# The Canadian Journal of Neurological Sciences

# Le Journal Canadien des Sciences Neurologiques



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The Canadian Neurological Society
The Canadian Neurosurgical Society
The Canadian Society of Clinical Neurophysiologists
The Canadian Association for Child Neurology

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Le Journal Canadien des Sciences Neurologiques

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# The Canadian Journal of Neurological Sciences

# Le Journal Canadien des Sciences Neurologiques




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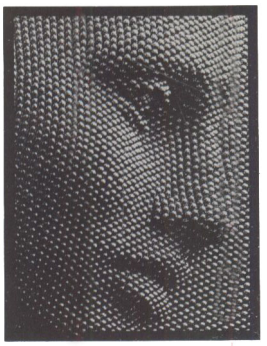

# Prescribing Information

**ACTION AND CLINICAL PHARMACOLOGY**

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

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

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

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

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

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

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

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

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

Table I: Pharmacokinetic parameters of flunarizine in healthy volunteers

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

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

**INDICATIONS AND CLINICAL USE**

SIBELIUM (flunarizine hydrochloride) is indicated in the prophylaxis of classic and common migraine. The safety of flunarizine in long-term use (i.e. for more than 4 months) has not been systematically evaluated in controlled clinical trials. Flunarizine is not indicated in the treatment of acute migraine attacks.

**CONTRAINDICATIONS**

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

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

**WARNINGS**

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

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

**PRECAUTIONS**

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

**Use in Pregnancy**

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

**Use During Lactation**

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

**Use in the Elderly**

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

**Use in Children**

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

**Use in Patients with Parkinson's Disease**

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

**Use in Depressive Patients**

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

**Endocrine Effects**

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

**Drug Interactions**

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

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

**Use in Patients with Impaired Hepatic Function**

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

**ADVERSE REACTIONS**

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

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

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

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

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

**SYMPTOMS AND TREATMENT OF OVERDOSE**

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

**DOSAGE AND ADMINISTRATION**

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

**Duration of Therapy**

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

**DOSAGE FORMS**

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

Product monograph available on request.

**REFERENCES**


**1.** Sibelium Product Monograph 1990. **2.** Amery WK et al. Flunarizine, a calcium entry blocker in migraine prophylaxis. *Headache* 1985; 25 (5): 249–54. **3.** Lucking CH et al. Flunarizine vs. propranolol in the prophylaxis of migraine: two double-blind comparative studies in more than 400 patients. *Cephalalgia* 1988; 8 (suppl 8): 21–6. **4.** Sorensen PS et al. A placebo-controlled, double-blind, cross-over trial of flunarizine in common migraine. *Cephalalgia* 1986; 6: 7–14. **5.** Steardo L et al. Prophylaxis of migraine attacks with a calcium-channel blocker: flunarizine vs. methysergide. *J Clin Pharmacol* 1986; 26: 524–8. **6.** Louis P and Spierings ELH. Comparison of flunarizine (Sibelium) and pizotifen (Sandomigran) in migraine treatment: A double-blind study. *Cephalalgia* 1982; 2: 197–203. **7.** Rascol A et al. Flunarizine versus pizotifen: a double-blind study in the prophylaxis of migraine. *Headache* 1986; 26: 83–5. **8.** Greenberg DA. Calcium channel antagonists and the treatment of migraine. *Clin Neuropharmacol* 1986; 9 (4): 311–28. **9.** Amery WK. Flunarizine, a calcium channel blocker: a new prophylactic drug in migraine. *Headache* 1983; 23: 70–4. **10.** Amery WK. Onset of action of various migraine prophylactics. *Cephalalgia* 1988; 8 (suppl 8): 11–3. **11.** Todd PA and Benfield P. Flunarizine: a reappraisal of its pharmacological properties and therapeutic use in neurological disorders. *Drugs* 1989; 38 (4): 481–99. **12.** Borgers M et al. Selective blockade of cellular $Ca^{2+}$-overload by flunarizine. *Inter Angio* 1984; 3: 25–31. **13.** Martinez-Lage JM. Flunarizine (Sibellum) in the prophylaxis of migraine. An open, long-term, multicenter trial. *Cephalalgia* 1988; 8 (suppl 8): 15–20.


