DATA SHEET

GUTRON

Midodrine hydrochloride 2.5 mg and 5 mg tablets.

Presentation

Midodrine hydrochloride as:
2.5 mg tablets: White, circular, flat tablets of 7 mm diameter scored on one side and embossed GU above the score and 2,5 below the score.
5 mg tablets: Orange, circular, flat tablets of 7 mm scored on one side and embossed GU above the score and 5,0 below the score.

Uses

Actions

Midodrine is a prodrug, i.e., 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 a methyl group on the side chain.

Desglymidodrine is a selective postsynaptic alpha adrenergic receptor stimulant with little effect on the beta-adrenergic receptors in the heart. The actions of midodrine on the cardiovascular and other organ systems are essentially identical with those of other alpha-adrenergic receptor stimulants such as phenylephrine or methoxamine.

The most prominent effects of midodrine are on the cardiovascular system, consisting of a rise in systolic and diastolic blood pressures, accompanied by a marked reflex bradycardia. The increase in blood pressure is due almost entirely to an increase in peripheral resistance. Midodrine slightly decreases cardiac output and renal blood flow. Acting on the urinary system, desglymidodrine increases the tone of the internal bladder sphincter and delays the emptying of the bladder.

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 (20mg daily), no effects were seen on plasma clotting factor, there was no activation of fibrinolysis, or effects on number and function of thrombocytes.

Pharmacokinetics

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

After the oral administration of 2.5 mg midodrine in a single dose to 12 volunteers, the peak concentration of unchanged midodrine is approximately 10 ng/mL and occurs after 30 minutes, with a terminal plasma half-life of 0.4 to 0.5 hours. Desglymidodrine reaches peak plasma concentrations (0.027 mg/L) about 1 hour after a 5 to 10mg oral dose of midodrine in fasted patients with orthostatic hypotention.The plasma half-life of of desglymidodrine is 2 – 3 hours after the oral administration of 2.5 mg midodrine.

Very little midodrine crosses the blood-brain barrier. Both midodrine and desglymidodrine are quickly eliminated from the body, mostly by the kidneys. Approximately 90% of the administered dose is excreted in the urine in 24 hours. Of the urinary material, 40 to 60% is present as desglymidodrine and approximately 2 – 5%, as midodrine. Unidentified breakdown products do not exceed 4% of the urinary material.

To date, there are no data on the pharmacokinetics of Midodrine or its metabolite desglymidodrine in elderly patients or in patients with renal and/or hepatic impairment.

Indications

GUTRON (midodrine hydrochloride) tablets may be added to an established treatment regimen in order to attenuate symptoms in the primary neurogenic types of idiopathic orthostatic hypotension, that is in the Bradbury-Eggleston or Shy-Drager syndromes, in those cases when the response to the standard therapy is not adequate.

The tablets may also be added to an established treatment regimen where hypotension is secondary to other medical disorders such as diabetes or Parkinson's disease.

The initiation of GUTRON therapy should be undertaken under close medical supervision in a controlled clinical setting such as in hospital, in the clinic or in the office.

Dosage and Administration

Adults and Adolescents: Treatment with GUTRON (midodrine hydrochloride) tablets should be started under close medical supervision in a controlled clinical setting such as in hospital, in the clinic, or in the office. Hourly measurements of blood pressure (supine and sitting or standing, if possible) should be made for 3 hours following the first dose and also the second dose of a three times daily dosage regimen.

It is recommended that treatment begin at the lowest level and be titrated at intervals of three to several days until the optimal response is obtained. Upon escalating the dosage, the supine and standing blood pressure should be closely monitored in hospital, in the clinic or in the office as for the initiation of therapy, hourly for 3 hours following the first two doses.

The usual starting dose of GUTRON tablets 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. GUTRON tablets can be given up to six times per day.

Some patients require a morning dose that is higher than that taken later in the day. In some instances GUTRON tablets have 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 is recommended that midodrine doses not be given after the evening meal. The maximum recommended dose should not exceed 30 mg daily.

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

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

Children: In view of the lack of experience in children, this medicine is not recommended for patients under 12 years of age.

Geriatric patients: No specific studies have been performed addressing a possible dose-reduction in the elderly population.

Patients with renal insufficiency: No specific studies have been performed addressing a possible dose-reduction in patients with renal insufficiency. Generally GUTRON is contraindicated in patients with acute renal disease and severe renal insufficiency.

Patients with hepatic impairment: No specific studies have been performed in this patient population, so experience is missing.

