DEPARTMENT OF HEALTH & HUMA N SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED VIA FACSIMILE

Algernon Thomas
Manager, Post-Marketing Regulatory Affairs
Shire Pharmaceutical Development, Inc.
1901 Research Blvd, Suite 500
Rockville, MD 20850

RE: NDA # 19-815
ProAmatine (midodrine hydrochloride) Tablets
MACMIS ID # 9990

Dear Mr. Thomas:

This letter concerns Shire Laboratories Inc.'s (Shire) dissemination of promotional materials for its accelerated approval product, ProAmatine Tablets. As part of its routine monitoring program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a sales aid (PRO 509) for ProAmatine. From its review, DDMAC has concluded that this piece is in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Specifically, your sales aid overstates the efficacy of ProAmatine and minimizes the serious risk of supine hypertension associated with the drug.

We refer you to our letters dated July 6, 2000, July 19, 2000, January 23, 2001, March 12, 2001, and our teleconference of February 15, 2001, where we outlined objections to similar claims and presentations.

Your sales aid contains the heading "ProAmatine raises patients' standing systolic blood pressure into the normal range." This claim suggests that patients with symptomatic orthostatic hypotension (OH) will maintain a normal standing systolic blood pressure as a result of taking ProAmatine. However, ProAmatine has not been demonstrated to maintain standing blood pressure in the "normal range" for patients with symptomatic OH. As stated in the approved product labeling (PI), "The indication is based on ProAmatine's effect on increases in 1-minute standing 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" (emphasis added). Furthermore, claims that suggest patients with symptomatic OH will have blood pressure in the "normal range" as a result of taking ProAmatine minimize the serious risk of supine hypertension associated with ProAmatine. As stated in the bolded **Warning** of the PI, "Systolic pressure of about 200 mmHg were seen overall in about 13.4% of patients given 10 mg of ProAmatine." Therefore, the claim is misleading because it overstates the efficacy of ProAmatine, is inconsistent with the PI, and minimizes the serious risk of supine hypertension that is associated with the use of this drug.

Shire should immediately cease dissemination of promotional materials or activities that contain these and similar claims or presentations concerning ProAmatine. In addition, Shire should respond in writing no later than May 21, 2001, describing its plan to comply. Shire should also include a list of materials being discontinued, as well as the date of discontinuation.

Your response should be directed to me by facsimile at 301-594-6771 or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857.

We remind you that only written communications are considered official. In all future correspondence regarding this particular matter please refer to MACMIS ID #9990 in addition to the NDA number.

Sincerely,

(see accompanying page for electronic signature)