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See pages iv, v

once-a-day

℞ SIBELIUM* flunarizine

Pinpoint accuracy in migraine prophylaxis.

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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 will be summarized here. Articles should be subdivided under conventional headings of "introduction", "methods and materials", "results" and "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 and telephone number of the author to whom communications should be addressed. 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.

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Poirier LJ, Filion M, Larochelle L, et al. Physipathology of experimental parkinsonism in the monkey. Can J Neurol Sci 1975; 2: 255-263.

**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.

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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. Other measurements should be reported in the metric system. English language text may use either British or American spelling, but should be consistent throughout.

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

**Letters to the Editor** are welcome. These should be limited to two double-spaced pages and may include one illustration and a maximum of four references.

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Le journal Canadien des Sciences Neurologiques publie des articles originaux dans les sciences neurologiques, cliniques et fondamentales. Les manuscrits ne sont considérés pour publication qu'à la condition expresse, à l'exception des articles de revue clairement identifiés comme tel, qu'ils n'aient pas été publiés ailleurs, sauf sous forme de résumé et qu'ils ne soient pas sous considération simultanée par un autre journal. Les *manuscrits doivent être soumis* à:

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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.

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*Le Journal publie également des* **articles de revue** *sur des sujets sélectionnés.* Ces articles sont généralement sur invitation, mais, à l'occasion, une revue non sollicitée peut être acceptée. Il serait préférable que les auteurs ayant l'intention de soumettre une telle revue contactent d'abord l'Editeur.

Nous accueillons les **lettres à l'Editeur**. Celles-ci doivent se limiter à deux pages, double interligne et peuvent contenir une seule illustration et ne doivent citer qu'un maximum de quatre références.

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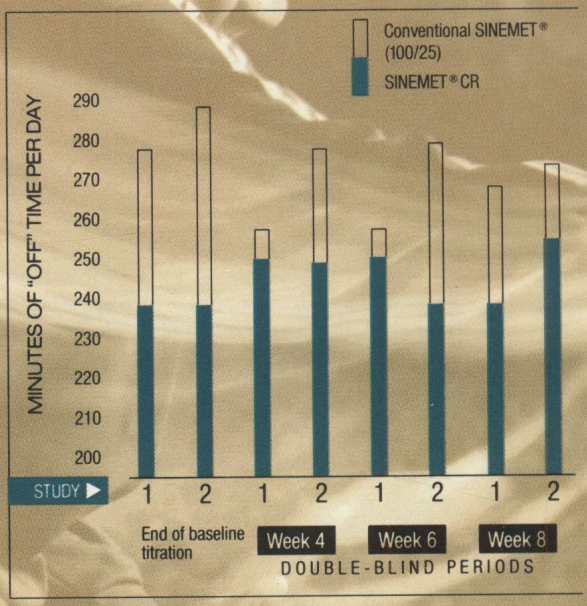


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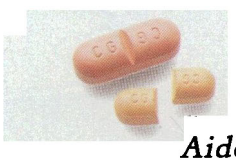