Contraindications

GUTRON tablets are contraindicated in patients with the following conditions/diseases: severe organic heart disease, hypertension, obliterative or spastic vessel disease; acute renal disease, renal insufficiency, hypertrophy of the prostate gland with formation of residual urine, urinary retention;

- pheochromocytoma
- hyperthyroidism
- narrow-angle glaucoma
- known hypersensitivity to any component of the product

Warnings and Precautions

Supine Hypertension: The most serious and frequent (*see Adverse Effects*) adverse reaction to GUTRON in patients suffering from primary neurogenic hypotension is the unacceptable 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 GUTRON therapy and during the titration period and patients should be monitored for possible secondary events to hypertension.

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

To minimise the incidence of supine hypertension, instructions 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 medicine and consult with the prescribing physician.

Patients in whom the blood pressure during treatment with GUTRON proves to be "brittle" (i.e. very variable) despite stabilisation of treatment, should not continue on GUTRON.

Bradycardia: Bradycardia may occur after GUTRON tablets administration, primarily due to vagal reflex. Patients on GUTRON should avoid concomitant use of other adreno-sympathicomimetic medicines, including over-the-counter remedies (see Interactions). In addition caution should be taken when using it together with other agents that directly or indirectly slow the heart rate (e.g. digitalis, psychopharmacologic agents). 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 stop taking the medication until they have consulted with the prescribing physician.

GUTRON tablets should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

Urinary Retention: GUTRON may induce an increase in the tone of the internal sphincter of the urinary bladder which may lead to urinary retention. GUTRON also may affect 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.

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

Glaucoma: The use of GUTRON in patients who have an increased risk of glaucoma/increased intra-ocular pressure, suffer from glaucoma/ increased intra-ocular pressure or who are treated with mineralcorticoids/Fludrocortisone acetate (which may increase the intra-ocular pressure) should be avoided or monitored very carefully.

It is advisable to always monitor the blood pressure and renal function in patients undergoing long-term treatment with GUTRON.

Treatment with GUTRON has not been studied in patients with liver impairment. It is therefore, recommended to evaluate hepatic parameters before starting treatment with GUTRON and on a continuous basis.

Use of GUTRON may produce minor or moderate adverse effects on the ability to drive or use machinery due to possible bradycardia, therefore, care should be taken until the effects on the individual patient are known.

Pregnancy: No teratogenic effects have been observed in studies in animals. At very high doses (20 mg/kg/day) the medicine was toxic to dams and foetal loss occurred. There are no data on the use of GUTRON in pregnant women. Therefore, GUTRON should be used during pregnancy only when the benefit to the mother exceeds the possible harm to the foetus.

Nursing Mothers: It is not known if GUTRON is excreted in human milk. Caution should be exercised when GUTRON is administered to nursing mothers.

Children: Safety and effectiveness in children have not been established.

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/dose).

Reproductive Studies: Midodrine administered to male CFLP mice in doses of up to 81 mg/kg/day for 5 days prior to pairing with untreated females did not cause any change in foetal implantation rate, litter size or post implantation loss when compared to controls.

Midodrine given to female Sprague Dawley rats during the sixth to fifteenth day of pregnancy caused reduction in foetal weight, dam weight and food consumption only at the highest dose studied. Similar results were seen in a rabbit study.

Carcinogenicity: There is no information regarding carcinogenicity studies in animals.

Other: No information known

Adverse Effects

Very common (>1/10); Common (>1/100, <1/10); Uncommon (>1/1000, <1/100); rare (>1/10.000, <1/1.000); Very rare (<1/10.000).

Psychiatric disorders
Uncommon: Sleep disorders. Insomnia.

Nervous system disorders
Common: Paraesthesia.
Uncommon: Headache. Restlessness. Excitability. Irritability.

Cardiac disorders
Uncommon: Reflex bradycardia.
Rare: Tachycardia

Vascular disorders
Common: supine hypertension (BP above or equal to 180/110mmHg) with daily doses above 30 mg.
Uncommon: supine hypertension (BP above or equal to 180/110mmHg) with daily doses up to 7.5 mg.

Gastrointestinal disorders
Common: Nausea. Heartburn. Stomatitis.

Hepato-biliary disorders
Rare: Hepatic function abnormal. Raised liver enzymes.