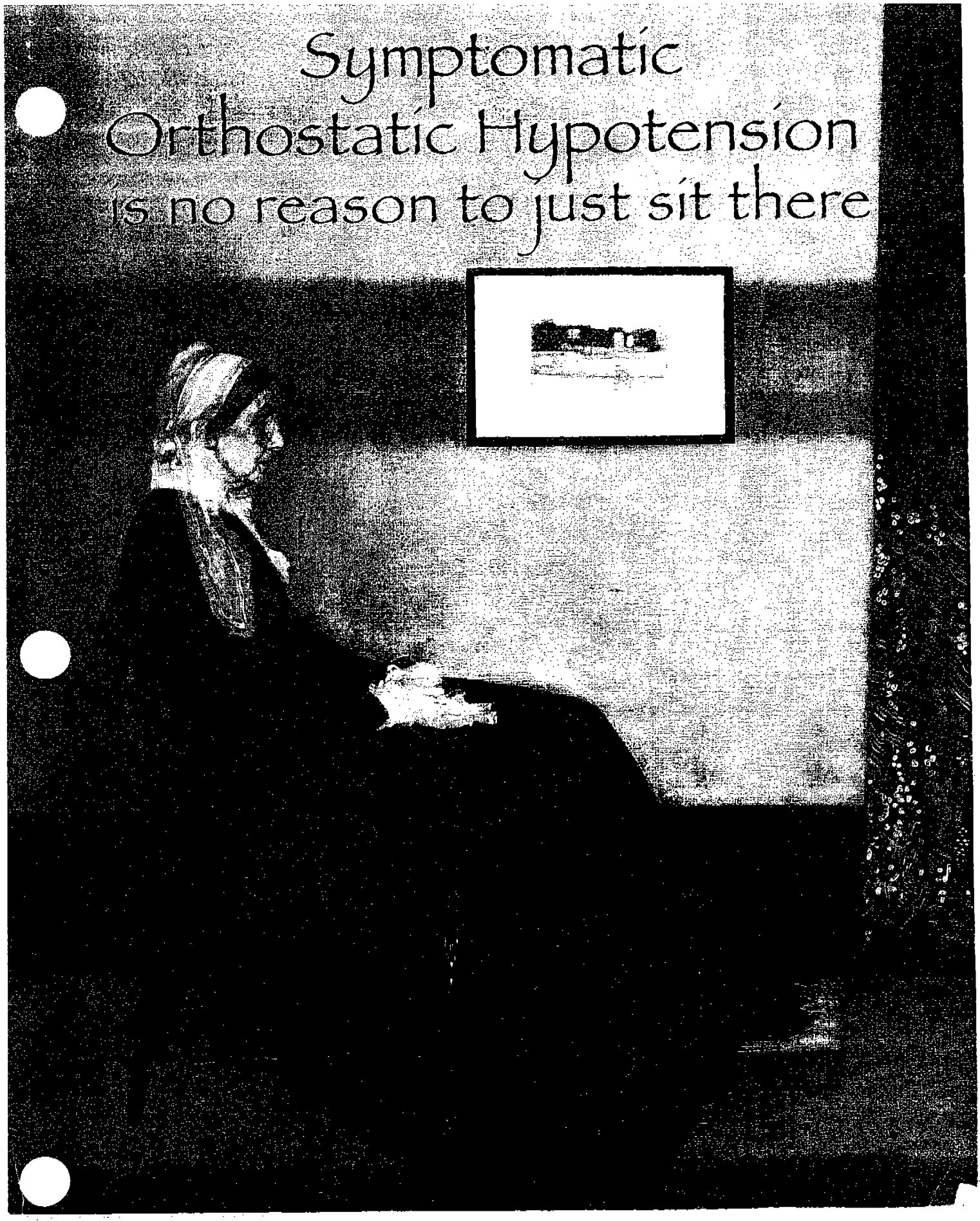
Andrew S.T. Haffer, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

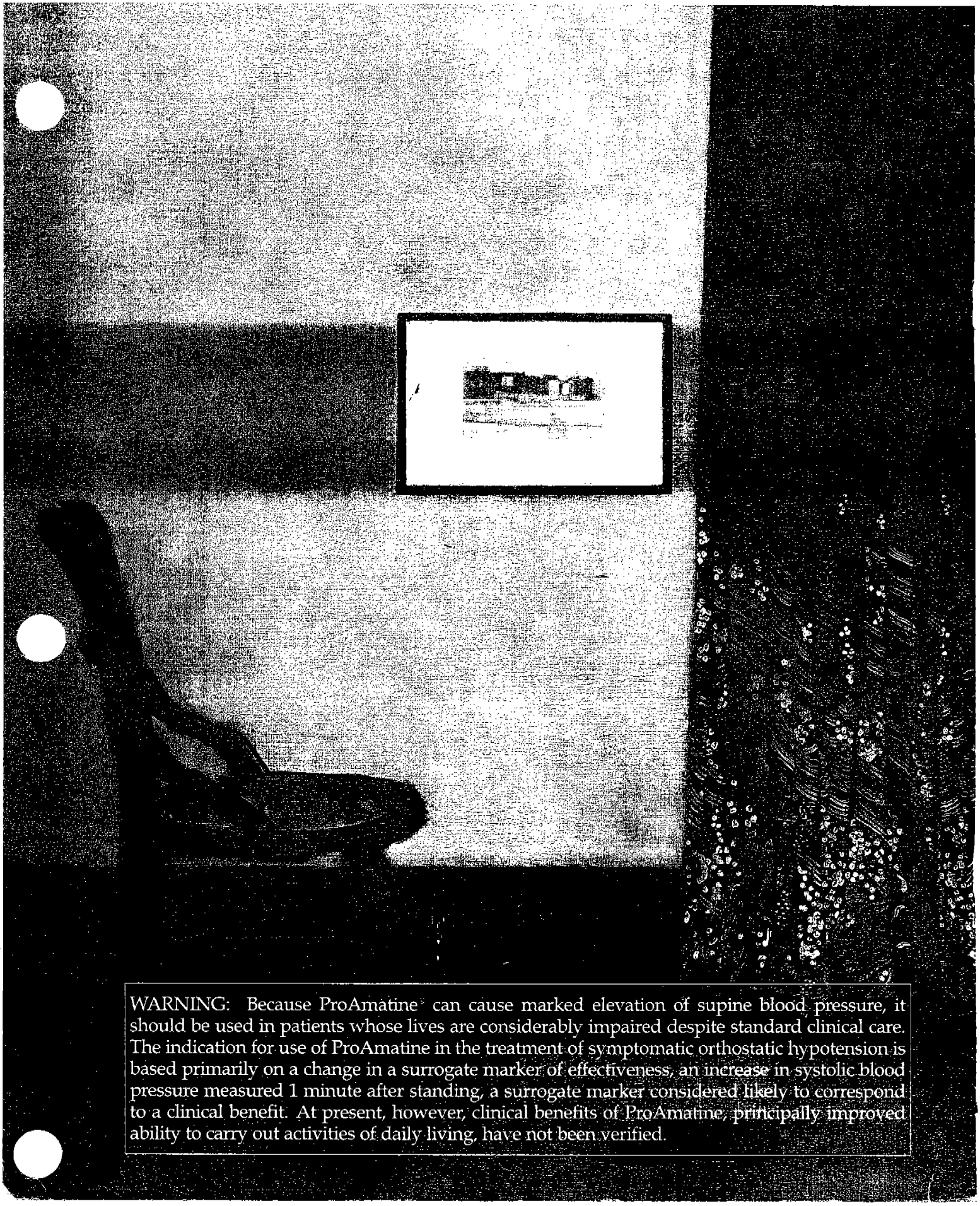
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Andrew Haffer
5/7/01 02:59:23 PM

