

PRODUCT MONOGRAPH

Pr AMATINE^{®*}

(Midodrine hydrochloride)

2.5, 5 & 10 mg Tablets

Vasopressor

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PRODUCT MONOGRAPH

NAME OF DRUG

Pr AMATINE®
(midodrine hydrochloride)
2.5, 5 & 10 mg Tablets

Therapeutic Classification

Vasopressor

ACTION AND CLINICAL PHARMACOLOGY

AMATINE (midodrine hydrochloride) is a prodrug, that is, the therapeutic effect of orally administered midodrine is due to and directly related to its conversion after absorption to desglymidodrine which differs chemically from methoxamine only by lacking in a methyl group on the α carbon of the side chain.

Desglymidodrine is an α_1 -adrenoceptor stimulant with little effect on cardiac β -adrenoceptors. The actions of desglymidodrine on the cardiovascular and other organ systems are essentially identical with those of other α_1 -adrenoceptor stimulants, such as phenylephrine or methoxamine.

The most prominent effects of midodrine are on the cardiovascular system, consisting of a rise in standing, sitting and supine systolic and diastolic blood pressures in patients with orthostatic hypotension. Standing systolic pressure is increased by 15 to 30 mm Hg at 1 hour after a 10 mg dose of AMATINE, with some effects persisting for another 2 to 3 hours. The increase in blood pressure is due almost entirely to an increase in peripheral resistance. AMATINE has no clinically significant effect on standing or supine pulse rate in patients with autonomic failure. It slightly decreases cardiac output and renal blood flow and increases the tone of the internal bladder sphincter and delays the emptying of the bladder.

Pharmacokinetics: After oral administration, midodrine is rapidly and almost completely absorbed, with a mean absolute bioavailability (as desglymidodrine) of 93%.

After the oral administration of 2.5 mg midodrine in a single dose to 12 volunteers, the mean peak concentration of unchanged midodrine is approximately 10 ng/mL and it occurs after 20-30 minutes, with a terminal plasma half-life of 0.4-0.5 hours. The mean plasma concentration of the active metabolite, desglymidodrine, peaks in approximately 1 hour, with a plasma half-life of approximately 3 hours after the oral administration of 2.5 mg midodrine.

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.

Both midodrine and desglymidodrine are quickly eliminated from the body, mostly by the kidneys. The renal clearance of desglymidodrine is approximately 385 mL/min, most, about 80%, by active 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 **PRECAUTIONS - Drug Interactions**). Approximately 91% of the administered dose is excreted in the urine in 24 hours. Of the urinary material, 40-60% is present as desglymidodrine and approximately 2-5%, as non-metabolized midodrine. Unidentified breakdown products do not exceed 3.9% of the urinary material. Midodrine diffuses poorly across the blood-brain barrier.

INDICATIONS AND CLINICAL USE

AMATINE (midodrine hydrochloride) may be used to attenuate symptoms of chronic orthostatic hypotension due to autonomic failure in patients with Bradbury-Eggleston syndrome, Shy-Drager syndrome, diabetes mellitus disease and Parkinson's disease.

The initiation and up-titration of midodrine therapy should be undertaken under close medical supervision in a controlled clinical setting (see **DOSAGE AND ADMINISTRATION**).

The safety of AMATINE in patients with orthostatic hypotension due to etiology other than those named above has not been established and its use is, therefore, not recommended.

Because AMATINE can cause marked elevation of supine blood pressure, it should be used in patients whose lives are considerably impaired despite standard clinical care including non-pharmacologic treatment, plasma volume expansion and lifestyle alterations. The use of AMATINE in the management of symptomatic orthostatic hypotension is based primarily on a change in a surrogate endpoint of effectiveness, an increase in systolic blood pressure measured one minute after standing, a surrogate endpoint considered likely to correspond to clinical benefits. At present, however, clinical benefits of AMATINE, principally improved ability to carry out activities of daily life, have not been verified.

