

**LACHMAN CONSULTANT SERVICES, INC.**  
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

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February 16, 2001

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**OVERNIGHT COURIER 2/16/01**

Dockets Management Branch  
Food and Drug Administration (HFA-305)  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**Citizen Petition**

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act and in accordance with 21 CFR 10.30 on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug product Midodrine Hydrochloride Tablets, 10 mg, is suitable for consideration in an abbreviated new drug application (ANDA).

**A. Action Requested**

The petitioner requests that the Commissioner of the Food and Drug Administration make a determination that Midodrine Hydrochloride Tablets, 15 mg is suitable for submission as an ANDA. The reference listed drug (RLD) product upon which this petition is based is ProAmatine® Tablets 2.5 mg and 5 mg, (see Attachment I, page 3-236 of the Approved Drug Products with Therapeutic Equivalence Evaluations, 20<sup>th</sup> Edition, "The Orange Book"). Therefore, the petitioner seeks a change in strength (from 2.5 mg and 5 mg tablets to include a 10 mg tablet) from that of the listed drug product.

**B. Statement of Grounds**

The Federal Food, Drug and Cosmetic Act provides for the submission of an Abbreviated New Drug Application for a new drug that differs in strength from a listed drug, provided the FDA has approved a petition that proposed the filing of such an application. This petition involves a change in strength for the proposed drug from that of the listed drug. The RLD on which this petition is based is ProAmatine® Tablets manufactured by Nycomed Austria GmbH for Roberts Laboratories, Inc. The RLD is marketed as a tablet dosage form containing 2.5 mg or 5 mg of Midodrine Hydrochloride. The proposed drug product represents the same dosage form and route of administration as the RLD, and differs only in strength (10 mg of Midodrine Hydrochloride).

01P-0081

CPI

The proposed 10 mg drug product offers an alternate strength of Midodrine Hydrochloride Tablets for use in the treatment of symptomatic Orthostatic Hypotension (OH). The approved labeling for ProAmatine indicates a recommended dose of 10 mg, 3 times daily. The strength (10 mg) of the proposed tablet is, therefore, clearly contemplated in the approved labeling of the listed drug product.

The availability of a 10 mg dosage strength will provide more convenient dosing for most patients, as only one tablet, rather than two, would need to be ingested during each of the recommended three daily dosings. Simplifying the dosing schedule by reducing the number of tablets a patient must take will likely improve compliance and reduce the risk of inadvertent medication errors. In addition, because dosing is recommended during the daytime hours when the patient is upright and pursuing routine activities, reducing the number of tablets to be taken will certainly be more convenient.

Therefore, the petitioner's request for the Commissioner to find that a change in strength for ProAmatine (Midodrine Hydrochloride) Tablets, from 5 mg and 2.5 mg to include 10 mg tablets, should not raise questions of safety or effectiveness, and the Agency should approve the petition.

A copy of the reference listed drug labeling is included in Attachment 2. Draft labeling for the proposed product is included in Attachment 3. The proposed drug product represents the same uses, dosage and indications as those for ProAmatine Tablets.

### **C. Environmental Impact**

An environmental assessment on the action requested in this petition qualifies for a categorical exclusion under 21 CFR 25.31.

### **D. Economic Impact**

Pursuant to 21 CFR 10.30 (b), economic impact information is to be submitted only when requested by the Commissioner. Lachman Consultant Services, Inc. will promptly provide such information if so requested.

### **E. Certification**

Lachman Consultant Services, Inc. certifies that, to its best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



Robert W. Pollock  
Vice President  
Lachman Consultant Services, Inc.  
1600 Stewart Avenue, Suite 604  
Westbury, NY 11590

Attachments: Page 3-236, Approved Drug Products with Therapeutic Equivalence Evaluations, 20<sup>th</sup> Edition  
ProAmatine (Midodrine Hydrochloride) Tablets Insert Labeling  
Draft Insert Labeling for Proposed Drug Product

RP/cc

cc: G. Davis (OGD), L. Lachman (LCS)

8411046a

LACHMAN CONSULTANT SERVICES, INC.  
Westbury, NY 11590

# ATTACHMENT 1

PRESCRIPTION DRUG PRODUCT LIST

3-236

MEXILETINE HYDROCHLORIDE

CAPSULE; ORAL  
MEXILETINE HCL  
 AB WATSON LABS 250MG N74711 003  
 FEB 26, 1997  
MEXITIL  
 AB BOEHRINGER INGELHEIM 150MG N18873 002  
 DEC 30, 1985  
 AB 200MG N18873 003  
 DEC 30, 1985  
 AB + 250MG N18873 004  
 DEC 30, 1985

MEZLOCILLIN SODIUM MONOHYDRATE

INJECTABLE; INJECTION  
 MEZLIN  
 + BAYER EQ 1GM BASE/VIAL N50549 001  
 EQ 1GM BASE/VIAL N62372 005  
 JAN 13, 1983  
 + EQ 2GM BASE/VIAL N50549 002  
 EQ 2GM BASE/VIAL N62372 001  
 MAY 13, 1982  
 + EQ 3GM BASE/VIAL N50549 003  
 EQ 3GM BASE/VIAL N62372 002  
 MAY 13, 1982  
 EQ 3GM BASE/VIAL N62697 001  
 JAN 22, 1987  
 + EQ 4GM BASE/VIAL N50549 004  
 EQ 4GM BASE/VIAL N62372 003  
 MAY 13, 1982  
 EQ 4GM BASE/VIAL N62697 002  
 JAN 22, 1987  
 + EQ 20GM BASE/VIAL N50549 005  
 EQ 20GM BASE/VIAL N62372 004  
 MAR 02, 1988  
 MAR 02, 1988

