

INFORMATION FOR AUTHORS

The Canadian Journal of Neurological Sciences publishes original articles in neurology, neurosurgery and basic neurosciences. Manuscripts are considered for publication with the understanding that they, or the essence of their content, have not been published elsewhere except in abstract form and are not under simultaneous consideration by another journal. Manuscripts should be submitted to:

James A. Sharpe
Editor
Canadian Journal of Neurological Sciences
P.O. Box 4220, Station "C"
Calgary, Alberta
T2T 5N1, Canada

Manuscript Preparation

Submit five high quality copies of the manuscript. Papers will be accepted in English or French. All papers should be accompanied by an abstract of 150 words or less on a separate page, preferably in both languages, although the Journal will provide the translation if required. Submit two original sets and three copies of illustrations. All manuscripts must be double spaced throughout including references and legends for illustrations. Margins of at least 25mm should be left on all sides.

For detailed instructions regarding style and layout, authors should refer to "Uniform requirements for manuscripts submitted to biomedical journals". Copies of this document may be obtained by writing to the Journal office, but the main points are summarized here. Articles should be submitted under conventional headings of "introduction", "methods and materials", "results", "discussion", but other headings and subheadings will be considered if more suitable for a particular manuscript.

A title page should identify the title of the article, authors, name of institution(s) from which the work originated and the address, telephone and fax numbers of the corresponding author. Pages of text should be numbered consecutively. Acknowledgements, including recognition of financial support should be typed on a separate page at the end of the text.

The SI system (système international d'unités) should be used in reporting all laboratory data, even if originally reported in another system. Temperatures are reported in degrees celsius. English language text may use either British or American spelling, but should be consistent throughout.

After the paper has been reviewed, the corresponding author will be requested to submit four printouts of the revised manuscript and a computer floppy disk (3 1/2" or 5 1/4" size) containing the article. Identify clearly on the disk: system - i.e.: MS dos or Macintosh; format - i.e.: saved in ASCII format; software program and version; first author's name printed on the disk.

Review Articles on selected topics are also published by the Journal. They are usually invited, but unsolicited reviews will be considered. It is recommended that authors intending to submit review articles contact the Editor in advance.

Letters to the Editor: Letters concerning matters arising in recent articles are welcome. Letters should be limited to two double-spaced pages and may include one illustration and a maximum of four references.

References

Number references in the order of their citation in the text. Those cited only in tables or in legends for illustrations are numbered according to the sequence established by the first identification in the text of a particular table or illustration. Titles of journals should be abbreviated according to the style used in Index Medicus. References should include the names of up to five authors; if there are more, cite the first three, then "et al.". Provide the full title, year of publication, volume number and inclusive pagination for journal articles. For any reference cited as "in press", five copies of the article must accompany the author's manuscript. Do not reference unpublished or "submitted" papers; these can be mentioned in the body of the text and authors must provide five copies of "submitted" manuscripts. Avoid "personal communications" and, if necessary, include them in the body of the text, not among the references. Reference citations should not include unpublished presentations or other non-accessible material. Books or chapter references should also include the place of publication and the name of the publisher. Examples of correct forms of reference follow:

Journals

Yang JF, Fung M, Edamura R, et al. H-Reflex modulation during walking in spastic paretic subjects. *Can J Neurol Sci* 1991; 18: 443-452.

Chapter in a book

McGeer PL, McGeer EG, Amino acid neurotransmitters. *In: Siegel GJ, Albers RW, Agranoff BW, Katzman R, eds. Basic Neurochemistry. Boston: Little, Brown & Co., 1981: 233-254.*

Illustrations

Submit two original sets of illustrations. Provide three additional sets for reviewers and editors; these may be prints or photocopies depending on the material to be illustrated. We will not return illustrations; therefore, authors should keep negatives for all photographs. Submit high quality glossy black and white photographs preferably 127 x 173 mm (5" x 7"). Original art work and radiographs should not be submitted. The additional cost of coloured illustration must be borne by the authors; quotations are available upon request from the Journal office. Identify each figure with a label at the back indicating top, figure number and first author. Letters and arrows applied to the figures to identify particular findings should be professional appliques suitable for publication. Photomicrographs should include a calibration bar with a scale indicated on the figure or in the legend. Legends for illustrations should be typed on a separate page from the illustrations.