CONTRAINDICATIONS

Midodrine is contraindicated in patients with:

- hypertension,
- obliterative or spastic vessel disease,
- severe organic heart disease,
- acute renal disease,
- renal insufficiency,
- urinary retention,
- hypertrophy of prostate gland with formation of residual urine,
- pheochromocytoma,
- hyperthyroidism or thyrotoxicosis
- narrow-angle glaucoma or
- known hypersensitivity to any component of the product (see COMPOSITION).

WARNINGS

Supine Hypertension: The most potentially serious adverse reaction associated with midodrine therapy is marked elevation of supine arterial blood pressure (supine hypertension), which, if sustained, may cause stroke, myocardial infarction, congestive heart failure, renal insufficiency or similar disorders which individually or collectively may be fatal. Symptoms of supine hypertension are more frequently detected at the initiation of midodrine therapy and during the titration period. It is essential to monitor supine and sitting blood pressures in patients maintained on midodrine.

Control of supine blood pressure has been obtained by an adjustment in midodrine dosage with or without a 45-degree elevation of the patient's head. If supine hypertension persists, treatment with midodrine should be discontinued, and appropriate therapy (e.g., phentolamine, a specific antagonist of midodrine pressor activity) instituted immediately.

Systolic hypertension of about 200 mm Hg were seen overall in about 11.6% of patients treated

with 10 mg of AMATINE, in 4 controlled clinical studies. Systolic elevation of this degree were most likely to be observed in patients with relatively elevated pre-treatment blood pressure (mean 170 mm Hg). There is no experience in patients with initial supine systolic pressure above 180 mm Hg as those patients were excluded from the clinical trials. Use of AMATINE in such patients is not recommended. Sitting blood pressures were also elevated by AMATINE therapy and it is, therefore, essential to monitor supine and sitting blood pressures in patients maintained on AMATINE (see **DOSAGE AND ADMINISTRATION**).

To minimize the incidence of supine hypertension, instruction how to initiate midodrine therapy should strictly be followed (see **DOSAGE AND ADMINISTRATION**). Patients should be cautioned to report symptoms of supine hypertension immediately. Symptoms may include cardiac awareness, pounding in the ears, headache, blurred vision, etc. If these occur, the patient should discontinue the drug and consult with the prescribing physician. Patients with persistent labile blood pressure after stabilisation on midodrine should discontinue treatment.

Bradycardia: Bradycardia may occur after AMATINE tablets administration, primarily due to vagal reflex. Caution should be exercised when AMATINE is used concomitantly with cardiac glycosides (such as digitalis), psychopharmacologic agents, beta blockers or other agents which directly or indirectly reduce heart rate. Patients who experience bradycardia should be told to report immediately any signs or symptoms suggesting bradycardia (pulse slowing, increased dizziness, syncope, cardiac awareness) and to take no more drug until they have consulted with the prescribing physician.

Cardiac Arrhythmias: AMATINE should not be administered in the presence of uncorrected tachyarrhythmias.

PRECAUTIONS

General: The potential for supine and sitting hypertension should be evaluated at the beginning of midodrine therapy. Supine hypertension can often be controlled by an adjustment in midodrine dosage and/or 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. Patients should be monitored for possible secondary events to hypertension. It is advisable always to monitor the blood pressure and renal function in patients undergoing long-term treatment with midodrine.

Patients with Diabetes Mellitus and/or increased intra-ocular pressure: Midodrine 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. The use of midodrine in patients who have an increased risk of or suffer from glaucoma/increased intra-ocular pressure should be avoided or monitored very closely (see **CONTRAINDICATIONS**).

Patients with Renal Impairment: Midodrine 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 should be used with caution in patients with renal impairment, with a starting dose not higher than 2.5 mg (see **DOSAGE AND ADMINISTRATION**) and the patient's blood pressure should be monitored closely. Renal function should be assessed prior to initial use of midodrine and when appropriate during therapy (see **CONTRAINDICATIONS**).

