

New Zealand Data Sheet



1. PRODUCT NAME

GUTRON® 2.5 and 5 mg tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each GUTRON 2.5 mg tablet contains 2.5 mg midodrine hydrochloride.

Each GUTRON 5 mg tablet contains 5 mg midodrine hydrochloride.

Excipient(s) with known effect

GUTRON 5 mg tablet contains Sunset yellow FCF. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

GUTRON 2.5 mg tablets are white, circular, flat tablets of 7 mm diameter scored on one side and embossed GU above the score and 2.5 below the score.

GUTRON 5 mg tablets are orange, circular, flat tablets of 7 mm scored on one side and embossed GU above the score and 5.0 below the score.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

GUTRON (midodrine hydrochloride) is indicated to attenuate symptoms of chronic orthostatic hypotension due to autonomic failure in patients with Bradbury-Eggleston or Shy-Drager syndromes and other medical disorders such as diabetes mellitus or Parkinson's disease.

Because midodrine can cause marked elevation of supine blood pressure, it should only be used in patients whose lives are considerably impaired despite standard clinical care including non-pharmacologic treatment, plasma volume expansion and lifestyle alterations.

The initiation of GUTRON therapy should be undertaken under close medical supervision in a controlled clinical setting.

4.2. Dose and method of administration

Dose

Adults

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, that is, 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.

Dosing of midodrine should take place during daytime hours, when the patient needs to be upright, pursuing the activities of daily life. A suggested dosing schedule of 3 to 4-hour intervals is as follows: shortly before or upon arising in the morning, midday and late afternoon (at least 4 hours before bedtime to reduce the risk of supine hypertension). The supine and standing blood pressure should be monitored regularly during initial treatment (at least two times a week) and the use of midodrine should be stopped if supine hypertension increases excessively.

Some patients require a morning dose that is higher than that taken later in the day.

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.

Special populations

Elderly population

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

Renal impairment

No specific studies have been performed addressing a possible dose-reduction in patients with renal impairment. Generally, GUTRON is contraindicated in patients with acute renal disease and severe renal impairment, see section 4.3.

Hepatic impairment

No specific studies have been performed in this patient population.

Paediatric population

In view of the lack of experience in children, this medicine is not recommended for patients under 18 years of age.

Method of Administration

Oral use. The tablets may be taken with food.

4.3. Contraindications

GUTRON tablets are contraindicated in patients with:

- Severe organic heart disease (e.g., bradycardia, ischaemic heart disease, congestive heart failure, cardiac conduction disturbances or aortic aneurism)
- Hypertension
- Serious obliterative or spastic vascular disorders (e.g., cerebrovascular occlusions and spasms)
- Acute renal disease
- Severe renal impairment
- Hypertrophy of the prostate gland with residual urine volume increased
- Urinary retention
- Proliferative diabetic retinopathy
- Pheochromocytoma
- Hyperthyroidism
- Narrow-angle glaucoma
- Known hypersensitivity to any component of the product

4.4. Special warnings and precautions for use

Supine Hypertension

The most serious and frequent (see section 4.8) adverse reaction to GUTRON 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 GUTRON therapy and during the titration period.

Systolic pressure of about 200 mm Hg was seen overall in about 13.4% of patients given 10 mg of midodrine hydrochloride. Systolic elevations of this degree were most likely to be observed in patients with relatively elevated pre-treatment systolic blood pressures (mean 170 mmHg).

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 midodrine hydrochloride in such patients is not recommended.

Sitting blood pressures were also elevated by midodrine hydrochloride therapy. It is essential to monitor supine and sitting blood pressures in patients maintained on midodrine.

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 (refer to section 4.2).

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.

Bradycardia

Bradycardia may occur after GUTRON tablets administration, primarily due to vagal reflex.

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.

Drug abuse or dependence

There is no potential for drug abuse or dependence with midodrine.

Paediatric population

Safety and effectiveness in children have not been established.

4.5. Interaction with other medicines and other forms of interaction

Simultaneous use of digitalis preparations is not recommended, since the bradycardia which occurs as a result of the use of midodrine is then potentiated and heart block may occur.

Midodrine is an inhibitor of Cytochrome P450 CYP2D6 and may, therefore, affect the metabolism of other medicines metabolised by this isozyme (e.g., perphenazine, amiodarone, metoclopramide). This may lead to increased systemic exposure and increased effects of these medicines.

Avoid the concomitant use of midodrine together with vasoconstrictor, sympathomimetic pressor agents and other medicines which cause hypertension (such as tricyclic antidepressants, antihistamines, thyroid hormones, MAO-inhibitors, as well as over the counter remedies) as this may cause excessive hypertension.

Midodrine may enhance or potentiate the possible hypertensive effects of corticosteroid preparations. Patients being treated with midodrine in combination with mineralocorticoids or glucocorticoids (e.g., fludrocortisone) may be at increased risk of glaucoma/increased intraocular pressure and should be carefully monitored.

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

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

Potential for drug interactions

It is 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 medicines as metformin, cimetidine, ranitidine, procainamide, triamterene, flecainide, and quinidine. Thus, it is possible that midodrine might interact with these medicines.

4.6. Fertility, pregnancy and lactation

Pregnancy

There is no data on the use of GUTRON in pregnant women. Animal studies are insufficient with respect to reproductive toxicity, see section 5.3. It is, therefore, not advisable to use GUTRON in women aiming to become pregnant. Any woman getting pregnant during treatment should be withdrawn from the treatment immediately upon pregnancy being confirmed.

Breast-feeding

It is not known if GUTRON is excreted in human milk. Therefore, GUTRON should not be used during lactation.

