PLATELET ADHESION INHIBITOR

Persantine®
(dipyridamole)
Tablets of 25, 50 and 75 mg

Prevents thromboembolic events when used in combination with coumarin anticoagulants in cardiac valve replacement

Indicate “Medically necessary”
Protect your choice of medication

Please see brief summary of prescribing information on next page.
Brief Summary of Prescribing Information

CONTRAINDICATIONS None known.

PRECAUTIONS General Persantine® (dipyridamole USP) should be used with caution in patients with hypotension since it can produce peripheral vasoconstriction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 111 week oral study in mice and a 128-142 week oral study in rats, Persantine produced no significant carcinogenic effects at doses of 8, 25 and 75 mg/kg (1.31 and 9.4 times the maximum recommended daily human dose). Mutagenicity testing with Persantine was negative. Reproduction studies with Persantine revealed no evidence of impaired fertility in rats at dosages up to 60 times the maximum recommended human dose. A significant reduction in number of corpora lutea with consequent reduction in implantations and live fetuses was, however, observed at 155 times the maximum recommended human dose.

Teratogenic Effects PREGNANCY CATEGORY B

Reproduction studies have been performed in mice and rats at doses up to 125 mg/kg (15.6 times the maximum recommended daily human dose) and rabbits at doses up to 20 mg/kg and have revealed no evidence of harm to the fetus due to Persantine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers As dipyridamole is excreted in human milk, caution should be exercised when Persantine is administered to a nursing woman.

Pediatric Use Safety and effectiveness in children below the age of 12 years has not been established.

ADVERSE REACTIONS Adverse reactions at therapeutic doses are usually minimal and transient. On long-term use of Persantine® (dipyridamole USP) initial side effects usually disappear. The following reactions were reported in two heart valve replacement trials comparing Persantine and warfarin therapy to either warfarin alone or warfarin and placebo.

<table>
<thead>
<tr>
<th>Persantine/ Warfarin</th>
<th>Placebo/ Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 147)</td>
<td>(N = 170)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13.6%</td>
</tr>
<tr>
<td>Abdominal distress</td>
<td>6.1%</td>
</tr>
<tr>
<td>Headache</td>
<td>2.3%</td>
</tr>
<tr>
<td>Rash</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

Other reactions from uncontrolled studies include diarrhea, vomiting, flushing and pruritus. In addition, angina pectoris has been reported rarely. On those uncommon occasions when adverse reactions have been persistent or intolerable, they have ceased on withdrawal of the medication.

When Persantine was administered concomitantly with warfarin, bleeding was no greater in frequency or severity than that observed when warfarin was administered alone.

HOW SUPPLIED Persantine® (dipyridamole USP) is available as round, orange, sugar-coated tablets of 25 mg, 50 mg and 75 mg in the following package sizes:

- 25 and 50 mg Tablets: Bottles of 100 and 1000, unit dose of 100
- 75 mg Tablets: Bottles of 100 and 500, unit dose of 100

Consult package insert before prescribing.

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- Stroke and the heart
- Cerebral monitoring during neurovascular surgery
- Complications of aneurysm surgery
- Present status of carotid surgery trials
- Carotid angioplasty for stroke
- Laser angioplasty
- Advances in brain imaging
- Advances in neurovascular imaging

Organising Committee:
J.W. Norris, MD
D.W. Rowed, MD
M.J. Gawel, MD
B.K.A. Weir, MD

Scientific Committee:
H.J.M. Barnett, MD - Canada
F. Plum, MD - USA
L. Symon, MD - UK
B.K.A. Weir, MD - Canada

Deadline for abstracts:
March 1, 1990

For further information and abstract forms:
Continuing Medical Education
Faculty of Medicine
Medical Sciences Bldg.
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Toronto, Canada
M5S 1A8
(416) 978-2718

Two CEREBROVASCULAR DISEASE FELLOWSHIPS are available, one or two years, beginning July 1, 1990, in the Department of Neurology, Henry Ford Hospital. These fellowships offer comprehensive training programs in pathophysiology, diagnosis and management of cerebrovascular disorders, including migraine, within an NIH funded center for cerebrovascular disease research. A Javits Junior Clinical Investigator Fellowship is available to one competitive candidate. The department evaluates almost 600 patients with cerebrovascular disease yearly, has a stroke and migraine clinic, and a clinical/clinical research four bed acute stroke unit. Clinical and basic science research opportunities available in: in-vivo NMR spectroscopy of human and animal cerebral ischemia, 133-Xenon inhalation regional cerebral blood flow, non-invasive carotid dopplers, transcranial doppler, platelet function laboratory, HFH stroke center data bank, and experimental drug studies in stroke and migraine. Applicants should have completed an accredited neurology residency and be board eligible/certified. Salary commensurate with experience. Please send letter of inquiry to: K.M.A. Welch, M.D., Chairman, or Steven R. Levine, M.D., Director, Center for Stroke Research, Department of Neurology, Henry Ford Hospital, 2799 West Grand Blvd., Detroit, Michigan 48202-2689 (ph 313-876-3396).