Patients with Hepatic Impairment: Midodrine has not been studied in patients with hepatic impairment. Midodrine should be used with caution in patients with hepatic impairment, as the liver has a role in the metabolism of midodrine. It is therefore recommended to evaluate the hepatic parameters before starting treatment with midodrine and on a continuous basis thereafter.

Urinary Retention: Midodrine may induce an increase in the tone of the internal sphincter of the urinary bladder which may lead to urinary retention. Midodrine also may effect the bladder trigone which may result in a delayed response to bladder filling. Initial signs of urinary retention are manifested clinically as hesitancy or change in frequency of micturition. Patients should be told to report promptly any indication of urinary retention (e.g., hesitancy or frequency of micturition) which may be a sign of urinary retention (see **CONTRAINDICATIONS**).

Midodrine should be used with caution in patients with urinary tract outflow obstruction, neurogenic bladder or similar conditions, since midodrine and desglymidodrine are eliminated by the kidneys and accumulation may occur in such patients.

Use in Children: Safety and effectiveness in children under the age of 12 have not been established. In view of the lack of experience in children, the drug is not recommended for patients under 12 years of age.

Use in Pregnancy: No teratogenic effects have been observed in studies in animals. At very high doses (20 mg/kg/day) the drug was toxic to dams and fetal loss occurred. There are no data on the use of midodrine in pregnant women. It is therefore not advisable to use midodrine hydrochloride in women aiming at becoming pregnant. Any woman getting pregnant during treatment should be withdrawn from the treatment immediately upon established pregnancy.

Nursing Mothers: It is not known if midodrine is excreted in human milk, therefore midodrine should not be used during lactation.

Effects of Ability to drive and use Machinery: Negligible influence; However, in case of dizziness or lightheadedness, care should be taken when driving vehicles or operating machinery.

Laboratory Tests: Evaluation of the patient should include assessment of renal and hepatic function prior to initiation of therapy, and during treatment, when appropriate.

Drug Interactions: *Glycosides:* When administered concomitantly with midodrine, glycosides

(e.g. digitalis) may enhance or precipitate bradycardia, A.V. block or arrhythmia.

Sympathomimetic and other vasopressor agents: The use of drugs that stimulate alpha-adrenoceptors (e.g., phenylephrine, pseudoephedrine, ephedrine, phenylpropanolamine dihydroergotamine, sympathomimetic/vasopressor antidepressants, thyroid hormones, or MAO-inhibitors) may enhance or potentiate the pressor effects of midodrine. Therefore, midodrine should not be used concomitantly with vasoconstrictor sympathomimetic agents and the patient should be warned not to use over-the-counter preparations containing these drugs.

Sympatholytic agents: Alpha-adrenoceptor antagonists such as phentolamine, prazosin, doxazosin and labetalol can inhibit the vasopressor effect of midodrine. Concomitant use of midodrine and alpha-receptor blocking agents and beta-receptor blocking agents which may reduce the heart rate; requires careful monitoring.

Corticosteroids: Patients on salt-retaining steroids (e.g., fludrocortisone), with or without salt supplementation, may experience an excessive pressor effect after midodrine therapy, especially in the supine posture. The possibility of hypertensive effects with midodrine can be minimized by either reducing the dose of fludrocortisone or decreasing the salt intake prior to initiation of treatment with midodrine. Patients being treated with midodrine in combination with mineralcorticoids or glucocorticoids (eg fludrocortisone) may be at increased risk of glaucoma/increased intraocular pressure, and should be carefully monitored.

Atropine: Midodrine may enhance or potentiate the blood-pressure raising effect of atropine.

Rauwolfia alkaloids: The presence of rauwolfia alkaloids (reserpine) slightly increases the pressor effects of midodrine.

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.