MICONAZOLE NITRATE

CREAM; TOPICAL  
 MONISTAT-DERM  
 + JOHNSON AND JOHNSON 2% N17494 001  
 INSERT, CREAM; VAGINAL, TOPICAL  
 MONISTAT DUAL- PAK  
 + ADVANCED CARE PRODS 1.2GM, 2% N20968 001  
 JUN 30, 1999

MICONAZOLE NITRATE

SUPPOSITORY; VAGINAL  
MICONAZOLE NITRATE  
 AB ALPHARMA US PHARM 200MG N73508 001  
 NOV 19, 1993  
MONISTAT 3  
 AB + JOHNSON RW 200MG N18888 001  
 AUG 15, 1984

MIDAZOLAM HYDROCHLORIDE

INJECTABLE; INJECTION  
 VERSED  
 + ROCHE EQ 1MG BASE/ML N18654 002  
 MAY 26, 1987  
 + EQ 5MG BASE/ML N18654 001  
 DEC 20, 1985  
 SYRUP; ORAL  
 VERSED  
 + ROCHE EQ 2MG BASE/ML N20942 001  
 OCT 15, 1998

MIDODRINE HYDROCHLORIDE

TABLET; ORAL  
 PROAMATINE  
 ROBERTS LABS 2.5MG N19815 001  
 SEP 06, 1996  
 + 5MG N19815 002  
 SEP 06, 1996

MIGLITOL

TABLET; ORAL  
 GLYSET  
 PHARMACIA AND UPJOHN 25MG N20682 001  
 DEC 18, 1996  
 50MG N20682 002  
 DEC 18, 1996  
 + 100MG N20682 003  
 DEC 18, 1996

ATTACHMENT 1

**LACHMAN CONSULTANT SERVICES, INC.**  
Westbury, NY 11590

## **ATTACHMENT 2**

## ProAmatine Tablets (Shire US)

**WARNING:** Because ProAmatine can cause marked elevation of supine blood pressure, it should be used in patients whose lives are considerably impaired despite standard clinical care. The indication for use of ProAmatine in the treatment of symptomatic orthostatic hypotension is based primarily on a change in a surrogate marker of effectiveness, an increase in systolic blood pressure measured one minute after standing, a surrogate marker considered likely to correspond to a clinical benefit. At present, however, clinical benefits of ProAmatine, principally improved ability to carry out activities of daily living, have not been verified.

## DESCRIPTION

**Name:** ProAmatine® (midodrine hydrochloride) Tablets

**Dosage Form:** 2.5-mg and 5-mg tablets for oral administration

**Active Ingredient:** Midodrine hydrochloride, 2.5 mg or 5 mg

**Inactive Ingredients:** Microcrystalline Cellulose NF, Colloidal Silicone Dioxide NF, Magnesium Stearate NF, Corn Starch NF, Talc USP, FD&C Yellow No. 6 Lake (5-mg tablet)

**Pharmacological Classification:** Vasopressor/Antihypotensive

**Chemical Names (USAN: Midodrine Hydrochloride):** (1) Acetamide, 2-amino- *N*-[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]-monohydrochloride, (±)-; (2) (±) -2-amino- *N*-((β)-hydroxy-2,5-dimethoxyphenethyl)acetamide monohydrochloride BAN, INN, JAN: Midodrine

### Structural Formula:

**Molecular Formula:** C<sub>12</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>HCl; **Molecular Weight:** 290.7

**Organoleptic Properties:** Odorless, white, crystalline powder

**pKa:** 7.8 (0.3% aqueous solution)

**pH:** 3.5 to 5.5 (5% aqueous solution)

**Melting Range:** 200 to 203°C

## CLINICAL PHARMACOLOGY

**Mechanism of Action:** ProAmatine forms an active metabolite, desglymidodrine, that is an alpha<sub>1</sub>-agonist, and exerts its actions via activation of the alpha-adrenergic receptors of the arteriolar and venous vasculature, producing an increase in vascular tone and elevation of blood pressure. Desglymidodrine does not stimulate cardiac beta-adrenergic receptors. Desglymidodrine diffuses poorly across the blood-brain barrier, and is therefore not associated with effects on the central nervous system. Administration of ProAmatine results in a rise in standing, sitting, and supine systolic and diastolic blood pressure in patients with orthostatic hypotension of various etiologies. Standing systolic blood pressure is elevated by approximately 15 to 30 mmHg at 1 hour after a 10-mg dose of midodrine, with some effect persisting for 2 to 3 hours. ProAmatine has no clinically significant effect on standing or supine pulse rates in patients with autonomic failure.

**Pharmacokinetics:** ProAmatine is a prodrug, i.e., the therapeutic effect of orally administered midodrine is due to the major metabolite desglymidodrine, formed by deglycination of midodrine. After oral administration, ProAmatine is rapidly absorbed. The plasma levels of the prodrug peak after about half an hour, and decline with a half-life of approximately 25 minutes, while the metabolite reaches peak blood concentrations about 1 to 2 hours after a dose of midodrine and has a half-life of about 3 to 4 hours. The absolute bioavailability of midodrine (measured as desglymidodrine) is 93%. The bioavailability of desglymidodrine is not affected by food. Approximately the same amount of desglymidodrine is formed after intravenous and oral administration of midodrine. Neither midodrine nor desglymidodrine is bound to plasma proteins to any significant extent.

**Metabolism and Excretion:** Thorough metabolic studies have not been conducted, but it appears that deglycination of midodrine to desglymidodrine takes place in many tissues, and both compounds are metabolized in part by the liver. Neither midodrine nor desglymidodrine is a substrate for monoamine oxidase.