NATIONAL STROKE ASSOCIATION
Announces
FELLOWSHIP AWARDS

Allied-Signal/National Stroke Association Fellowships are being offered to young investigators interested in making a career of research into the causes, mechanisms and treatment of stroke. $30,000/year stipends are available for one to three years. Applicants must have a doctoral degree and be affiliated with an institution in the United States. Application and supporting materials due by Jan. 1, 1990

For information or application write:
Research Program Coordinator
National Stroke Association
300 E. Hampden Ave, #240
Englewood, CO 80110

National Stroke Association
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Physicians and investigators are encouraged to submit abstracts on the clinical or experimental aspects of the pathogenesis, diagnosis, and medical and surgical management of vascular diseases of the brain and spinal cord. Abstracts accepted for presentation will be published in the January 1990 issue of Stroke, a journal of the American Heart Association.

Abstract deadline
September 1, 1989

Further information may be obtained through:
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National Center
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International Society for Heart Research

For further information contact:
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Scientific and Corporate Meetings
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MILES INTRODUCES

AN AGENT THAT IMPROVES NEUROLOGIC OUTCOME ASSOCIATED WITH VASOSPASM IN ANEURYSMAL SUBARACHNOID HEMORRHAGE

(Hunt and Hess Grades I-III Patients)

Color enhanced digital subtraction angiographic depiction of cerebral aneurysm.

CEREBROSELECTIVE

NIMOTOP
nimodipine/Miles
CAPSULES 30 mg

Please see references and Brief Summary of prescribing information on last page of this advertisement.
IMPROVES NEUROLOGIC OUTCOME ASSOCIATED WITH VASOSPASM BY REDUCING ISCHEMIC NEUROLOGIC DEFICITS IN ANEURYSMAL SUBARACHNOID HEMORRHAGE (Hunt and Hess Grades I-III Patients)

**SIGNIFICANT REDUCTION IN THE SEVERITY OF DELAYED ISCHEMIC DEFICITS ASSOCIATED WITH VASOSPASM IN GOOD GRADE PATIENTS**

- As demonstrated in four double-blind, randomized clinical studies involving 823 evaluable patients
- Treatment initiated within 96 hours of the event

*Two clinical trials also included patients with Hunt and Hess Grades IV-V.*

*For the side effects, please see prescribing information.

**LOW INCIDENCE OF SIDE EFFECTS AT RECOMMENDED DOSAGE REGIMEN**

- Decreased blood pressure is most common side effect, occurring in 3.8% (19/494) of patients. Carefully monitor blood pressure during therapy — see Precautions section in the prescribing information.
- Other side effects occurring at a frequency of ≥1.0% include headache, nausea, and bradycardia.
- No clinically significant effects on hematologic factors, renal or hepatic function, or carbohydrate metabolism have been causally associated with NIMOTOP.

**SIGNIFICANT INCREASE IN NUMBER OF PATIENTS WITH GOOD RECOVERY AND SIGNIFICANT DECREASE IN NUMBER OF PATIENTS WITH SEVERE DISABILITY IN NIMOTOP-TREATED PATIENTS VS. PLACEBO**

<table>
<thead>
<tr>
<th></th>
<th>NIMOTOP</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>278</td>
<td>276</td>
</tr>
<tr>
<td>Good recovery</td>
<td>199*</td>
<td>169</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>Severe disability</td>
<td>12*</td>
<td>31</td>
</tr>
<tr>
<td>Death</td>
<td>43*</td>
<td>60</td>
</tr>
</tbody>
</table>

*90% of patients in this study were Hunt and Hess Grades I-III.

*p = 0.0444 good and moderate vs. severe and death.

*p = 0.001 severe disability.

*p = 0.056 death. Effect on mortality is not yet clear.

Dose: 60 mg (two 30 mg capsules) every 4 hours within 96 hours of SAH and for 21 days.

Adapted from Pickard, et al.
HEMODYNAMIC PROFILE COMPATIBLE WITH SURGERY\textsuperscript{6}

- Minimal decreases in arterial blood pressure
- Minimal changes in heart rate

DOSAGE RECOMMENDATION\textsuperscript{6}

- NIMOTOP therapy should begin within 96 hours of the aneurysmal subarachnoid hemorrhage regardless of angiographic evidence of vasospasm

- Recommended dosage regimen is 60 mg (two 30 mg liquid-filled capsules) every 4 hours for 21 consecutive days in Hunt and Hess Grades I-III patients

- NIMOTOP can be given orally or can be administered via nasogastric tubing as described in the prescribing information

\textsuperscript{6}Please see references and Brief Summary of full prescribing information on next page.
FOR IMPROVED NEUROLOGIC OUTCOME

INDICATIONS AND USAGE

Nimotop® (nimodipine/Miles) CAPSULES
For Oral Use

Nimodipine/Miles is indicated for the improve- ment of neurological deficits due to spasm following subarachnoid hemorrhage from ruptured cerebral aneurysms and other intracranial aneurysms and in patients who are in good neurological condition post-craniotomy (e.g. Hunt and Hess Grades 3-6). Oral Nimotop® therapy should begin within 96 hours of the subarachnoid hemorrhage and continue for 21 days.