ADVERSE REACTIONS

AMATINE (midodrine hydrochloride) has been evaluated for safety in Phase III clinical trials in 938 patients with symptomatic orthostatic hypotension due to autonomic failure (Bradbury-Eggleston, 26.7%; Shy-Drager Syndrome, 17.8%; Parkinson's disease, 11%; diabetes mellitus, 21.2%; other conditions, 23.3%). There were 245 patients who received AMATINE in double-blinded, placebo-controlled trials.

In the placebo-controlled studies, adverse events regardless of causality were reported in 40.4% of the patients on midodrine 10 mg t.i.d. compared to 18.6% on placebo.

In placebo-controlled trials, the rate of discontinuation of patients on midodrine 10 mg t.i.d. due to adverse events, regardless of causality, was 15.8% compared to 0% on placebo. Discontinuation due to urinary disturbance, pilomotor reactions and supine hypertension were the reasons for premature withdrawal that were more common on midodrine.

In patients treated with midodrine in which a causal relationship could not be excluded, there was one case of a serious adverse reaction reported, i.e. central retinal vein occlusion.

The most frequent (>2%) adverse events in placebo-controlled trials were supine and sitting hypertension; paraesthesia and pruritus, mainly of the scalp; goose bumps; chills; urinary urge; urinary retention and urinary frequency.

The incidence of these events in a 3-week placebo-controlled trial is shown in the following table.

	PLACEBO	MIDODRINE
Adverse Event	% of patients	% of patients
Paraesthesia ¹	4.5	18.3
Piloerection	0	13.4
Dysuria ²	0	13.4
Pruritus ³	2.3	12.2
Supine hypertension ⁴	0	7.3
Chills	0	4.9
Pain ⁵	0	4.9
Rash	1.1	2.4

¹ Includes paraesthesia, paraesthesia of scalp and hyperesthesia of skin.

² Includes dysuria, increased urinary frequency, impaired urination, urinary retention (6%), urinary urgency.

³ Includes scalp pruritus (11%).

⁴ Includes patients with increased supine hypertension (2.4%).

⁵ Includes abdominal pain and pain increase.

In the 938 patients treated in controlled and uncontrolled trials, the following adverse events, regardless of causality, occurred at a frequency greater than 0.5% or occurred at a lower rate but were potentially important: asthenia, chills, dizziness, dyspepsia, dyspnea, hair disease, headache, hypertension, nausea, nervousness, pain, paraesthesia, paraesthesia scalp, piloerection, vasodilation, pruritus, pruritus scalp, rash, supine hypertension, urine retention, urine urgency.

The most potentially serious adverse reaction associated with midodrine therapy is supine hypertension. The feelings of paraesthesia, 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.

Laboratory Abnormalities: There were no clinical significant changes to laboratory parameters.

Postmarketing events

The following adverse events have also been reported with the use of midodrine:

Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1 000, <1/100); rare (>1/10 000, < 1/1 000);very rare (<1/10 000)

Psychiatric disorders: Uncommon: sleep disorders, insomnia

Nervous system disorders: Uncommon: restlessness, excitability, irritability

Cardiac disorders: Uncommon: reflex bradycardia; Rare: tachycardia

Gastrointestinal disorders: Common: heartburn, stomatitis

Hepatobiliary disorders: Rare: Hepatic function abnormal, raised liver enzymes

Skin and subcutaneous tissue disorders: Common: flushing, skin rash

Vascular disorders: Common: supine hypertension (blood pressure above 180/110mmHg) with daily doses above 30mg; Uncommon: supine hypertension (blood pressure above 180/110mmHg) with daily doses above 7.5mg.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms of overdose could include hypertension, piloerection (goose bumps), a sensation of coldness and urinary retention. There are 2 reported cases of overdosage with AMATINE (midodrine hydrochloride), both in young males. One patient ingested AMATINE drops, 250 mg, experienced systolic blood pressure of greater than 200 mm Hg, 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 AMATINE (41 x 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 LD₅₀ is approximately 30 to 50 mg/kg in rats, 675 mg/kg in mice, and 125 to 160 mg/kg in dogs.