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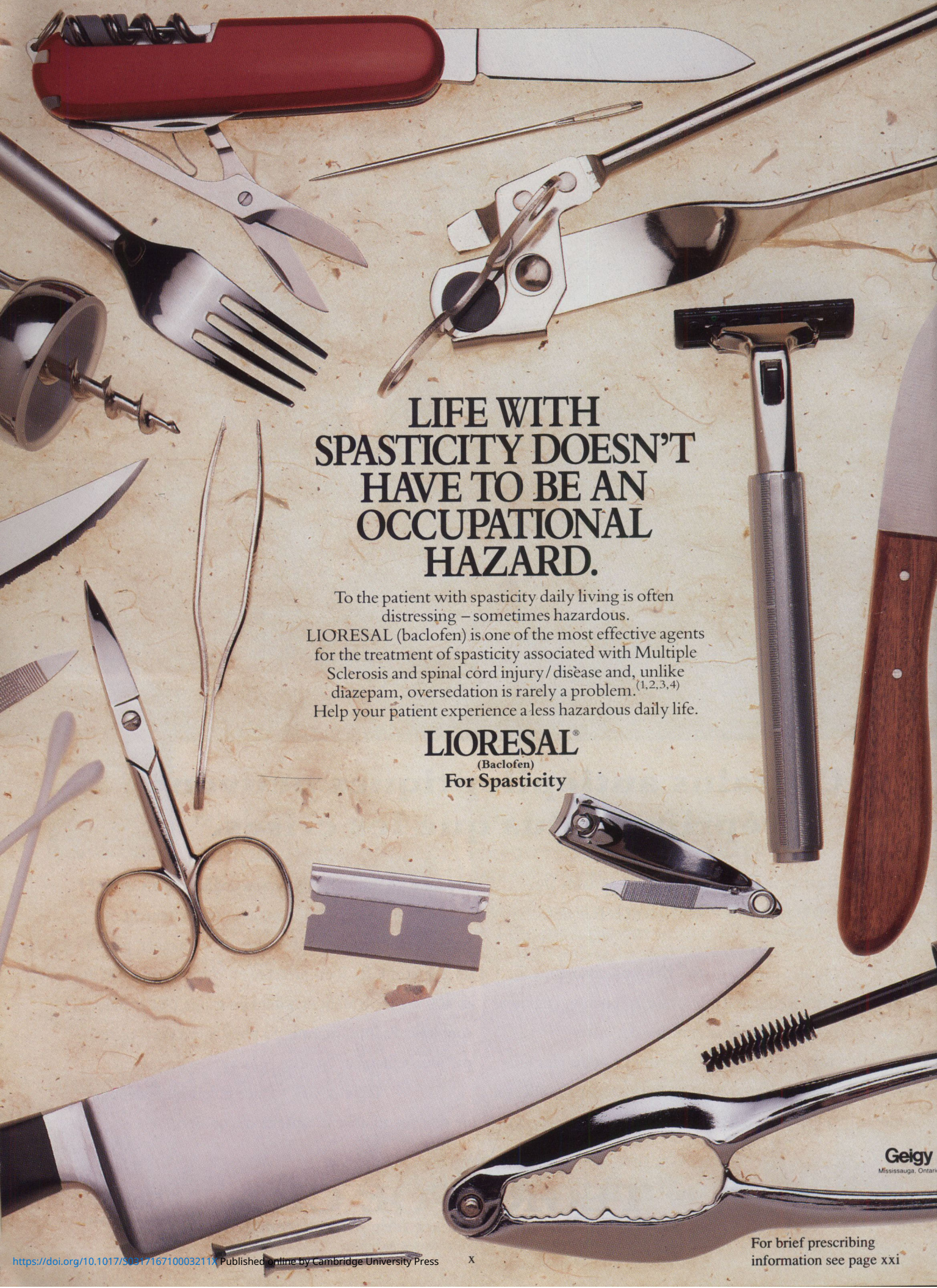