CONTRAINDICATIONS

None known

PRECAUTIONS

General: Blood Pressure Changes: Nimodipine has the hemodynamic effects expected of a calcium channel blocker, although they are generally not marked. In patients with subarachnoid hemorrhage given Nimotop® in clinical studies, about 3% were reported to have had lowering of the blood pressure and about 1% left the study because of this (not all could be attributed to nimodipine). Nevertheless, blood pressure should be carefully monitored during treatment with Nimotop® based on its known pharmacology and the known effects of calcium channel blockers.

Hepatic Disease: Nimodipine/Miles is not increased in patients with hepatic function. Such patients should have their blood pressure and pulse rate monitored closely and should be given a lower dose (see Dosage and Administration).

Laboratory Test Interactions: None known

Drug Interactions: It is possible that the cardiovascular actions of other calcium channel blockers could be enhanced by the addition of Nimotop®. In Europe, Nimotop® was observed to occasionally intensify the effects of antihypertensive compounds other than calcium channel blockers (e.g. from hyperension). This phenomenon was not observed in North American clinical trials.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study, higher incidences of neoplasms of the spine and peripheral nerve of the skin in animals treated with nimodipine/Miles were noted. In a 91-week mouse study but the high dose of 1800 ppm nimodipine in-feed (546 to 774 mg/kg/day) shortened the life expectancy of the animals. Mutagenic studies, including the Ames, rat is about 4 times the equivalent clinical dose of 60 mg q4h in a 50 kg patient.

Pregnancy: Nimodipine and/or its metabolites have been shown to appear in rat milk at about 1% left the study because of this (not all could be attributed to nimodipine). Nevertheless, blood pressure should be carefully monitored during treatment with Nimotop® based on its known pharmacology and the known effects of calcium channel blockers.

Lactation: Nimodipine/Miles is not increased in patients with hepatic function. Such patients should have their blood pressure and pulse rate monitored closely and should be given a lower dose (see Dosage and Administration).

Nursing Mothers: Nimodipine/Miles should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Nimodipine/Miles should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS

Adverse experiences were reported by 97 of 823 patients with subarachnoid hemorrhage (11.2%) who were given nimodipine. The most frequently reported adverse experience was decreased blood pressure in 4.6% of these patients. Twenty-one of 479 (6.1%) placebo treated patients also reported adverse experiences. The events reported with a frequency greater than 1% are listed below by dose.

<table>
<thead>
<tr>
<th>DOSE q4h</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nimodipine</td>
</tr>
<tr>
<td>Sign/Symptom</td>
<td>Number of Patients (%)</td>
</tr>
<tr>
<td>0.35 mg/kg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Abnormal Liver</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal Symptoms</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (1.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DOSE q4h</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nimodipine</td>
</tr>
<tr>
<td>90 mg</td>
<td>7 (0.8)</td>
</tr>
<tr>
<td>120 mg</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>

There were no other adverse experiences reported by the patients who were given 0.35 mg q4h, 30 mg q4h or 120 mg q4h. Adverse experiences with an incidence of less than 1% in the 60 mg q4h dose group were hepatitis, anemia, gastroesophageal hemorrhage, amnesia, palpitations, vomiting, flu-like manifestation, diarrhoea, nausea, hypotension, pyrexia, hyperglycemia, etc.

DIAGNOSIS

Deep vein thrombosis, as can be seen from the table, side effects that appear related to nimodipine use based on increased incidence with higher dose or a higher rate compared to placebo control, included decreased blood pressure, edema and headaches which are known pharmacologic actions of calcium channel blockers. It must be noted, however, that SAH is frequently accompanied by alterations in consciousness which lead to an under reporting of adverse experiences. Patients who received nimodipine in clinical trials for other indications reported flushing (2.1%), headache (4.1%) and fluid retention (0.6%), typical responses to calcium channel blocker, although they are generally not marked. In patients with subarachnoid hemorrhage given Nimotop® in clinical studies, about 3% were reported to have had lowering of the blood pressure and about 1% left the study because of this (not all could be attributed to nimodipine). Nevertheless, blood pressure should be carefully monitored during treatment with Nimotop® based on its known pharmacology and the known effects of calcium channel blockers.

OVERDOSAGE

There have been no reports of overdosage from the oral administration of Nimotop®. Symptoms of overdosage from Nimotop® are not known due to the short duration of the clinical studies. Nimodipine/Miles does not appear to be lethal in rodents. In animals, no lethal effects were observed up to a single oral dose of 400 mg/kg or a daily dose of 30 mg/kg/day for 29 days. Acute effects observed at intravenous doses up to 50 mg/kg in dogs included decreased blood pressure.

DOSAGE AND ADMINISTRATION

Nimotop® is given orally in the form of scored, soft gelatin 30 mg capsules for subarachnoid hemorrhage.

Intravenous Administration: Nimotop® solution should be reconstituted in a 10 mL syringe. The contents should then be emptied into the patient's naso-gastro-jejunostomy tube and washed down the tube with 30 mL of normal saline (0.9%).

Discharge should then be reduced to 30 mg every 4 hours, with close monitoring of blood pressure and heart rate.

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