Beside basic life support, recommended general treatment, based on the pharmacology of the drug, includes induced emesis and administration of alpha-sympatholytic drugs (e.g., phentolamine, nitroprusside, nitroglycerin). Bradycardia and bradycardic conduction defects can be counteracted by atropine.

Desglymidodrine is dialyzable.

DOSAGE AND ADMINISTRATION

Treatment with AMATINE (midodrine hydrochloride) should be started under close medical supervision in a controlled clinical setting such as in hospital, in clinic, or in the office. Hourly measurements of blood pressure (supine and sitting) should be made for 3 hours after the first dose and also the second dose of a three times daily dosage regimen. This procedure should be followed also when the dose is increased.

During the period of close medical supervision, the patient or a person living with the patient should be trained to measure blood pressure. Supine and sitting blood pressures should be measured daily for at least one month after the initiation of treatment and twice per week afterwards.

The administration of AMATINE should be stopped and the attending physician notified immediately, if the blood pressure in either position increases above 180/100 mm Hg.

The usual starting dose of AMATINE is 2.5 mg three times daily. Single doses of 2.5, 5 and 10 mg have been successfully employed. Most patients are controlled at or below 30 mg per day given in three or four divided doses. AMATINE can be given up to six times per day but a total daily dose of 30 mg should not be exceeded. Some patients require a morning dose that is higher than that taken later in the day. In some instances AMATINE has been given on a three times per day schedule as follows: 1 to 2 hours before arising in the morning, mid-morning and mid-afternoon. In order to reduce the potential for supine hypertension, it may be recommended that midodrine doses not be given after the evening meal or less than 4 hours before bedtime.

Therapy with AMATINE should be continued only in patients who appear to obtain symptomatic improvement during initial treatment.

The maximum recommended dose should not exceed 30 mg daily.

Dosing in children has not been studied as patients 18 years or younger were excluded from the clinical trials.

Use in the Elderly: Blood levels of midodrine and desglymidodrine were similar in patients 65 years or older versus those younger than 65 years suggesting that dosage adjustment is not necessary in elderly patients provided that their renal and liver functions are adequate.

Use in Patients with Hepatic and/or Renal Impairment: AMATINE should be used cautiously and the starting dose should not be higher than 2.5 mg (See **PRECAUTIONS - Patients with Renal Impairment and Patients with Hepatic Impairment**).

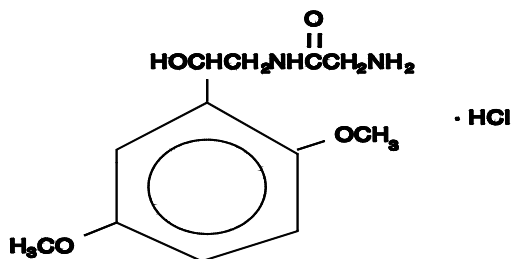
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: midodrine hydrochloride

Chemical Name: 2-amino-*N*-[2-(2,5-dimethoxy-phenyl)-2-hydroxyethyl]-monohydro-chloride,(±)-acetamide

Structural Formula:



Molecular formula: C₁₂H₁₈N₂O₄HCl

Molecular weight: 290.74

Description: Midodrine hydrochloride is an odourless, white crystalline powder.

