Contraindications
METLIGINE is contraindicated in the following patients.
• Patients with hyperthyroidism: There is a risk that patients with hyperthyroidism may show an excessive response to sympathomimetic agents (i.e., noradrenaline-mimic drugs). Midodrine has noradrenaline-like pharmacological properties.
• Patients with pheochromocytoma: Their condition may worsen with the use of this product, because excessive amounts of catecholamines (including noradrenaline) can be released from pheochromocytoma.

Formulation
Brand name
METLIGINE Tablets 2 mg
Active ingredient
Midodrine hydrochloride 2 mg/tablet
Inactive ingredients
Corn starch, D-Mannitol, Microcrystalline cellulose, Sucrose fatty acid ester
Dosage form
White uncoated scored tablet
ID code
T65
Appearance, size, etc.
T 65
Diameter ca. 6 mm, Thickness ca. 2.6 mm, Weight ca. 100 mg

Indications
Essential hypotension and orthostatic hypotension

Dosage and Administration
For adults: The usual oral dose of METLIGINE is 4 mg per day in 2 divided doses. The dose may be increased or decreased depending on the patient’s condition. If symptoms are severe, the dose can be increased to 8 mg per day.
For children: The recommended oral dose of METLIGINE is 4 mg per day in 2 divided doses. The dose may be increased or decreased depending on the patient’s condition; however, the total daily dose of METLIGINE should not exceed 6 mg.

Precautions
1. Special Precautions for Use
METLIGINE should be administered with caution in the following patients.
(1) Patients with severe cardiac disease: Since METLIGINE forms a pharmacologically active metabolite, desglymidodrine, which acts on the heart by increasing venous return, this product may aggravate cardiac disease if administered to patients whose venous return is reduced for therapeutic reasons.
(2) Patients with severe vascular disorders: If METLIGINE is administered to patients with severe vascular occlusion, for example due to atherosclerosis obliterans, their condition may worsen.
(3) Patients with advanced renal impairment: Since the elimination half-life of midodrine and its active metabolite desglymidodrine is prolonged in such patients, higher blood levels would be expected in them; accordingly, this product should be administered at longer intervals.
(4) Patients with hypertension: If METLIGINE is administered to patients with orthostatic hypotension who have high blood pressure as a pre-existing disease, it may induce excessive rise in blood pressure.
(5) Patients with dysuria associated with prostatic hypertrophy: Since the active metabolite desglymidodrine is an alpha-1-agonist and acts on the alpha-adrenergic receptors of the bladder neck, dysuria may worsen with the use of this product.

2. Important Precautions
Many cases of excessive elevation of supine blood pressure (supine hypertension) have been reported in overseas clinical trials of midodrine in patients with neurogenic orthostatic hypotension; therefore, pay special attention to this potentially serious adverse reaction during METLIGINE therapy. Symptoms such as palpitations and headache may be due to this elevation of supine blood pressure. Supine hypertension can be managed by dose reduction or by lying with the head elevated. If supine hypertension persists, discontinue the medication immediately.
3. Adverse Reactions
A total of 154 adverse reactions were encountered in 121 (1.32%) of 9,156 patients treated with midodrine. The most common adverse reactions included headache in 14 cases, nausea in 13 cases, and abdominal pain in 12 cases. [Results of pre-approval clinical trials and post-marketing clinical experience studies submitted for reexamination]
The following adverse reactions may occur. If any abnormalities related to these adverse reactions are observed, appropriate measures should be instituted.

<table>
<thead>
<tr>
<th>Neuro-psychiatric/ CNS</th>
<th>Incidence 1% &gt; ≥ 0.1%</th>
<th>Incidence &lt; 0.1%</th>
<th>Incidence unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Sleepiness, irritability, dizziness</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastro-intestinal</th>
<th>Nausea, abdominal pain</th>
<th>Vomiting, stomatitis, bloated feeling, constipation</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardio-vascular</td>
<td>Hypertension, palpitations, ventricular extrasystoles</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dermatologic</th>
<th>Rash*, piloerection*, pruritus*, urticaria*, redness*</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatobiliary</td>
<td>Hepatic function disorder, increased ALT (GPT), increased AST (GOT), increased ALP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Feeling of hot flushes, chills, malaise, increased urinary frequency, excessive sweating, shoulder muscle stiffness</td>
<td>Dysesthesia, dysuria</td>
<td></td>
</tr>
</tbody>
</table>

* If any of these symptoms develop, METLIGINE should be discontinued.