Renal elimination of midodrine is insignificant. The renal clearance of desglymidodrine is of the order of 385 mL/minute, most, about 80%, by active renal secretion. The actual mechanism of active secretion has not been studied, but it is possible that it occurs by the base-secreting pathway responsible for the secretion of several other drugs that are bases (see also **Potential for Drug Interactions**).

## Clinical Studies

Midodrine has been studied in 3 principal controlled trials, one of 3-weeks duration and 2 of 1 to 2 days duration. All studies were randomized, double-blind and parallel-design trials in patients with orthostatic hypotension of any etiology and supine-to-standing fall of systolic blood pressure of at least 15 mmHg accompanied by at least moderate dizziness/lightheadedness. Patients with pre-existing sustained supine hypertension above 180/110 mmHg were routinely excluded. In a 3-week study in 170 patients, most previously untreated with midodrine, the midodrine-treated patients (10 mg t.i.d., with the last dose not later than 6 P.M.) had significantly higher (by about 20 mmHg) 1-minute standing systolic pressure 1 hour after dosing (blood pressures were not measured at other times) for all 3 weeks. After week 1, midodrine-treated patients had small improvements in dizziness/lightheadedness/unsteadiness scores and global evaluations, but these effects were made difficult to interpret by a high early drop-out rate (about 25% vs 5% on placebo). Supine and sitting blood pressure rose 16/8 and 20/10 mmHg, respectively, on average.

In a 2-day study, after open-label midodrine, known midodrine responders received midodrine 10 mg or placebo at 0, 3, and 6 hours. One-minute standing systolic blood pressures were increased 1 hour after each dose by about 15 mmHg and 3 hours after each dose by about 12 mmHg; 3-minute standing pressures were increased also at 1, but not 3, hours after dosing. There were increases in standing time seen intermittently 1 hour after dosing, but not at 3 hours.

In a 1-day, dose-response trial, single doses of 0, 2.5, 10, and 20 mg of midodrine were given to 25 patients. The 10- and 20-mg doses produced increases in standing 1-minute systolic pressure of about 30 mmHg at 1 hour; the increase was sustained in part for 2 hours after 10 mg and 4 hours after 20 mg. Supine systolic pressure was  $\geq 200$  mmHg in 22% of patients on 10 mg and 45% of patients on 20 mg; elevated pressures often lasted 6 hours or more.

## INDICATIONS AND USAGE

ProAmatine is indicated for the treatment of symptomatic orthostatic hypotension (OH). Because ProAmatine can cause marked elevation of supine blood pressure (BP  $> 200$  mmHg systolic), it should be used in patients whose lives are considerably impaired despite standard clinical care, including non-pharmacologic treatment (such as support stockings), fluid expansion, and lifestyle alterations. The indication is based on ProAmatine's effect on increases in 1-minute standing systolic blood pressure, a surrogate marker considered likely to correspond to a clinical benefit. At present, however, clinical benefits of ProAmatine, principally improved ability to perform life activities, have not been established. Further clinical trials are underway to verify and describe the clinical benefits of ProAmatine.

After initiation of treatment, ProAmatine should be continued only for patients who report significant symptomatic improvement.

## CONTRAINDICATIONS

ProAmatine is contraindicated in patients with severe organic heart disease, acute renal disease, urinary retention, pheochromocytoma or thyrotoxicosis. ProAmatine should not be used in patients with persistent and excessive supine hypertension.

## WARNINGS

**Supine Hypertension:** The most potentially serious adverse reaction associated with ProAmatine therapy is marked elevation of supine arterial blood pressure (supine hypertension). Systolic pressure of about 200 mmHg were seen overall in about 13.4% of patients given 10 mg of ProAmatine. Systolic elevations of this degree were most likely to be observed in patients with relatively elevated pretreatment systolic blood pressures (mean 170 mmHg). There is no experience in patients with initial supine systolic pressure above 180 mmHg, as those patients were excluded from the clinical trials. Use of ProAmatine in such patients is not recommended. Sitting blood pressures were also elevated by ProAmatine therapy. It is essential to monitor supine and sitting blood pressures in patients maintained on ProAmatine.

## PRECAUTIONS

**General:** The potential for supine and sitting hypertension should be evaluated at the beginning of ProAmatine therapy. Supine hypertension can often be controlled by preventing the patient from becoming fully supine, i.e., sleeping with the head of the bed elevated. The patient should be cautioned to report symptoms of supine hypertension immediately. Symptoms may include cardiac awareness, pounding in the ears, headache, blurred vision, etc. The patient should be advised to discontinue the medication immediately if supine hypertension persists. Blood pressure should be monitored carefully when ProAmatine is used concomitantly with other agents that cause vasoconstriction, such as phenylephrine, ephedrine, dihydroergotamine, phenylpropanolamine, or pseudoephedrine. A slight slowing of the heart rate may occur after administration of ProAmatine, primarily due to vagal reflex. Caution should be exercised when ProAmatine is used concomitantly with cardiac glycosides (such as digitalis), psychopharmacologic agents, beta blockers or other agents that directly or indirectly reduce heart rate. Patients who experience any signs or symptoms suggesting bradycardia (pulse slowing, increased dizziness, syncope, cardiac awareness) should be advised to discontinue ProAmatine and should be re-evaluated.

ProAmatine should be used cautiously in patients with urinary retention problems, as desglymidodrine acts on the alpha-adrenergic receptors of the bladder neck.

ProAmatine should be used with caution in orthostatic hypotensive patients who are also diabetic, as well as those with a history of visual problems who are also taking fludrocortisone acetate, which is known to cause an increase in intraocular pressure and glaucoma.