Solubility in water: 9.3 g/100 mL

Solubility in methanol: 1.6 g/100 mL

pK: 7.8 (0.3% in water)

pH: 3.5 - 5.5 (5% in water)

Melting point: 205 - 207°C

COMPOSITION

Midodrine hydrochloride 2.5 mg, 5 mg or 10 mg

Highly dispersed silicone dioxide

Colour FD&C Yellow #6 Lake (5 mg only) & FD&C Blue #2 Lake (10 mg only)

Microcrystalline cellulose (Avicel PH 101)

Corn Starch

Talc

Magnesium stearate

STABILITY AND STORAGE RECOMMENDATIONS

Store between 15 - 25°C

AVAILABILITY OF DOSAGE FORMS

AMATINE is supplied as: oral white tablets 2.5 mg, oral orange tablets 5 mg and oral blue tablets 10 mg, scored on one side, in amber glass bottles with plastic cap to cap LDPE closures of 100's.

PHARMACOLOGY

Preclinical Studies: Intraduodenally, midodrine was effective in rats at 2.5 to 20 mg/kg. Phentolamine (5 mg/kg i.v.), an alpha-adrenergic antagonist, inhibited the pressor response to midodrine (5 mg/kg i.v.). Other pharmacological agents including the beta-adrenergic antagonist propranolol (5 mg/kg, i.v.) and the parasympathetic antagonist atropine (5 mg/kg, i.v.), had no influence on the pressor response.

Midodrine (1 mg/kg, i.v.) and desglymidodrine (250 µg/kg, i.v.) did not significantly affect the actions of the beta-adrenergic agonist isoprenaline (0.4 µg/kg, i.v.) on systolic or diastolic pressure, dP/dT, heart rate or femoral blood flow in the anaesthetized cat.

Desglymidodrine (10^{-6} to 10^{-4} M) caused a dose-related increase in tension of isolated femoral artery and femoral vein strips from dogs while midodrine had no effect at concentrations up to 10^{-3} M. These response curves were shifted to the right in a parallel fashion by phentolamine indicating competitive antagonism.

Neither midodrine nor desglymidodrine affected acetylcholine induced bronchospasms in guinea pigs. Neither midodrine nor desglymidodrine had any significant CNS activity in the mouse.

Clinical Studies: In human studies, midodrine did not affect blood sugar or urea levels in hypotensive patients or did not have any adverse effects on glucose tolerance, serum lipids, insulin or uric acid in diabetic patients. During a three-week treatment with midodrine (20 mg daily), no effects were seen on plasma clotting factor, there was no activation of fibrinolysis, or effects on number and function of thrombocytes.

Midodrine has been studied in four principal controlled trials of 4 weeks, 3 weeks, 4 days and 1 day duration, respectively. All studies were randomized, double-blind trials in patients with orthostatic hypotension of any etiology and supine-to-standing fall of systolic blood pressure of at least 15 mm Hg accompanied by at least moderate dizziness/lightheadedness. Patients with pre-existing sustained supine hypertension above 180/110 mm Hg were routinely excluded. In the 4-week study in 104 patients, midodrine (10 mg) significantly elevated standing systolic blood pressure 22 mm Hg (28%) compared to 3 mm Hg (4%) for the placebo group. The 2.5 mg dose elevated blood pressure 9 mm Hg (14%). The percent increase in standing systolic pressure for all midodrine doses (2.5, 5 and 10 mg) and the 5 and 10 mg doses together was significantly superior to placebo and the dose response was linear.

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 pm) had significantly higher (by about 20 mm Hg) 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 mm Hg, respectively, on average.

In a 4-day, 4-way crossover 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 mm Hg 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 mm Hg in 22% of patients on 10 mg and 45% of patients on 20 mg; elevated pressures often lasted 6 hours or more.

In a 1-day study in 70 patients, 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 mm Hg and 3 hours after each dose by about 12 mm Hg; 3-minute standing pressures were increased also at 1 but not at 3 hours after dosing. There were increases in standing time seen intermittently 1 hour after dosing, but not at 3 hours.

TOXICOLOGY

Acute Toxicity: The acute toxicity of midodrine is as follows:

	LD ₅₀ mg/kg		
	Mouse	Rat	Dog
Intravenous	107.7	17.69	---
Intraperitoneal	199.9	25.55	---
Subcutaneous	196.6	30.18	---
Oral	675.0	32.90	126.0 - 159.0

The toxicity pattern is identical in all 3 animal species and is characterized by exophthalmus, piloerection, dyspnea, salivation and tonoclonic spasms.