Fertility

Refer to section 5.3.

4.7. Effects on ability to drive and use machines

GUTRON have negligible influence on the ability to drive and use machines. However, patients who experience dizziness or light-headedness should refrain from driving or operating machinery.

4.8. Undesirable effects

In the placebo-controlled studies, adverse events regardless of causality were reported in 40.4% of the patients on midodrine 10 mg three times per day compared to 18.6% on placebo. In placebo-controlled trials, the rate of discontinuation of patients on midodrine 10 mg three times per day 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.

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). Not known (cannot be estimated from the available data).

Psychiatric disorders

Uncommon: Sleep disorders, insomnia, restlessness, excitability, irritability

Not known: Anxiety, confusional state

Nervous system disorders

Common: Paraesthesia

Uncommon: Headache

Cardiac disorders

Uncommon: Reflex bradycardia.

Rare: Tachycardia

Vascular disorders

Common: Supine hypertension (BP above or equal to 180/110 mmHg) with daily doses above 30 mg, flushing

Uncommon: Supine hypertension (BP above or equal to 180/110 mmHg) with daily doses up to 7.5 mg

Unknown frequency: Peripheral ischaemia

Gastrointestinal disorders

Common: Nausea, heartburn, stomatitis

Not known: Abdominal pain, discomfort, vomiting, diarrhoea

Hepato-biliary disorders

Rare: Hepatic function abnormal

Investigations

Rare: 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, skin rash

General disorders and administration site conditions

Common: Chills

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9. Overdose

Signs and symptoms

Overdose symptoms are those seen as undesirable effects, particularly hypertension, piloerection (goosebumps), and sensation of coldness, bradycardia and urinary retention.

Management

Besides basic life support recommended general treatment based on the pharmacology of GUTRON includes induced emesis and administration of alpha-sympatholytic medicines (e.g. nitroprusside, phentolamine, nitroglycerin). Bradycardia and bradycardic conduction defects can be counteracted by atropine. The active metabolite desglymidodrine is dialyzable.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, adrenergic and dopaminergic agents; ATC code: C01CA17

Actions

The sympathomimetic agent midodrine is a prodrug that is converted to its pharmacologically active metabolite desglymidodrine after oral administration.

Desglymidodrine is a selective postsynaptic alpha₁ adrenergic receptor stimulant devoid of myocardial beta adrenoreceptor activity. 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 a constriction mainly of the smaller veins and to a lesser extent of the arterioles, i.e. due to an increase in peripheral resistance.

Midodrine slightly decreases cardiac output and renal blood flow.

Acting on the urinary system, midodrine increases the tone of the internal bladder sphincter and delays the emptying of the bladder.

5.2. Pharmacokinetic properties

After oral administration, midodrine is rapidly and almost completely absorbed, achieving maximum plasma concentrations (C_{max}) of about 0.01 mg/L within 30 minutes after a 2.5 mg dose. Desglymidodrine reaches peak plasma concentrations (0.027 mg/L) about 1 hour after a 5 to 10 mg oral dose of midodrine in fasted patients with orthostatic hypotension. The absolute bioavailability of midodrine (as desglymidodrine) is 93% after oral administration.

AUC and C_{max} increase proportionally over the dose range of 2.5 to 22.5 mg.

Administration with food increases the AUC by approximately 25% and the C_{max} decreases by approximately 30%. The pharmacokinetics of desglymidodrine is not affected.

The distribution of midodrine in humans has not been established.

Midodrine and desglymidodrine binding to plasma proteins is less than 30%. Studies in animals show that desglymidodrine is distributed in the target organs. There is diffusion across the blood brain barrier, placenta and into human milk.

Midodrine is extensively metabolized via enzymatic cleavage in various tissues (including the liver) to the active moiety desglymidodrine.

Midodrine is extensively and rapidly cleared from plasma after oral administration (elimination half-life of 0.49 h), whereas desglymidodrine is cleared more slowly (elimination half-life of 2 to 3 h).

Midodrine and desglymidodrine are nearly completely (approximately 91% of the administered dose) excreted in the urine within 24 h, about 40 – 60% as the active metabolite, 2- 5% as non-metabolised midodrine, and the rest as pharmacologically inactive metabolites. Accumulation has not been observed. Faecal elimination of midodrine or desglymidodrine is insignificant.

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

5.3. Preclinical safety data

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 tonic clonic 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.

Pharmacology safety studies and repeat-dose toxicity studies in animals did not reveal safety concerns for humans at the recommended dose levels. The preclinical tests conducted revealed that midodrine is non-teratogenic and non-mutagenic.

In carcinogenic trials in rats, an increased tumour incidence in the testicular interstitial cells was observed; the relevance of this for humans is however, unclear. However, increased rate of embryo resorption, reduced foetal body weight in rats and rabbits, and decreased foetal survival in rabbits was observed when given in doses that caused maternal toxicity.

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).

Carcinogenicity

There is no information regarding carcinogenicity studies in animals.

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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

GUTRON tablets contain magnesium stearate, microcrystalline cellulose, purified talc, silicon dioxide and starch.

GUTRON 5 mg tablets also contain Sunset yellow FCF.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

60 months.

6.4. Special precautions for storage

Store at or below 25°C.

6.5. Nature and contents of container

Bottle, plastic, HDPE, 100 tablets.

Not all strengths may be marketed.

6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd
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Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

30 April 1992

10. DATE OF REVISION OF THE TEXT

05 November 2021

Summary table of changes

Section Changed	Summary of new information
4.6	Addition of animal reproductive toxicity information.
4.8	MedDRA SOC reclassification.
5.3	Addition of animal reproductive toxicity information.