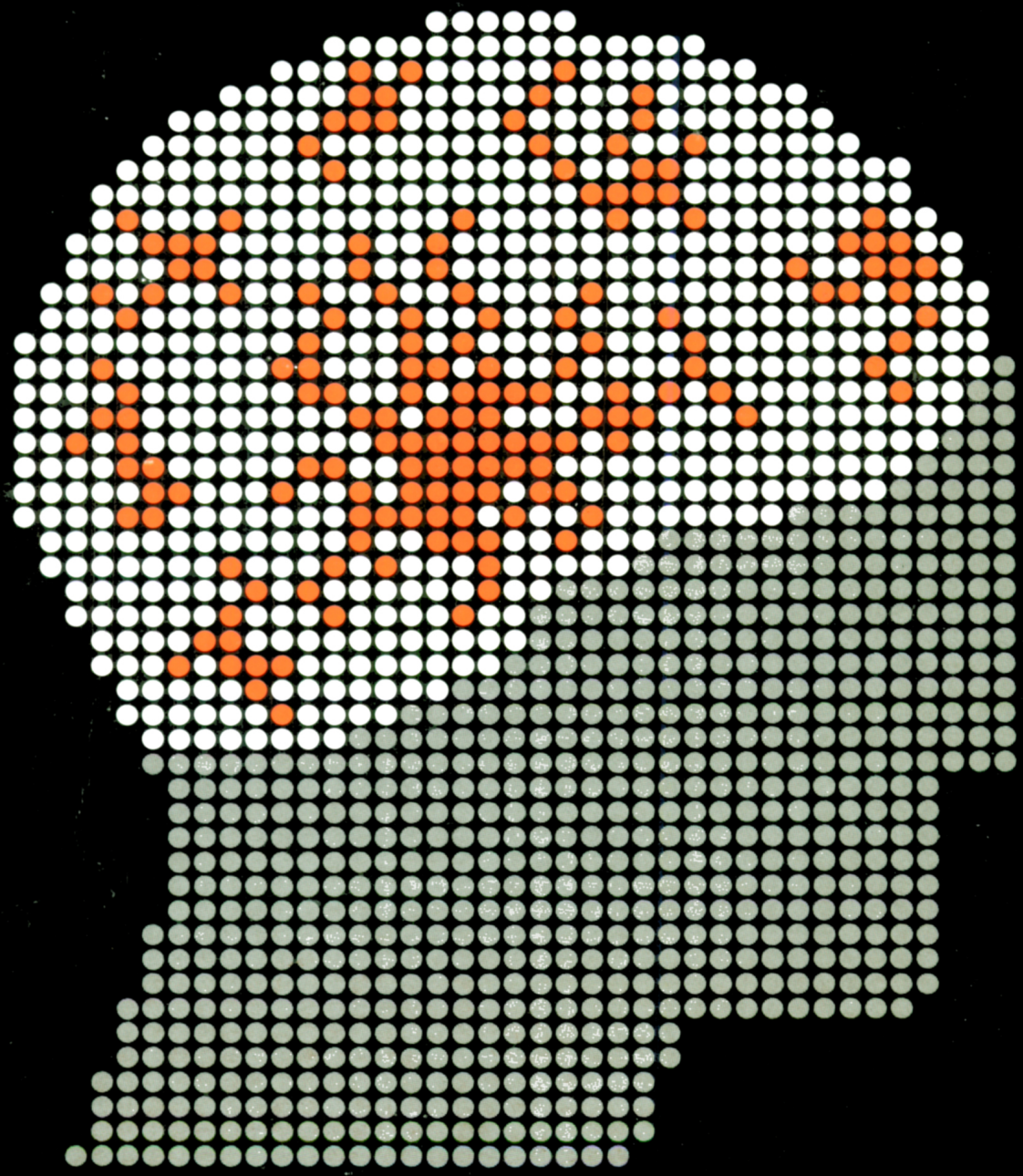
Tegretol®

carbamazepine

To help control refractory generalized tonic-clonic seizures

without excessive sedation



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Geigy

For Brief Prescribing Information see Page (xii)