Midodrine Hydrochloride Tablets, USP

Rx only

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MIDODRINE HYDROCHLORIDE TABLETS, USP

Midodrine hydrochloride is a vasopressor/orthostatic hypotensive. The chemical name for midodrine hydrochloride is acetamide, 2-amino-1H-benzo[4,5]imidazol-3-yl acetamide, (x)-. The molecular weight of midodrine hydrochloride is 293.1. Its structural formula and molecular weight are shown in Figure 1.

Midodrine hydrochloride, USP is an odorless, white, crystalline powder. It is soluble in water and sparingly soluble in methanol and has a pKa of 7.8 (0.3% aqueous solution) and a pH of 5.5 to 5.5 (5% aqueous solution). It has a melting range of 200° to 203°C.

Each midodrine hydrochloride tablet, USP for oral administration contains 2.5 mg, 5 mg or 10 mg of midodrine hydrochloride, USP. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, microcrystalline cellulose, pregelatinized starch (magnesium stearate and sodium lauryl sulphate). CLINICAL PHARMACOLOGY

Mechanism of Action: Midodrine hydrochloride forms an active metabolite, desglymidodrine, that is an alpha, agonist, and exerts its actions via activation of the alpha-adrenergic receptors of the arteriolar and venous vasculature, resulting in vasoconstriction 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. Following oral 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 insufficiency.

Pharmacokinetics: Midodrine hydrochloride is a prodrug, i.e., the therapeutic effect of orally administered midodrine is due to the major metabolite desglymidodrine formed by deconjugation and initial metabolic deamination. The 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 deconjugation of midodrine is considered likely to occur 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/min, most, about 80%, by active renal secretion. The actual mechanism of active secretion has not been studied, but it is possible that it is due to the base-secretary pathway responsible for the secretion of other several drugs that are bases (See also PRECAUTIONS: Potential for Drug Interactions).

Midodrine hydrochloride 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 20 mmHg after administration of a test dose of midodrine. Prior to 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/uneasiness scores and global evaluations, but there were no long-term treatment evaluation of the patient should include assessment of renal and hepatic function prior to initial use of midodrine hydrochloride. Midodrine hydrochloride use has not been studied in patients with hepatic impairment, as the liver has a role in the metabolism of midodrine hydrochloride. 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.

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Midodrine hydrochloride tablets, USP are indicated for the treatment of symptomatic orthostatic hypotension. Midodrine hydrochloride tablets, USP are indicated for the treatment of symptomatic orthostatic hypotension.

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Midodrine hydrochloride increased the rate of embryo abortion, reduced fetal weight in rats and rabbits, and decreased fetal survival in rabbits when given in doses 13 (oral) 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. 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 if 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. Other adverse reactions that occurred rarely were visual field defect; dizziness; skin rash. Other adverse reactions that occurred rarely were headache; feeling of pressure/fullness in the head; nausea; vomiting; emesis; temperature elevation; rash; fever; diaphoresis; urticaria and angioedema.

**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.** One patient ingested midodrine hydrochloride drops, 250 mg, experienced systolic blood pressure greater than 200 mmHg, was treated with an I.V. infusion of 90 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, apneic 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 would be potentially life-threatening are unknown. The oral LD₅₀ is approximately 30 to 50 mg/kg in rats, 6/5 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 tablets is 10 mg. 3 times daily. Doses should be increased gradually until the patient has reached the maximum effectiveness. The single doses that would be associated with symptoms of overdose or would be potentially life-threatening are unknown. The oral LD₅₀ is approximately 30 to 50 mg/kg in rats, 6/5 mg/kg in mice, and 125 to 160 mg/kg in dogs.

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**HOW SUPPLIED**

Midodrine Hydrochloride Tablets, USP are available for oral administration, containing 2.5 mg, 5 mg or 10 mg of midodrine hydrochloride, USP.

- **FOR ORAL USE:**
  - Bottles of 10 tablets NDC 49884-949-01
  - Bottles of 50 tablets NDC 49884-949-05

**Storage:**

Store at 20° to 25°C (68° to 77°F) (see USP Controlled Room Temperature).

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

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