Symptomatic Orthostatic Hypotension is no reason to just sit there



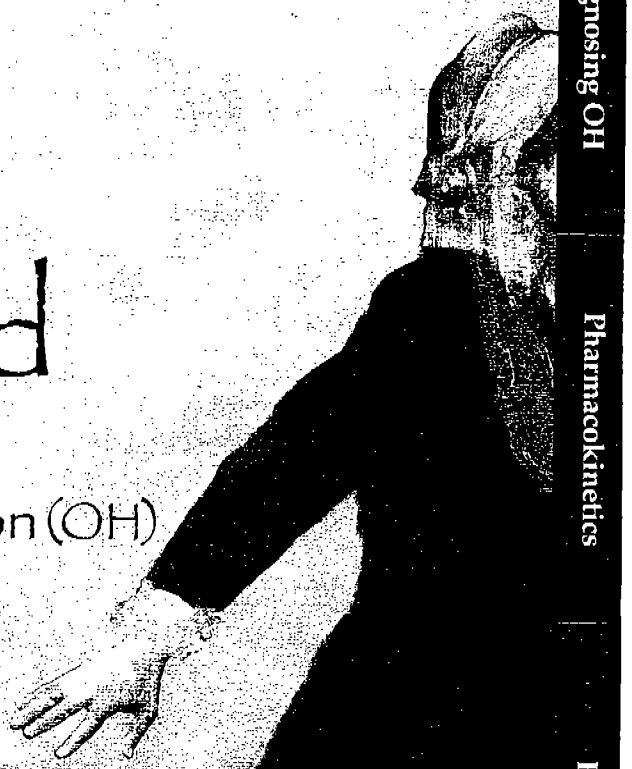


WARNING: Because ProAmatine can cause marked elevation of supine blood pressure, it should be used in patients whose lives are considerably impaired despite standard clinical care. The indication for use of ProAmatine in the treatment of symptomatic orthostatic hypotension is based primarily on a change in a surrogate marker of effectiveness, an increase in systolic blood pressure measured 1 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.

When nonpharmacologic options have failed

Take a stand

against symptomatic orthostatic hypotension (OH) with ProAmatine®



For patients with symptomatic OH

ProAmatine® 5-mg tablets

(midodrine hydrochloride)

2.5-mg tablet • 5-mg tablet

Safely keeps patients' blood pressure from falling

OH may be masked by symptoms*† such as...

- Dizziness and lightheadedness[1]
- Syncope[2]
- Visual disturbances[1]
- Impaired cognition[1]
- Unsteadiness[1]
- Fatigue[1]
- Loss of consciousness[2]
- Neck pain[1]

Or be a complication in patients with*...

- Parkinson's disease
- Diabetic neuropathy‡
- Multiple system atrophy and pure autonomic failure
- Neurally mediated syncope
- Other medical conditions that result in orthostatic symptoms

* Not all patients with these symptoms or diseases will manifest symptomatic OH.