Renal and urinary disorders

Very common: Dysuria (13%).
Common: Urinary retention (6%)
Uncommon: Urinary urgency

Skin and subcutaneous tissue disorders
Very common: Pilo-erection (goosebumps) (13%)
Common: Pruritus. Chills, flushing, Skin rash.
Although a causal relationship has not been identified, there have been cases of serious skin reactions, including Stevens-Johnson Syndrome, associated with the use of midodrine.

Laboratory Interactions
No information known

Interactions

When administered concomitantly with GUTRON, cardiac glycosides may enhance or precipitate bradycardia, heart block or arrhythmia.

The use of medicines which stimulate alpha adrenergic receptors (e.g. phenylephrine, methoxamine, tricyclic antidepressants, antihistamines, thyroid hormones, MAO-inhibitors, dihydroergotamine or any OTC medicine) that may enhance or potentiate the pressor effects of GUTRON. Therefore, when GUTRON is used concomitantly with vasoconstrictor sympathomimetic agents, caution is required.

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 GUTRON can be minimised by either reducing the dose of fludrocortisone or decreasing the salt intake prior to initiation of treatment with GUTRON.

The effect of GUTRON may be antagonised by α-adrenergic blocking drugs, such as prazosine and phentolamine. Concomitant use of GUTRON with alpha- or beta-receptor blocking agents, which may reduce the heart rate requires careful monitoring.

The use of rauwolfia alkaloid medicines (e.g. reserpine) slightly increases the pressor effects of GUTRON.

GUTRON may enhance or potentiate the blood-pressure raising effect of atropine.

GUTRON may enhance or potentiate the possible blood-pressure raising effect of corticosteroid preparations

Overdosage

Signs: Overdose symptoms are those seen as undesirable effects, in particular hypertension, piloerection (goosebumps), and sensation of coldness, bradycardia and urinary retention.
Treatment: Besides basic life support, recommended general treatment based on the pharmacology of GUTRON includes induced emesis and administration of alpha-sympatholytic drugs (e.g.nitroprusside, phentolamine, nitroglycerin).

Bradycardia and bradycardic conduction defects can be counteracted by atropine.

The active metabolite Desglymidodrine is dialyzable.

Pharmaceutical Precautions

Protect from light and moisture. Store below 25°C. Keep out of reach of children.

Medicine Classification

Prescription Medicine.

Package Quantities

2.5 mg and 5 mg tablets: 100 tablets.

Further Information

Midodrine hydrochloride is: 2-amino-N-[2-(2, 5-dimethoxyphenyl) -2-hydroxyethyl]-monohydrochloride, (±)-acetamide, or (±)-2-Amino-N-(□-hydroxy-2, 5-dimethoxyphenethyl) acetamide monohydrochloride. It has a molecular formula and weight of $C_{12}H_{18}N_2O_4$.HCl and 290.74 respectively.

Experiments, both *in-vitro* and *in-vivo*, in several species of animal such as rats, dogs and cats have shown that midodrine and desglymidodrine have alpha-receptor agonist activity that is mediated peripherally with no significant CNS activity involved.

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 characterised by exophthalmus, piloerection, dyspnoea, salivation and tonoclonic spasms.

Subacute Toxicity: Rats given midodrine orally at doses of 5, 10 and 20 mg/kg/day for up to 20 days exhibited changes, that were not dose dependent, in the myocardium comprising foci of degenerative myocardial fibres and an increase in connective tissue cells. Liver changes were also observed that were dose dependent.

Chronic Toxicity: Two studies in rats given midodrine orally at doses of 0.3, 1, 5 and 20mg /kg/day for six months showed little difference between treated animals or controls except slight fatty infiltration of the liver in males dosed at 5 mg/kg.

Two studies in dogs given oral doses of up to 27 mg/kg/day for 6 months showed little difference between treated animals and controls at low to medium doses except for piloerection, mydriasis and vomiting which disappeared with continued treatment. At the highest dose used decreased food intake and decreased weight gain associated with a decrease in heart and spleen weight was noted. Lung, liver and kidney weight increased.

Other ingredients of the tablets are:

2.5 mg tablets: Magnesium stearate, Microcrystalline cellulose, Purified talc, Silicon dioxide, and Starch.

5 mg tablets: Magnesium stearate, Microcrystalline cellulose, Purified talc, Silicon dioxide, Starch and Sunset yellow FCF.

This medicine has been granted provisional consent for distribution under Section 23 of the Medicines Act 1981

Name and Address

Douglas Pharmaceuticals Ltd
PO Box 45-027
Auckland 0651
New Zealand

Ph: (09) 835-0660, Fax: (09) 835-0665

Date of Preparation

October 2010