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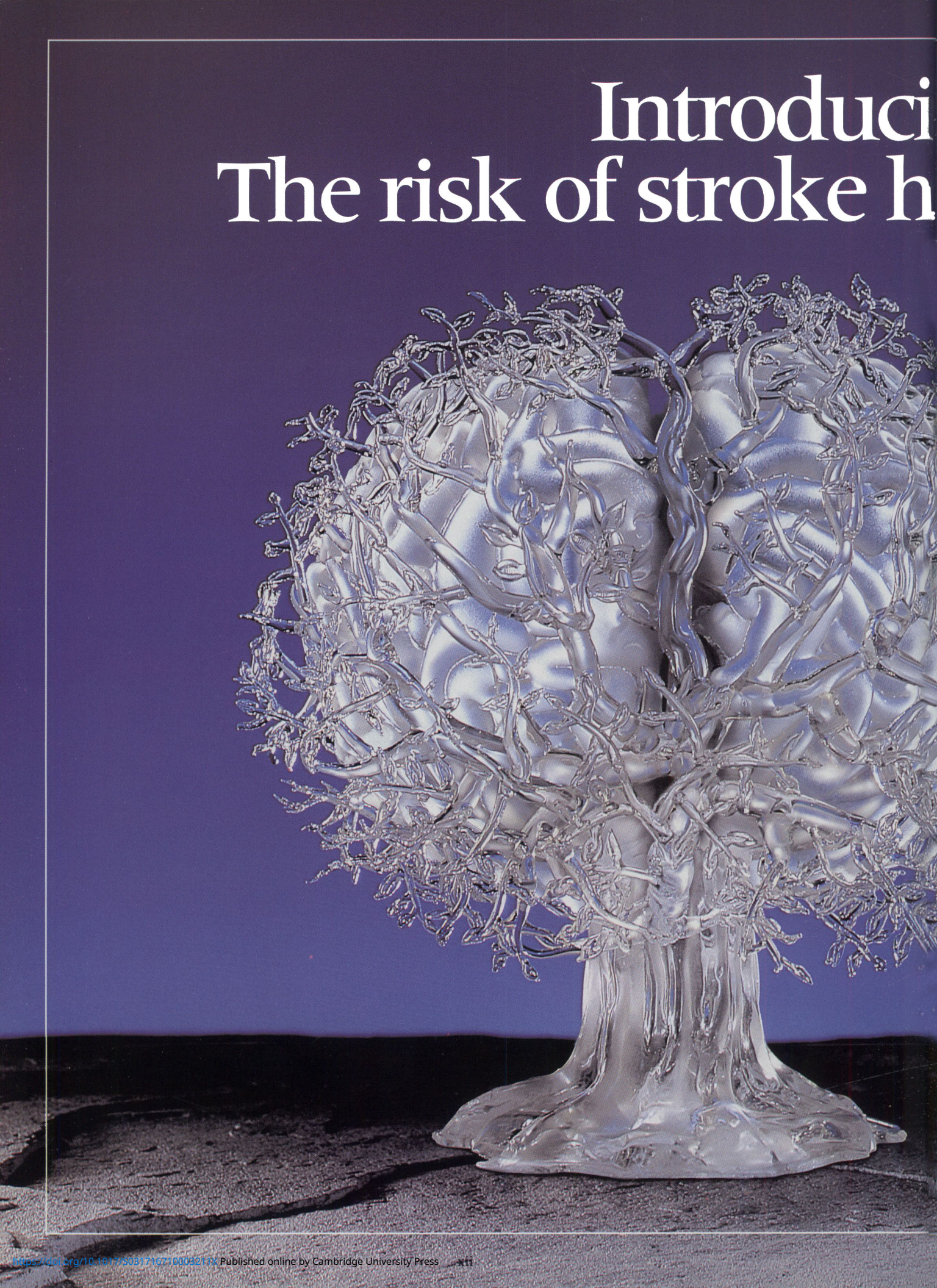
# Introduci
# The risk of stroke h



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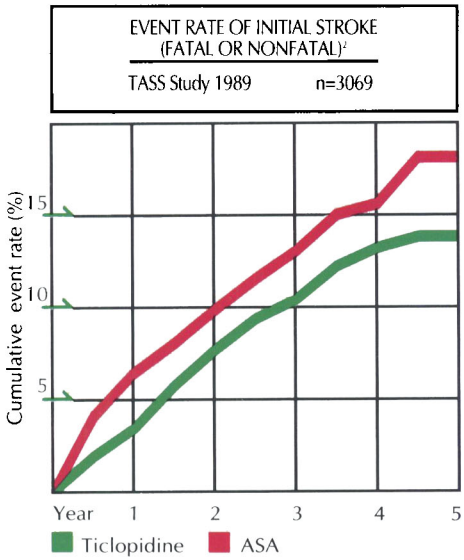
# Two landm establish the superio lowering the