Tables

Type tables double-spaced on pages separate from the text. Provide a table number and title for each. Particular care should be taken in the preparation of tables to ensure that the data are presented clearly and concisely. Each column should have a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Do not submit tables as photographs.

RENSEIGNEMENTS À L'INTENTION DES AUTEURS

Le Journal canadien des sciences neurologiques publie des articles originaux en neurologie, en neurochirurgie et en sciences neurologiques fondamentales. Les manuscrits sont pris en considération en vue de la publication à la condition qu'ils, ou leur teneur, n'aient pas été publiés ailleurs sauf sous forme de résumé, et qu'ils n'aient pas été soumis en même temps à un autre journal. Les manuscrits doivent être soumis à :

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Préparation des manuscrits

Soumettre le manuscrit en cinq exemplaires de haute qualité. Les communications sont acceptées en français ou en anglais. Elles doivent toutes être accompagnées séparément d'un résumé de 150 mots ou moins, dans les deux langues de préférence, bien que le Journal puisse au besoin fournir une traduction. Soumettre deux séries d'originaux et trois copies des illustrations. Tous les manuscrits doivent être tapés à double interligne, y compris les références et les légendes des illustrations. Les marges doivent mesurer au moins 25 mm de tous les côtés.

Pour des renseignements détaillés sur le style et la présentation, les auteurs doivent consulter le document intitulé «Règlements uniformes pour les manuscrits soumis aux journaux biomédicaux». On peut obtenir des exemplaires de ce document en s'adressant au bureau du journal, mais les points principaux sont résumés ici. Les articles doivent être soumis sous les titres conventionnels d'«introduction», de «méthodes et matériel», de «résultats», de «discussion», mais d'autres titres et sous-titres pourront être pris en considération s'ils conviennent mieux à un manuscrit en particulier.

Une page titre doit indiquer le titre de l'article, les auteurs, le nom de l'établissement ou des établissements d'où les travaux tirent leur origine, ainsi que l'adresse et les numéros de téléphone et de télécopieur de l'auteur correspondant. Les numéros de page du texte doivent se suivre. Les remerciements, y compris la reconnaissance d'un appui financier, doivent être tapés sur une page distincte à la fin du texte.

Il faut employer le système international d'unités pour mentionner toutes les données de laboratoire, même si elles ont déjà été rapportées dans un autre système. Les températures doivent être mentionnées en degrés Celsius. Les autres mesures doivent être mentionnées selon le système métrique. L'orthographe du texte peut être soit britannique, soit américaine, mais elle doit être uniforme dans tout le texte.

Après la révision de la communication, l'auteur correspondant devra soumettre quatre imprimés du manuscrit révisé et une disquette d'ordinateur (3 1/2 po ou 5 1/4 po) contenant l'article. Sur la disquette, identifier clairement le système : MS DOS ou Macintosh; le format, par exemple sauvegardé en format ASCII; le logiciel et sa version; le nom du premier auteur.

Le journal publie également des **articles de revue** sur des sujets choisis. Habituellement, ceux-ci sont sollicités, mais les revues non sollicitées seront prises en considération. On recommande aux auteurs qui ont l'intention de soumettre des articles de revue de communiquer à l'avance avec le rédacteur en chef.

Lettres au rédacteur en chef : Les lettres concernant des questions soulevées par des articles récents sont les bienvenues. Les lettres doivent se limiter à deux pages à double interligne et peuvent comprendre une illustration et un maximum de quatre références.