† At present, clinical benefits of ProAmatine®, principally involving improved ability to carry out activities of daily living, have not been verified. Shire US Inc. is in the process of conducting Phase IV studies to verify and describe the drug's clinical benefit.

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

The most potentially serious adverse reaction associated with ProAmatine therapy is marked elevation of supine arterial blood pressure (supine hypertension). ProAmatine should be used in patients whose lives are considerably impaired despite standard nonpharmacologic clinical care, such as support stockings, sleeping in the head-up tilt position, and increased salt intake.

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 1 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.

See full Prescribing Information located on last tab.

Check their standing blood pressure. They may have symptomatic orthostatic hypotension.

Measure systolic and diastolic blood pressure, plus heart rate, according to the following time schedule

Begin with patient seated	
For accurate results, have the patient lie down for several (about 15) minutes	
Have patient stand and—with a standard sphygmomanometer—measure blood pressure Repeat at 1-minute intervals for 3 to 5 minutes	

If: 1. systolic blood pressure falls more than 20 mm Hg[1]

2. diastolic blood pressure falls more than 10 mm Hg[1]

3. and heart rate does not rise 10 beats per minute over the values at baseline[1]

autonomic dysfunction is likely

For patients with symptomatic OH

ProAmatine® 5-mg tablets

(midodrine hydrochloride)

2.5-mg tablet • 5-mg tablet

Safely keeps patients' blood pressure from falling

Control blood pressure fall when your patients rise, with ProAmatine®

Increases standing BP through alpha$_1$-specific peripheral vasoconstriction[3,4]

- Does not readily cross blood-brain barrier[4]
  - — Minimal CNS side effects[5]
- Does not increase circulating volume[4]
  - — Avoids the risk of volume-expanding therapy[4]

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 1 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.

See full Prescribing Information located on last tab.

Mean standing blood pressure increases of 17.3 mm Hg were maintained throughout the course of the trial*[3]

The duration of the BP-raising effect of a single 10-mg dose of ProAmatine is approximately 3 hours†[5]

- Offers the safety and flexibility to increase blood pressure only during the active daytime hours[5]
- The last dose should be taken before 6 PM to reduce the risk of nighttime supine hypertension, which occurred in 7% of patients in a 3-week, placebo-controlled trial[5]

*Patients were treated with ProAmatine (10 mg t.i.d.) or placebo t.i.d. in a 6-week study that included a 1-week, single-blind, run-in phase; a double-blind phase during weeks 2 to 4; and washout at weeks 5 and 6.

†Randomized, double-blind, four-way, complete-crossover, single-dose trial in patients with neurogenic orthostatic hypotension.

The only FDA-approved drug for symptomatic OH...

For patients with symptomatic OH

ProAmatine® 5-mg tablets

(midodrine hydrochloride)

2.5-mg tablet • 5-mg tablet

Safely keeps patients' blood pressure from falling

ProAmatine raises patients' standing systolic blood pressure into the normal range*

In a dose-response study† that included 23 patients with a mean predose standing systolic blood pressure of 87.6 mm Hg[6]:

- 10 mg of midodrine brought severely hypotensive patients' standing systolic blood pressure to a mean of 121.9 mm Hg

Tested in OH patients with the common combination of supine or seated hypertension and standing hypotension

*As defined by AHA (<120/<80 = optimal; <130/<85 = normal).