ProAmatine use has not been studied in patients with renal impairment. Because desglymidodrine is eliminated via the kidneys, and higher blood levels would be expected in such patients. ProAmatine should be used with caution in patients with renal impairment, with a starting dose of 2.5 mg (see **DOSAGE AND ADMINISTRATION**). Renal function should be assessed prior to initial use of ProAmatine.

ProAmatine use has not been studied in patients with hepatic impairment. ProAmatine should be used with caution in patients with hepatic impairment, as the liver has a role in the metabolism of midodrine.

**Information for Patients:** Patients should be told that certain agents in over-the-counter products, such as cold remedies and diet aids, can elevate blood pressure, and therefore, should be used cautiously with ProAmatine, as they may enhance or potentiate the pressor effects of ProAmatine (see **Drug Interactions**). Patients should also be made aware of the possibility of supine hypertension. They should be told to avoid taking their dose if they are to be supine for any length of time, i.e., they should take their last daily dose of ProAmatine 3 to 4 hours before bedtime to minimize nighttime supine hypertension.

**Laboratory Tests:** Since desglymidodrine is eliminated by the kidneys and the liver has a role in its metabolism, evaluation of the patient should include assessment of renal and hepatic function prior to initiating therapy and subsequently, as appropriate.

**Drug Interactions:** When administered concomitantly with ProAmatine, cardiac glycosides may enhance or precipitate bradycardia, A.V. block or arrhythmia.

The use of drugs that stimulate alpha-adrenergic receptors (e.g., phenylephrine, pseudoephedrine, ephedrine, phenylpropanolamine or dihydroergotamine) may enhance or potentiate the pressor effects of ProAmatine. Therefore, caution should be used when ProAmatine is administered concomitantly with agents that cause vasoconstriction.

ProAmatine has been used in patients concomitantly treated with salt-retaining steroid therapy (i.e., fludrocortisone acetate), with or without salt supplementation. The potential for supine hypertension should be carefully monitored in these patients and may be minimized by either reducing the dose of fludrocortisone acetate or decreasing the salt intake prior to initiation of treatment with ProAmatine. Alpha-adrenergic blocking agents, such as prazosin, terazosin, and doxazosin, can antagonize the effects of ProAmatine.

**Potential for Drug Interactions:** It appears possible, although there is no supporting experimental evidence, that the high renal clearance of desglymidodrine (a base) is due to active tubular secretion by the base-secreting system also responsible for the secretion of such drugs as metformin, cimetidine, ranitidine, procainamide, triamterene, flecainide, and quinidine. Thus there may be a potential for drug-drug interactions with these drugs.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies have been conducted in rats and mice at dosages of 3 to 4 times the maximum recommended daily human dose on a mg/m<sup>2</sup> basis, with no indication of carcinogenic effects related to ProAmatine. Studies investigating the mutagenic potential of ProAmatine revealed no evidence of mutagenicity. Other than the dominant lethal assay in male mice, where no impairment of fertility was observed, there have been no studies on the effects of ProAmatine on fertility.

**Pregnancy: Pregnancy Category C.** ProAmatine increased the rate of embryo resorption, reduced fetal body weight in rats and rabbits, and decreased fetal survival in rabbits when given in doses 13 (rat) and 7 (rabbit) times the maximum human dose based on body surface area (mg/m<sup>2</sup>). There are no adequate and well-controlled studies in pregnant women. ProAmatine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No teratogenic effects have been observed in studies in rats and rabbits.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ProAmatine is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

## ADVERSE REACTIONS

The most frequent adverse reactions seen in controlled trials were supine and sitting hypertension; paresthesia and pruritus, mainly of the scalp; goosebumps; chills; urinary urge; urinary retention and urinary frequency. The frequency of these events in a 3-week placebo-controlled trial is shown in the following table:

Adverse Events				
	Placebo n=88		Midodrine n=82	
Event	#of reports	% of patients	#of reports	% of patients
Total # of reports	22		77	
Paresthesia <sup>1</sup>	4	4.5	15	18.3
Piloerection	0	0	11	13.4
Dysuria <sup>2</sup>	0	0	11	13.4
Pruritus <sup>2</sup>	2	2.3	10	12.2
Supine hypertension <sup>4</sup>	0	0	6	7.3
Chills	0	0	4	4.9
Pain <sup>2</sup>	0	0	4	4.9
Rash	1	1.1	2	2.4
<sup>1</sup> Includes hyperesthesia and scalp paresthesia				
<sup>2</sup> Includes dysuria (1), increased urinary frequency (2), impaired urination (1), urinary retention (5), urinary urgency (2)				

<sup>b</sup> Includes scalp pruritis

<sup>a</sup> Includes patients who experienced an increase in supine hypertension

<sup>b</sup> Includes abdominal pain and pain increase

Less frequent adverse reactions were headache; feeling of pressure/fullness in the head; vasodilation/flushing face; confusion/thinking abnormality; dry mouth; nervousness/anxiety and rash. Other adverse reactions that occurred rarely were visual field defect; dizziness; skin hyperesthesia; insomnia; somnolence; erythema multiforme; canker sore; dry skin; dysuria; impaired urination; asthenia; backache; pyrosis; nausea; gastrointestinal distress; flatulence and leg cramps.

The most potentially serious adverse reaction associated with ProAmatine therapy is supine hypertension. The feelings of paresthesia, pruritus, piloerection and chills are pilomotor reactions associated with the action of midodrine on the alpha-adrenergic receptors of the hair follicles. Feelings of urinary urgency, retention and frequency are associated with the action of midodrine on the alpha-receptors of the bladder neck.