Subacute Toxicity: Midodrine was given to rats (10 males and 10 females per dose) by stomach tube for up to 20 days at doses of 5, 10 and 20 mg/kg/day. Alterations of the myocardium characteristic of those produced by sympathomimetic agents, taking the form of foci of degenerative myocardial fibers and an increase in connective tissue cells, were observed and these were not clearly dose dependent. Females administered oral midodrine in doses of 5, 10 and 20 mg/kg showed fatty degeneration in the periphery of liver lobes with a decrease in glycogen content; males show cellular enlargement of the liver without fatty accumulation with cells rich in glycogen. These liver changes were dose dependent.

Chronic Toxicity: Six month toxicity studies were carried out in rats and dogs. In one experiment, Sprague-Dawley rats (10 males and 10 females per dose) were dosed orally with 1, 5 and 20 mg/kg. In a second experiment, rats (10 males and 10 females per dose) were dosed orally with 0.3 mg/kg. There was slight fatty infiltration of the liver in male rats dosed with 5 mg/kg. Changes in hepatic and plasma enzyme activities did not follow any pattern that could be related clearly to midodrine. Chronic toxicity studies for 6 months in dogs (2 males and 2 females per dose) in doses up to 12.5 mg/kg/day showed sporadic degeneration of myocardial fibers with rows of fibrocytes in the myocardium. Liver function tests remained within normal limits. Piloerection and mydriasis, initially prominent and dose dependent, gradually disappeared over several weeks of continued treatment. Vomiting occurred in the first and second week, over a period of 1-5 days. In another chronic toxicity study, dogs (3 males and 3 females per dose) were treated orally with midodrine in doses of up to 27 mg/kg/day for 6 months. The dose of 9 mg/kg/day initially produced piloerection, mydriasis and vomiting, each of which dissipated with time. At 27 mg/kg/day, mild and moderate sedation was evident and was associated with decreased food intake and weight gain. There was a significant decrease in heart and spleen weight, and a significant increase in lung, liver, and kidney weight.

Mutagenicity: No mutagenicity was seen with midodrine, according to either the Ames test, using 5 strains of *Salmonella typhimurium* (up to 1000 mg/dish), or the micronucleus test in mice

(up to 50 mg/kg with 5 males and 5 females per dose).

Reproductive Studies: The effect of midodrine on reproductive function was tested by the dominant lethal assay in male CFLP mice. Oral midodrine was administered for 5 consecutive days in doses of 9, 27 and 81 mg/kg/day to male mice (20 per dose). Two days after the end of treatment, the mice were paired for one week with untreated females (120 per dose). Fetal implantation rate, litter size and post implantation loss were unaffected by treatment. Midodrine was given by gavage to Sprague-Dawley rats (20 females per dose) in dose levels of 0.1, 1.5 and 20 mg/kg/day during the sixth to the fifteenth day of pregnancy. There was no effect on pregnancy or the fetus at doses of 0.1 and 1.5 mg/kg/day. At 20 mg/kg/day, there were significant reductions in the reabsorption rate and body weight of fetuses. Dams showed significant reductions in food consumption and rate of weight gain. The effect of oral gavage of midodrine at doses of 0.1, 1.5 and 20 mg/kg/day from the sixth to the eighteenth day of pregnancy was studied in New Zealand white rabbits (10 females per dose). The progress of pregnancy and the development of the fetus was normal at the two lower doses. At a dose of 20 mg/kg/day, a post-implantation loss rate of 88.2% occurred and body weight of fetuses delivered was significantly reduced. Dams were ataxic and showed significantly reduced food intake and body weight gain.

Carcinogenicity: 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 midodrine.

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