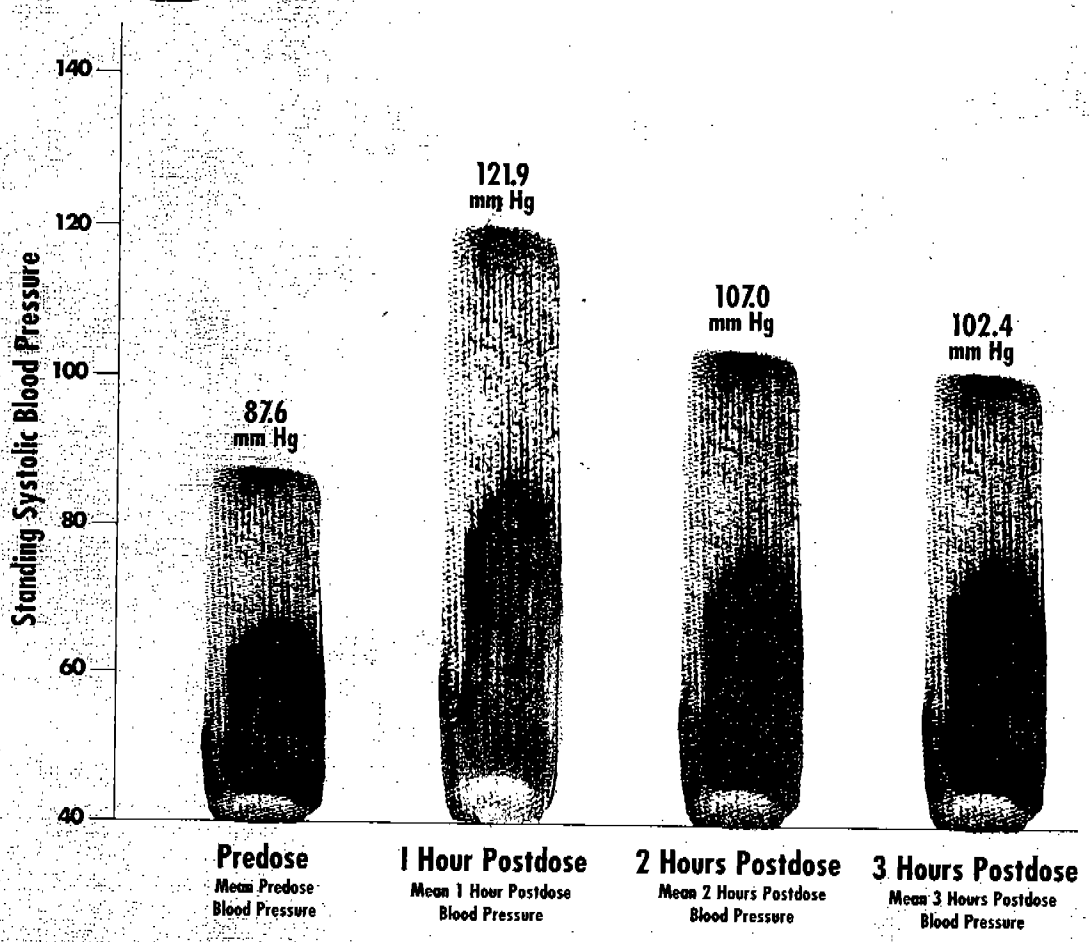
† Double-blind, four-way, complete-crossover, single-dose study.

The most potentially serious adverse reaction associated with ProAmatine therapy is marked elevation of supine arterial blood pressure (supine hypertension). ProAmatine should be used in patients whose lives are considerably impaired despite standard nonpharmacologic clinical care, such as support stockings, sleeping in the head-up tilt position, and increased salt intake.

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 1 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.

See full Prescribing Information located on last tab.

Dose-response study measuring mean 1-minute standing systolic blood pressure before and after administration of 10 mg of midodrine[6] (n=23)



For patients with symptomatic OH

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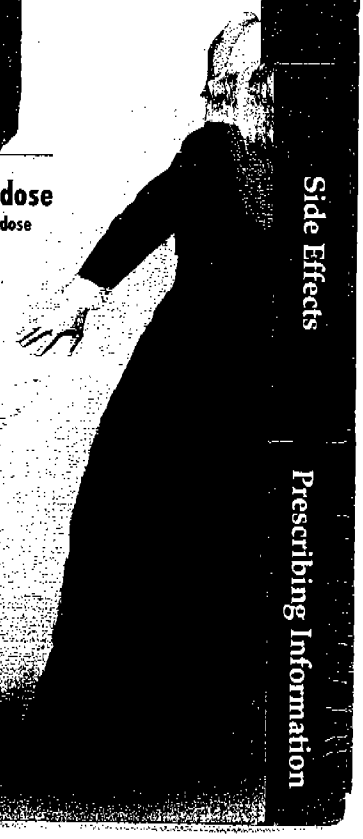
2.5-mg tablet • 5-mg tablet

Safely keeps patients' blood pressure from falling



Efficacy | Side Effects | Prescribing Information

Results with suggested dosing of 10 mg t.i.d. (q3-4h)*

Rapid efficacy was achieved with suggested daily dose[3,6]