## OVERDOSAGE

Symptoms of overdose could include hypertension, piloerection (goosebumps), a sensation of coldness and urinary retention. There are 2 reported cases of overdose with ProAmatine, both in young males. One patient ingested ProAmatine drops, 250 mg, experienced systolic blood pressure of greater than 200 mmHg, was treated with an IV injection of 20 mg of phentolamine, and was discharged the same night without any complaints. The other patient ingested 205 mg of ProAmatine (41 5-mg tablets), and was found lethargic and unable to talk, unresponsive to voice but responsive to painful stimuli, hypertensive and bradycardic. Gastric lavage was performed, and the patient recovered fully by the next day without sequelae.

The single doses that would be associated with symptoms of overdose or would be potentially life-threatening are unknown. The oral LD<sub>50</sub> is approximately 30 to 50 mg/kg in rats, 675 mg/kg in mice, and 125 to 160 mg/kg in dogs. Desglymidodrine is dialyzable.

Recommended general treatment, based on the pharmacology of the drug, includes induced emesis and administration of alpha-sympatholytic drugs (e.g., phentolamine).

## DOSAGE AND ADMINISTRATION

The recommended dose of ProAmatine is 10 mg, 3 times daily. Dosing should take place during the daytime hours when the patient needs to be upright, pursuing the activities of daily life. A suggested dosing schedule of approximately 4-hour intervals is as follows: shortly before or upon arising in the morning, midday, and late afternoon (not later than 6 P.M.). Doses may be given in 3-hour intervals, if required, to control symptoms, but not more frequently. Single doses as high as 20 mg have been given to patients, but severe and persistent systolic supine hypertension occurs at a high rate (about 45%) at this dose. In order to reduce the potential for supine hypertension during sleep, ProAmatine should not be given after the evening meal or less than 4 hours before bedtime. Total daily doses greater than 30 mg have been tolerated by some patients, but their safety and usefulness have not been studied systematically or established. Because of the risk of supine hypertension, ProAmatine should be continued only in patients who appear to attain symptomatic improvement during initial treatment.

The supine and standing blood pressure should be monitored regularly, and the administration of ProAmatine should be stopped if supine blood pressure increases excessively.

Because desglymidodrine is excreted renally, dosing in patients with abnormal renal function should be cautious; although this has not been systematically studied, it is recommended that treatment of these patients be initiated using 2.5-mg doses.

Dosing in children has not been adequately studied.

Blood levels of midodrine and desglymidodrine were similar when comparing levels in patients 65 or older vs. younger than 65 and when comparing males vs. females, suggesting dose modifications for these groups are not necessary.

## HOW SUPPLIED

ProAmatine is supplied as 2.5-mg and 5-mg tablets for oral administration. The 2.5-mg tablet is white, round, and biplanar, with a bevelled edge, and is scored on 1 side with "RPC" above and "2.5" below the score, and "003" on the other side. The 5-mg tablet is orange, round, and biplanar, with a bevelled edge, and is scored on 1 side with "RPC" above and "5" below the score, and "004" on the other side.

2.5-milligram Tablets: NDC 54092-003-01	Bottle of 100
5-milligram Tablets: NDC 54092-004-01	Bottle of 100

Store from 15°C to 25°C (59°F to 77°F).

Rx only

### ROBERTS® PHARMACEUTICALS

Manufactured by NYCOMED Austria GmbH

for Roberts Laboratories Inc.,

a subsidiary of ROBERTS PHARMACEUTICAL CORPORATION, Eatontown, NJ 07724-2274, USA

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**ATTACHMENT 3**

## Midodrine Hydrochloride Tablets

**WARNING:** Because Midodrine Hydrochloride can cause marked elevation of supine blood pressure, it should be used in patients whose lives are considerably impaired despite standard clinical care. The indication for use of Midodrine Hydrochloride in the treatment of symptomatic orthostatic hypotension is based primarily on a change in a surrogate marker of effectiveness, an increase in systolic blood pressure measured one minute after standing, a surrogate marker considered likely to correspond to a clinical benefit. At present, however, clinical benefits of Midodrine Hydrochloride, principally improved ability to carry out activities of daily living, have not been verified.

## DESCRIPTION

**Name:** Midodrine Hydrochloride Tablets

**Dosage Form:** 2.5-mg, 5-mg, and 10 mg tablets for oral administration

**Active Ingredient:** Midodrine hydrochloride, 2.5 mg, 5 mg, or 10 mg

**Inactive Ingredients:** To be listed.

**Pharmacological Classification:** Vasopressor/Antihypotensive

**Chemical Names (USAN: Midodrine Hydrochloride):** (1) Acetamide, 2-amino- *N*-[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]-monohydrochloride, (±)-; (2) (±) -2-amino- *N*-((β)-hydroxy-2,5-dimethoxyphenethyl)acetamide monohydrochloride BAN, INN, JAN: Midodrine

**Structural Formula:**

**Molecular Formula:** C<sub>12</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>HCl; **Molecular Weight:** 290.7

**Organoleptic Properties:** Odorless, white, crystalline powder

**pKa:** 7.8 (0.3% aqueous solution)

**pH:** 3.5 to 5.5 (5% aqueous solution)

**Melting Range:** 200 to 203°C

## CLINICAL PHARMACOLOGY

**Mechanism of Action:** Midodrine Hydrochloride forms an active metabolite, desglymidodrine, that is an alpha<sub>1</sub>-agonist, and exerts its actions via activation of the alpha-adrenergic receptors of the arteriolar and venous vasculature, producing an increase in vascular tone and elevation of blood pressure. Desglymidodrine does not stimulate cardiac beta-adrenergic receptors. Desglymidodrine diffuses poorly across the blood-brain barrier, and is therefore not associated with effects on the central nervous system. Administration of Midodrine Hydrochloride results in a rise in standing, sitting, and supine systolic and diastolic blood pressure in patients with orthostatic hypotension of various etiologies. Standing systolic blood pressure is elevated by approximately 15 to 30 mmHg at 1 hour after a 10-mg dose of midodrine, with some effect persisting for 2 to 3 hours. Midodrine Hydrochloride has no clinically significant effect on standing or supine pulse rates in patients with autonomic failure.