Références

Numéroter les références dans l'ordre selon lequel elles sont mentionnées dans le texte. Celles qui ne sont mentionnées que dans les tableaux ou les légendes des illustrations sont numérotées selon la séquence établie par la première identification d'un tableau ou d'une illustration en particulier dans le texte. Les titres des journaux doivent être abrégés selon le style utilisé dans Index Medicus. Les références doivent comprendre les noms des auteurs, à concurrence de cinq; s'il y a en plus de cinq, mentionner les trois premiers, puis indiquer «et al». Donner le titre au complet, l'année de publication, le numéro de volume et le numéro de page dans le cas des articles de journal. Pour les références mentionnées comme «sous presse», cinq exemplaires de l'article doivent accompagner le manuscrit de l'auteur. Ne pas mentionner de référence à des communications non publiées ou «soumises»; celles-ci peuvent être mentionnées dans le corps du texte et les auteurs doivent soumettre cinq exemplaires des manuscrits «soumis». Éviter les communications personnelles et, au besoin, les inclure dans le corps du texte au lieu de les mentionner dans les références. Les citations de références ne doivent pas comprendre de présentations non publiées ou d'autre documentation non accessible. Les références à des livres ou des chapitres doivent aussi comprendre le lieu d'édition et le nom de l'éditeur. Des exemples de bonnes présentations de références sont donnés ci-dessous :

Journal

Yang JF, Fung M, Edamura R, et al. H Reflex modulation during walking in spastic paretic subjects. *Can J Neurol Sci* 1991; 18: 443-452

Chapitre d'un livre

McGeer PL, McGeer EG, Amino acid neurotransmitters. In: Siegel GJ, Albers RW, Agranoff BW, Katzman R, eds. *Basic neurochemistry*. Boston: Little, Brown & Co., 1981: 233-254

Illustrations

Soumettre deux séries d'originaux des illustrations. Inclure trois séries supplémentaires pour les réviseurs et les éditeurs; celles-ci peuvent être imprimées ou photocopiées selon le sujet de l'illustration. Les illustrations ne sont pas retournées; par conséquent, les auteurs doivent conserver les négatifs de toutes les photographies. Soumettre des photographies de haute qualité, en noir et blanc sur papier brillant, de format 127 par 173 mm (5 par 7 po). Ne pas soumettre les originaux des illustrations d'artiste (cartons rigides) et des radiographies. Les frais supplémentaires d'une illustration en couleur seront à la charge de l'auteur; le bureau du journal peut donner des prix sur demande. Identifier chaque figure au moyen d'une étiquette fixée au verso, sur laquelle sont mentionnés le haut, le numéro de figure et le premier auteur. Les lettres et les flèches apposées aux figures afin d'identifier des conclusions particulières doivent être des appliqués préparés professionnellement pour la publication. Les photomicrographies doivent comporter une barre étalon dont l'échelle est mentionnée dans la figure ou la légende. Les légendes des illustrations doivent être tapées sur une page autre que celle des illustrations.

Tableaux

Taper les tableaux à double interligne sur des pages distinctes. Donner à chacun un numéro de tableau et un titre. Des soins particuliers doivent être accordés à la préparation des tableaux afin d'assurer que les données soient présentées clairement et avec concision. Chaque colonne doit porter un titre court ou abrégé. Donner les explications en note au bas de la page, pas dans le titre. Ne pas soumettre de tableau sous forme de photographie.

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IN EPILEPSY
Frisium® 10 mg
(clobazam)
TO ACHIEVE SEIZURE CONTROL

Frisium (clobazam) Tablets, 10 mg
THERAPEUTIC CLASSIFICATION Anticonvulsant for adjunctive therapy.
ACTIONS Frisium (clobazam) is a 1,5-benzodiazepine with anticonvulsant 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-physiologic 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. **CONTRAINDICATIONS** 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]. **Potential 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, diphenylhydantoin, 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 diphenylhydantoin. **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% with 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 OVERDOSSAGE 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. Respiration, 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. **DOSEAGE 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. **DOSEAGE 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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