- 1 hour after the first dose, ProAmatine® 10 mg increased standing systolic BP by a mean of 17.7 mm Hg vs placebo ($p<.001$)[7]
- Supine systolic BP was increased by 16.2 mm Hg vs placebo ($p<.01$)[7]
- Standing diastolic BP was increased by 10.1 mm Hg vs placebo ($p<.01$)[7]
- Mean systolic blood pressure increases of 17.3 mm Hg vs placebo were maintained throughout the course of the trial[†3]
- The last dose should be taken before 6 PM to reduce the risk of nighttime supine hypertension, which occurred in 7% of patients in a 3-week, placebo-controlled trial[5]

Experience in long-term use

- Nearly 1,000 patients in the United States have been treated in clinical trials with ProAmatine®, some for up to 8 years[3]
- Over 400,000 prescriptions have been written for ProAmatine since its introduction to the market in October 1996[8]

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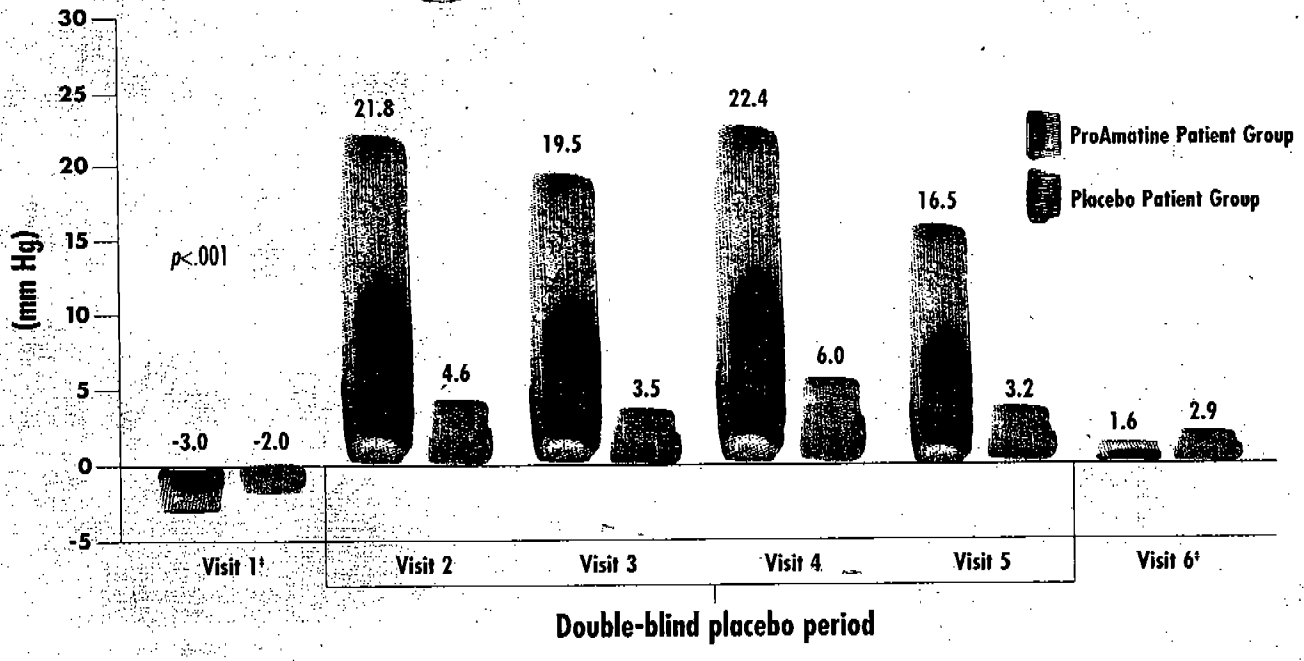
*See full Prescribing Information located on last tab.

Change in mean 1-minute standing systolic blood pressure—ProAmatine vs placebo[7]

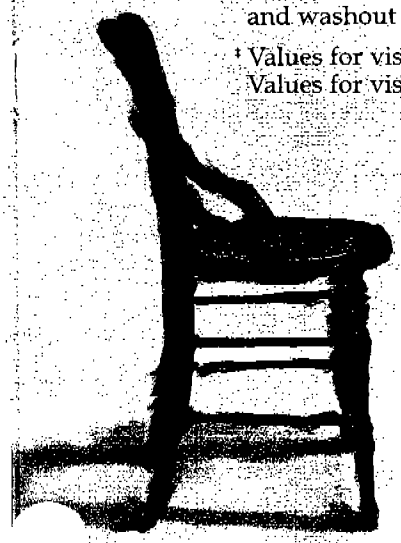


Change in systolic blood pressure between predose and 1 hour postdose of ProAmatine and placebo

*Three-week, double-blind, placebo-controlled comparison of ProAmatine® 10 mg t.i.d. vs placebo t.i.d., preceded by a 1-week, single-blind, run-in period and followed by a 2-week washout period.