**Pharmacokinetics:** Midodrine Hydrochloride is a prodrug, i.e., the therapeutic effect of orally administered midodrine is due to the major metabolite desglymidodrine, formed by deglycination of midodrine. After oral administration, Midodrine Hydrochloride is rapidly absorbed. The plasma levels of the prodrug peak after about half an hour, and decline with a half-life of approximately 25 minutes, while the metabolite reaches peak blood concentrations about 1 to 2 hours after a dose of midodrine and has a half-life of about 3 to 4 hours. The absolute bioavailability of midodrine (measured as desglymidodrine) is 93%. The bioavailability of desglymidodrine is not affected by food. Approximately the same amount of desglymidodrine is formed after intravenous and oral

administration of midodrine. Neither midodrine nor desglymidodrine is bound to plasma proteins to any significant extent.

**Metabolism and Excretion:** Thorough metabolic studies have not been conducted, but it appears that deglycination of midodrine to desglymidodrine takes place in many tissues, and both compounds are metabolized in part by the liver. Neither midodrine nor desglymidodrine is a substrate for monoamine oxidase.

Renal elimination of midodrine is insignificant. The renal clearance of desglymidodrine is of the order of 385 mL/minute, most, about 80%, by active renal secretion. The actual mechanism of active secretion has not been studied, but it is possible that it occurs by the base-secreting pathway responsible for the secretion of several other drugs that are bases (see also **Potential for Drug Interactions**).

## Clinical Studies

Midodrine has been studied in 3 principal controlled trials, one of 3-weeks duration and 2 of 1 to 2 days duration. All studies were randomized, double-blind and parallel-design trials in patients with orthostatic hypotension of any etiology and supine-to-standing fall of systolic blood pressure of at least 15 mmHg accompanied by at least moderate dizziness/lightheadedness. Patients with pre-existing sustained supine hypertension above 180/110 mmHg were routinely excluded. In a 3-week study in 170 patients, most previously untreated with midodrine, the midodrine-treated patients (10 mg t.i.d., with the last dose not later than 6 P.M.) had significantly higher (by about 20 mmHg) 1-minute standing systolic pressure 1 hour after dosing (blood pressures were not measured at other times) for all 3 weeks. After week 1, midodrine-treated patients had small improvements in dizziness/lightheadedness/unsteadiness scores and global evaluations, but these effects were made difficult to interpret by a high early drop-out rate (about 25% vs 5% on placebo). Supine and sitting blood pressure rose 16/8 and 20/10 mmHg, respectively, on average.

In a 2-day study, after open-label midodrine, known midodrine responders received midodrine 10 mg or placebo at 0, 3, and 6 hours. One-minute standing systolic blood pressures were increased 1 hour after each dose by about 15 mmHg and 3 hours after each dose by about 12 mmHg; 3-minute standing pressures were increased also at 1, but not 3, hours after dosing. There were increases in standing time seen intermittently 1 hour after dosing, but not at 3 hours.

In a 1-day, dose-response trial, single doses of 0, 2.5, 10, and 20 mg of midodrine were given to 25 patients. The 10- and 20-mg doses produced increases in standing 1-minute systolic pressure of about 30 mmHg at 1 hour; the increase was sustained in part for 2 hours after 10 mg and 4 hours after 20 mg. Supine systolic pressure was  $\geq 200$  mmHg in 22% of patients on 10 mg and 45% of patients on 20 mg; elevated pressures often lasted 6 hours or more.

## INDICATIONS AND USAGE

Midodrine Hydrochloride is indicated for the treatment of symptomatic orthostatic hypotension (OH). Because Midodrine Hydrochloride can cause marked elevation of supine blood pressure (BP  $> 200$  mmHg systolic), it should be used in patients whose lives are considerably impaired despite standard clinical care, including non-pharmacologic treatment (such as support stockings), fluid expansion, and lifestyle alterations. The indication is based on Midodrine Hydrochloride's effect on increases in 1-minute standing systolic blood pressure, a surrogate marker considered likely to correspond to a clinical benefit. At present, however, clinical benefits of Midodrine Hydrochloride, principally improved ability to perform life activities, have not been established. Further clinical trials are underway to verify and describe the clinical benefits of Midodrine Hydrochloride.

After initiation of treatment, Midodrine Hydrochloride should be continued only for patients who report significant symptomatic improvement.

## CONTRAINDICATIONS

Midodrine Hydrochloride is contraindicated in patients with severe organic heart disease, acute renal disease, urinary retention, pheochromocytoma or thyrotoxicosis. Midodrine Hydrochloride should not be used in patients with persistent and excessive supine hypertension.

## WARNINGS

**Supine Hypertension:** The most potentially serious adverse reaction associated with Midodrine Hydrochloride therapy is marked elevation of supine arterial blood pressure (supine hypertension). Systolic pressure of about 200 mmHg were seen overall in about 13.4% of patients given 10 mg of Midodrine Hydrochloride. Systolic elevations of this degree were most likely to be observed in patients with relatively elevated pretreatment systolic blood pressures (mean 170 mmHg). There is no experience in patients with initial supine systolic pressure above 180 mmHg, as those patients were excluded from the clinical trials. Use of Midodrine Hydrochloride in such patients is not recommended. Sitting blood pressures were also elevated by Midodrine Hydrochloride therapy. It is essential to monitor supine and sitting blood pressures in patients maintained on Midodrine Hydrochloride.