## The first agent proven more effective than ASA in preventing initial stroke.

Ticlid (ticlopidine HCl) is a unique antiplatelet therapy that inhibits ADP-induced platelet-fibrinogen binding. Unlike ASA, Ticlid does not inhibit prostacyclin, thromboxane or prostaglandins.[5]

In the Ticlopidine Aspirin Stroke Study (TASS) involving 3,069 TIA and minor stroke patients, Ticlid was shown to reduce the risk of initial stroke by a considerable margin compared with ASA.[1]




TICLID REDUCED THE RISK 47.6% RELATIVE TO ASA IN THE FIRST YEAR (p=0.011)[2]

"The benefit of ticlopidine was apparent early in the first year and persisted for the entire five years of follow-up."

Ticlopidine Aspirin Stroke Study (TASS)
New England Journal of Medicine 1989

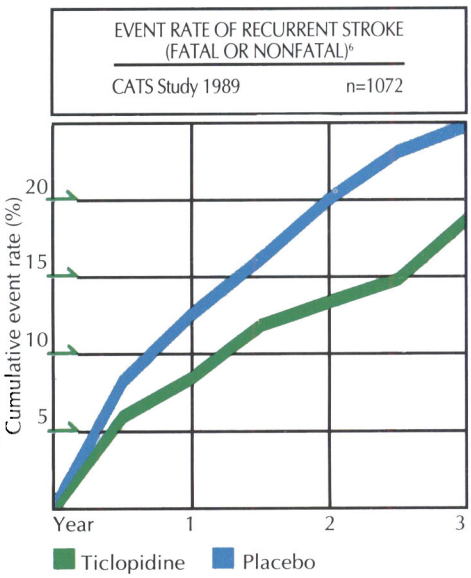
## Proven effective in preventing recurrent stroke.

In the placebo-controlled Canadian American Ticlopidine Study (CATS), 1,072 patients who had experienced a recent thromboembolic stroke were treated and observed for up to 3 years.

Over the course of the study, Ticlid was shown to reduce the risk of non-cardiogenic stroke by 34%.[6]

"...the efficacy of ticlopidine was consistent and significant for both men and women."

Canadian American Ticlopidine Study (CATS)
The Lancet 1989




TICLID REDUCED THE RISK 34% RELATIVE TO PLACEBO OVER 3 YEARS (p=0.017)[6]

## Proven safety profile

The most common side effects were generally mild, transient and occurred early in therapy.[5] Often they were resolved by a temporary dose reduction.[1]

In both studies, severe neutropenia occurred in less than 1% of Ticlid patients and only during the first 3 months of therapy. It was always reversible upon discontinuation of therapy.[1,3]

"...the benefits of ticlopidine clearly outweigh the associated risks."

Canadian American Ticlopidine Study (CATS)
The Lancet 1989

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# ark studies r efficacy of Ticlid in risk of stroke.

TICLID IS INDICATED FOR PATIENTS WHO HAVE EXPERIENCED ANY OF THE FOLLOWING EVENTS:[5]

- Transient Ischemic Attack (TIA)
- Transient Monocular Blindness (TMB)
- Reversible Ischemic Neurological Deficit (RIND)
- Minor stroke (minimal deficit, >80% recovery)
- Complete thromboembolic stroke

Blood monitoring is required every 2 weeks for the first 3 months of Ticlid therapy.

Dosage: 250 mg BID with meals

**For information on this unique stroke prevention therapy, call the Ticlid Information Hotline 1-800-263-8918.**

SYNTEX®

**Ticlid®**

The risk of stroke has never been lower.

For brief prescribing information see page xix

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For brief prescribing information see page xxiv



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