† Patients were treated with ProAmatine (10 mg t.i.d.) or placebo t.i.d. in a 6-week study that included a 1-week, single-blind, run-in phase; a double-blind phase during weeks 2 to 4; and washout at weeks 5 and 6.

‡ Values for visits 1 and 6 obtained during single-blind placebo period. Values for visits 2 through 5 obtained for double-blind period.



For patients with symptomatic OH

ProAmatine® 5-mg tablets

(midodrine hydrochloride)

2.5-mg tablet • 5-mg tablet

Safely keeps patients' blood pressure from falling

A low incidence of side effects at 10 mg t.i.d.

Minimal CNS effects[5]

- Does not readily cross blood-brain barrier[4]

Avoids the risks of volume-expanding therapy[4]

- Works without increasing circulating volume[4]

Enables blood pressure to rise only when needed

- Duration of action ≈ 3 hours[2]
- Short duration of action offers safety and flexibility in dosing
- The last dose should be taken before 6 PM to reduce the risk of nighttime supine hypertension, which occurred in 7% of patients in a 3-week, placebo-controlled trial[5]

Risk information

The most potentially serious adverse reaction associated with ProAmatine therapy is marked elevation of supine arterial blood pressure (supine hypertension). ProAmatine should be used in patients whose lives are considerably impaired despite standard nonpharmacologic clinical care, such as support stockings, sleeping in the head-up tilt position, and increased salt intake.

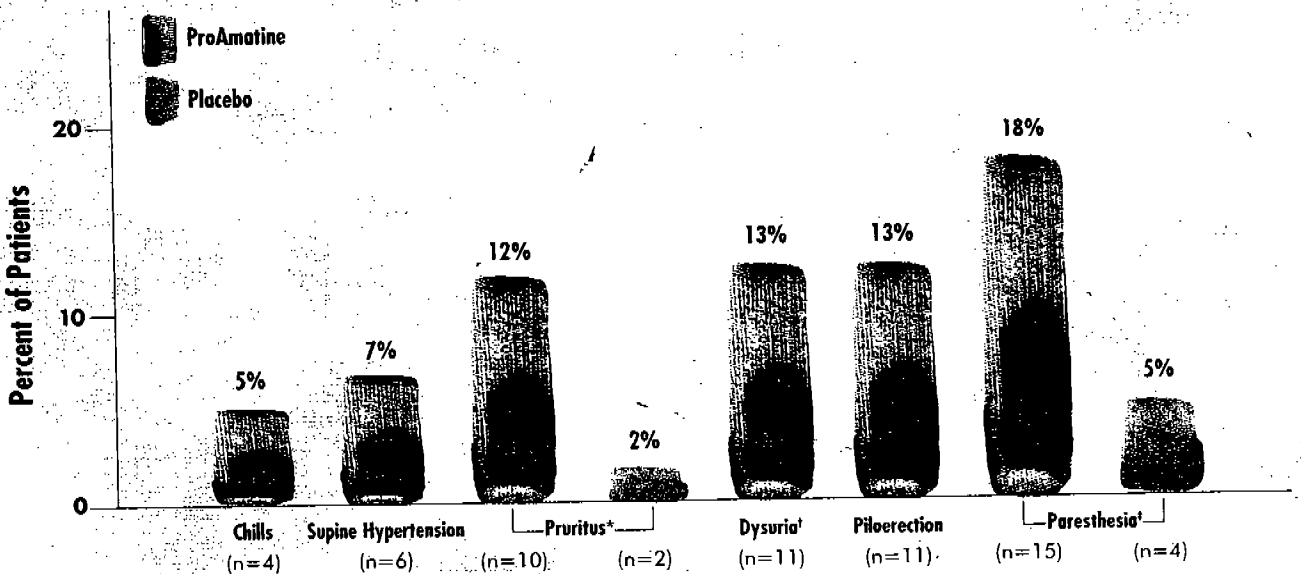
Patients should be told that certain agents (eg, phenylephrine, phenylpropanolamine) in over-the-counter products such as cold remedies and diet aids should be used cautiously, since they may potentiate the pressor effects of ProAmatine®.

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

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 1 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.

See full Prescribing Information located on last tab.