## PRECAUTIONS

**General:** The potential for supine and sitting hypertension should be evaluated at the beginning of Midodrine Hydrochloride therapy. Supine hypertension can often be controlled by preventing the patient from becoming fully supine, i.e., sleeping with the head of the bed elevated. The patient should be cautioned to report symptoms of supine hypertension immediately. Symptoms may include cardiac awareness, pounding in the ears, headache, blurred vision, etc. The patient should be advised to discontinue the medication immediately if supine hypertension persists. Blood pressure should be monitored carefully when Midodrine Hydrochloride is used concomitantly with other agents that cause vasoconstriction, such as phenylephrine, ephedrine, dihydroergotamine, phenylpropanolamine, or pseudoephedrine.

A slight slowing of the heart rate may occur after administration of Midodrine Hydrochloride, primarily due to vagal reflex. Caution should be exercised when Midodrine Hydrochloride is used concomitantly with cardiac glycosides (such as digitalis), psychopharmacologic agents, beta blockers or other agents that directly or indirectly reduce heart rate. Patients who experience any signs or symptoms suggesting bradycardia (pulse slowing, increased dizziness, syncope, cardiac awareness) should be advised to discontinue Midodrine Hydrochloride and should be re-evaluated. Midodrine Hydrochloride should be used cautiously in patients with urinary retention problems, as desglymidodrine acts on the alpha-adrenergic receptors of the bladder neck.

Midodrine Hydrochloride should be used with caution in orthostatic hypotensive patients who are also diabetic, as well as those with a history of visual problems who are also taking fludrocortisone acetate, which is known to cause an increase in intraocular pressure and glaucoma.

Midodrine Hydrochloride use has not been studied in patients with renal impairment. Because desglymidodrine is eliminated via the kidneys, and higher blood levels would be expected in such patients. Midodrine Hydrochloride should be used with caution in patients with renal impairment, with a starting dose of 2.5 mg (see **DOSAGE AND ADMINISTRATION** ). Renal function should be assessed prior to initial use of Midodrine Hydrochloride.

Midodrine Hydrochloride use has not been studied in patients with hepatic impairment. Midodrine Hydrochloride should be used with caution in patients with hepatic impairment, as the liver has a role in the metabolism of midodrine.

**Information for Patients:** Patients should be told that certain agents in over-the-counter products, such as cold remedies and diet aids, can elevate blood pressure, and therefore, should be used cautiously with Midodrine Hydrochloride, as they may enhance or potentiate the pressor effects of Midodrine Hydrochloride (see **Drug Interactions** ). Patients should also be made aware of the possibility of supine hypertension. They should be told to avoid taking their dose if they are to be supine for any length of time, i.e., they should take their last daily dose of Midodrine Hydrochloride 3 to 4 hours before bedtime to minimize nighttime supine hypertension.

**Laboratory Tests:** Since desglymidodrine is eliminated by the kidneys and the liver has a role in its metabolism, evaluation of the patient should include assessment of renal and hepatic function prior to initiating therapy and subsequently, as appropriate.

**Drug Interactions:** When administered concomitantly with Midodrine Hydrochloride, cardiac glycosides may enhance or precipitate bradycardia, A.V. block or arrhythmia.

The use of drugs that stimulate alpha-adrenergic receptors (e.g., phenylephrine, pseudoephedrine, ephedrine, phenylpropanolamine or dihydroergotamine) may enhance or potentiate the pressor effects of Midodrine Hydrochloride. Therefore, caution should be used when Midodrine Hydrochloride is administered concomitantly with agents that cause vasoconstriction.

Midodrine Hydrochloride has been used in patients concomitantly treated with salt-retaining steroid therapy (i.e., fludrocortisone acetate), with or without salt supplementation. The potential for supine hypertension should be carefully monitored in these patients and may be minimized by either reducing the dose of fludrocortisone acetate or decreasing the salt intake prior to initiation of treatment with Midodrine Hydrochloride. Alpha-adrenergic blocking agents, such as prazosin, terazosin, and doxazosin, can antagonize the effects of Midodrine Hydrochloride.

**Potential for Drug Interactions:** It appears possible, although there is no supporting experimental evidence, that the high renal clearance of desglymidodrine (a base) is due to active tubular secretion by the base-secreting system also responsible for the secretion of such drugs as metformin, cimetidine, ranitidine, procainamide, triamterene, flecainide, and quinidine. Thus there may be a potential for drug-drug interactions with these drugs.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies have been conducted in rats and mice at dosages of 3 to 4 times the maximum recommended daily human dose on a mg/m<sup>2</sup> basis, with no indication of carcinogenic effects related to Midodrine Hydrochloride. Studies investigating the mutagenic potential of Midodrine Hydrochloride revealed no evidence of mutagenicity. Other than the dominant lethal assay in male mice, where no impairment of fertility was observed, there have been no studies on the effects of Midodrine Hydrochloride on fertility.