Most commonly reported side effects for patients receiving ProAmatine® 10 mg t.i.d. (n=82) or placebo (n=88) in a 3-week trial[5]



* Includes scalp pruritus

† Includes dysuria (1), increased urinary frequency (2), impaired urination (1), urinary retention (5), and urinary urgency (2)

‡ Includes hyperesthesia and scalp paresthesia

For patients with symptomatic OH

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(midodrine hydrochloride)

2.5-mg tablet • 5-mg tablet

Safely keeps patients' blood pressure from falling

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DESCRIPTION

Name: ProAmatine (midodrine hydrochloride) Tablets

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

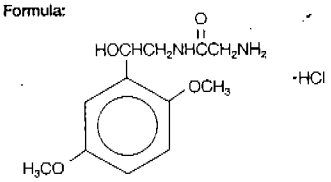
Active Ingredient: Midodrine hydrochloride, 2.5 mg or 5 mg

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: $C_{12}H_{18}N_2O_4HCl$; **Molecular Weight:** 290.7

Organoleptic Properties: Odorless, white, crystalline powder

Solubility: Water: Soluble
Methanol: Sparingly soluble

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$_1$-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 ≥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 pre-treatment 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®** (midodrine hydrochloride). Therefore, ...n should be used when **ProAmatine** is administered concomitantly with agents ...se vasoconstriction.

...tine has been used in patients concomitantly treated with salt-retaining steroid ... (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/m² 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/m²). 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	
...aresthesia[1]	4	4.5	15	18.3
...erection	0	0	11	13.4
...suria[2]	0	0	11	13.4
Pruritus[3]	2	2.3	10	12.2
Supine hypertension[4]	0	0	6	7.3
Chills	0	0	4	4.9
Pain[5]	0	0	4	4.9
Rash	1	1.1	2	2.4

1 Includes hyperesthesia and scalp paresthesia
2 Includes dysuria (1), increased urinary frequency (2), impaired urination (1), urinary retention (5), urinary urgency (2)
3 Includes scalp pruritus
4 Includes patients who experienced an increase in supine hypertension
5 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 overdosage 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 overdosage or would be potentially life-threatening are unknown. The oral LD_{50} 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

References

1. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *Neurology*. 1996;46:1470. 2. Mathias CJ. Orthostatic hypotension: causes, mechanisms, and influencing factors. *Neurology*. 1995;45:S6-S11. 3. Data on file, Shire US Inc. 4. McTavish D, Goa KL. Midodrine: a review of its pharmacological properties and therapeutic use in orthostatic hypotension and secondary hypotensive disorders. *Drugs*. 1989;38:757-777. 5. ProAmatine® (midodrine hydrochloride) Package Insert. 6. Wright RA, Kaufmann HC, Perera R, et al. A double-blind, dose-response study of midodrine in neurogenic orthostatic hypotension. *Neurology*. 1998;51:120-124. 7. Low PA, Gilden JL, Freeman R, Sheng K-N, McElligott MA, for the Midodrine Study Group. Efficacy of midodrine vs placebo in neurogenic orthostatic hypotension: a randomized, double-blind multicenter study. *JAMA*. 1997;277:1046-1051. 8. IMS Data.

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Prescribing Information

Control blood pressure fall when your patients rise, with ProAmatine®

Rapid response in standing BP achieved with suggested daily dose[3,6]

- 1 hour after the first dose, ProAmatine 10 mg increased standing systolic BP by a mean of 17.7 mm Hg vs placebo ($p<.001$)[7]
- Supine systolic BP was increased by 16.2 mm Hg vs placebo ($p<.01$)[7]

Short duration of action offers safety and flexibility in dosing

- The last dose should be taken before 6 PM to reduce the risk of nighttime supine hypertension, which occurred in 7% of patients in a 3-week, placebo-controlled trial[5]

Experience in long-term use

- Over 400,000 prescriptions written since introduction in October 1996[8]

Dosing Guidelines

Suggested dose 10 mg t.i.d. (q3-4h)

Suggested dosing schedule
Dose 1: Shortly before or upon rising in the morning
Dose 2: Midday
Dose 3: Late afternoon (no later than 6 PM) to reduce the risk of nighttime supine hypertension[5]

For patients with symptomatic OH

ProAmatine® 5-mg tablets
(midodrine hydrochloride)
2.5-mg tablet • 5-mg tablet

Safely keeps patients' blood pressure from falling

See full Prescribing Information located on last tab.

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