**Pregnancy:** *Pregnancy Category C.* Midodrine Hydrochloride increased the rate of embryo resorption, reduced fetal body weight in rats and rabbits, and decreased fetal survival in rabbits when given in doses 13 (rat) and 7 (rabbit) times the maximum human dose based on body surface area (mg/m<sup>2</sup>). There are no adequate and well-controlled studies in pregnant women. Midodrine Hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No teratogenic effects have been observed in studies in rats and rabbits.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Midodrine Hydrochloride is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

## ADVERSE REACTIONS

The most frequent adverse reactions seen in controlled trials were supine and sitting hypertension; paresthesia and pruritus, mainly of the scalp; goosebumps; chills; urinary urge; urinary retention and urinary frequency. The frequency of these events in a 3-week placebo-controlled trial is shown in the following table:

Adverse Events				
Event	Placebo n=88		Midodrine n=82	
	#of reports	% of patients	#of reports	% of patients
Total # of reports	22		77	
Paresthesia <sup>1</sup>	4	4.5	15	18.3
Piloerection	0	0	11	13.4
Dysuria <sup>2</sup>	0	0	11	13.4
Pruritus <sup>3</sup>	2	2.3	10	12.2
Supine hypertension <sup>4</sup>	0	0	6	7.3
Chills	0	0	4	4.9

Pain <sup>2</sup>	0	0	4	4.9
Rash	1	1.1	2	2.4
<sup>1</sup> Includes hyperesthesia and scalp paresthesia				
<sup>2</sup> Includes dysuria (1), increased urinary frequency (2), impaired urination (1), urinary retention (5), urinary urgency (2)				
<sup>3</sup> Includes scalp pruritis				
<sup>4</sup> Includes patients who experienced an increase in supine hypertension				
<sup>5</sup> Includes abdominal pain and pain increase				

Less frequent adverse reactions were headache; feeling of pressure/fullness in the head; vasodilation/flushing face; confusion/thinking abnormality; dry mouth; nervousness/anxiety and rash. Other adverse reactions that occurred rarely were visual field defect; dizziness; skin hyperesthesia; insomnia; somnolence; erythema multiforme; canker sore; dry skin; dysuria; impaired urination; asthenia; backache; pyrosis; nausea; gastrointestinal distress; flatulence and leg cramps.

The most potentially serious adverse reaction associated with Midodrine Hydrochloride therapy is supine hypertension. The feelings of paresthesia, pruritus, piloerection and chills are pilomotor reactions associated with the action of midodrine on the alpha-adrenergic receptors of the hair follicles. Feelings of urinary urgency, retention and frequency are associated with the action of midodrine on the alpha-receptors of the bladder neck.

## OVERDOSAGE

Symptoms of overdose could include hypertension, piloerection (goosebumps), a sensation of coldness and urinary retention. There are 2 reported cases of overdose with Midodrine Hydrochloride, both in young males. One patient ingested Midodrine Hydrochloride drops, 250 mg, experienced systolic blood pressure of greater than 200 mmHg, was treated with an IV injection of 20 mg of phentolamine, and was discharged the same night without any complaints. The other patient ingested 205 mg of Midodrine Hydrochloride (41 5-mg tablets), and was found lethargic and unable to talk, unresponsive to voice but responsive to painful stimuli, hypertensive and bradycardic. Gastric lavage was performed, and the patient recovered fully by the next day without sequelae.

The single doses that would be associated with symptoms of overdose or would be potentially life-threatening are unknown. The oral LD<sub>50</sub> is approximately 30 to 50 mg/kg in rats, 675 mg/kg in mice, and 125 to 160 mg/kg in dogs. Desglymidodrine is dialyzable.

Recommended general treatment, based on the pharmacology of the drug, includes induced emesis and administration of alpha-sympatholytic drugs (e.g., phentolamine).

## DOSAGE AND ADMINISTRATION

The recommended dose of Midodrine Hydrochloride is 10 mg, 3 times daily. Dosing should take place during the daytime hours when the patient needs to be upright, pursuing the activities of daily life. A suggested dosing schedule of approximately 4-hour intervals is as follows: shortly before or upon arising in the morning, midday, and late afternoon (not later than 6 P.M.). Doses may be given in 3-hour intervals, if required, to control symptoms, but not more frequently. Single doses as high as 20 mg have been given to patients, but severe and persistent systolic supine hypertension occurs at a high rate (about 45%) at this dose. In order to reduce the potential for supine hypertension during sleep, Midodrine Hydrochloride should not be given after the evening meal or less than 4 hours before bedtime. Total daily doses greater than 30 mg have been tolerated by some patients, but their safety and usefulness have not been studied systematically or established. Because of the risk of supine hypertension, Midodrine Hydrochloride should be continued only in patients who appear to attain symptomatic improvement during initial treatment.

The supine and standing blood pressure should be monitored regularly, and the administration of Midodrine Hydrochloride should be stopped if supine blood pressure increases excessively.

Because desglymidodrine is excreted renally, dosing in patients with abnormal renal function should be cautious; although this has not been systematically studied, it is recommended that treatment of these patients be initiated using 2.5-mg doses.

Dosing in children has not been adequately studied.

Blood levels of midodrine and desglymidodrine were similar when comparing levels in patients 65 or older vs. younger than 65 and when comparing males vs. females, suggesting dose modifications for these groups are not necessary.

## **HOW SUPPLIED**

Midodrine Hydrochloride is supplied as 2.5-mg, 5-mg, and 10 mg tablets for oral administration. The 2.5-mg tablet is white, round, is scored on 1 side with [tablet description to be determined]. The 5-mg tablet is [tablet color to be determined], and is scored on 1 side with [tablet description to be determined]. The 10 mg tablet is [tablet color to be determined], and is scored on 1 side with [tablet description to be determined].

Packaging configurations for all strengths (2.5 mg, 5 mg, and 10 mg tablets):

- Bottles of 90 and 100
- Cartons of 100 for unit dose dispensing

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