4. Geriatric Use
Since physiological function is, in general, decreased in elderly patients, caution should be exercised in the administration of this product (e.g., reduction of dosage).

5. Use during Pregnancy, Delivery, or Lactation
(1) The safety of METLIGINE during pregnancy has not been established; accordingly, it is recommended not to administer this product to women known or suspected to be pregnant.
(2) Nursing mothers should discontinue breast-feeding during METLIGINE therapy; in rats, midodrine has been demonstrated to be excreted in breast milk.

6. Precautions concerning Use
When METLIGINE is provided in a press-through package (PTP) sheet (a blister sheet), instruct the patient to remove each tablet from the package sheet prior to swallowing. It has been reported that, if a small part of the package is mistakenly swallowed along with a tablet, its sharp corners may penetrate and eventually perforate the esophageal mucosa, leading to serious complications (e.g., mediastinitis).

PHARMACOKINETICS
1. Blood levels
Following oral administration of a single 2-mg dose of midodrine hydrochloride to healthy adult volunteers, the pharmacokinetic parameters were as follows:

<table>
<thead>
<tr>
<th></th>
<th>Cmax (ng/mL)</th>
<th>Tmax (hr)</th>
<th>T1/2 (hr)</th>
<th>AUC0-24 (ng·hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midodrine HCl</td>
<td>2.8</td>
<td>1.1</td>
<td>1.0</td>
<td>5.2</td>
</tr>
<tr>
<td>(unchanged form*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desglymidodrine</td>
<td>5.3</td>
<td>1.5</td>
<td>2.4</td>
<td>19.1</td>
</tr>
<tr>
<td>(active moiety*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*(n = 12)*

* Midodrine hydrochloride is a prodrug, which is converted to its pharmacologically active metabolite desglymidodrine after oral administration.

2. Absorption and excretion
When single doses of 1, 2, and 4 mg of midodrine hydrochloride were administered to healthy adults under fasting conditions, the serum levels of the prodrug (midodrine) peaked after approx. one hour and dropped rapidly to nearly zero within 4 hours of dosing, while the serum levels of the active metabolite (desglymidodrine) peaked after 1.5 to 2 hours and declined gradually according to an elimination half-life of approx. 2 hours. The maximum concentration (Cmax) of desglymidodrine was much higher than that of midodrine. The Cmax and AUC of desglymidodrine increased in a dose-dependent manner.
The majority of the drug is excreted as metabolites (including desglymidodrine) in the urine. The urinary excretion is almost complete within 24 hours of administration.

No significant differences have been found in the pharmacokinetic parameters (i.e., the Cmax, Tmax, T1/2, and AUC of midodrine and desglymidodrine) and urinary excretion rates seen after the first dose and after the final (13th) dose of midodrine hydrochloride (2 mg per dose twice daily for 7 consecutive days [26 mg in total] or 4 mg per dose twice daily for 7 consecutive days [52 mg in total]), suggesting no accumulation of the drug.

3. Improvement of bioavailability by prodrug derivatization
A single 2-mg (0.0069 mmole) dose of the prodrug (midodrine hydrochloride) or an equimolar (0.0069 mmole) dose of the active moiety (desglymidodrine) itself was administered orally to healthy adults, and the AUC of desglymidodrine was measured. The AUC of the active moiety, desglymidodrine, was significantly higher after the administration of midodrine hydrochloride than after the administration of desglymidodrine, showing that the prodrug derivatization of the active moiety resulted in an increase in its oral bioavailability.
4. Metabolism

The metabolites in the serum consisted of the active metabolite desglymidodrine (67%) and unchanged midodrine (28%) 1–2 hours after the oral administration of a single 4-mg dose of midodrine hydrochloride to healthy adults. As for urinary metabolites, the two major metabolites were identified as desglymidodrine (21% of the administered dose) and the O-demethylated, oxidatively deaminated metabolite of desglymidodrine (35% of the dose).

The in vitro protein binding in human serum is low (i.e., 24%–31% for midodrine and 27%–28% for desglymidodrine).

5. Urinary metabolites in pediatric patients

When a single 2-mg oral dose of midodrine hydrochloride was administered to pediatric patients with orthostatic hypotension, 29% of the drug was excreted in the urine as the active metabolite desglymidodrine and 3.3% was excreted as non-metabolized midodrine within 24 hours of dosing. These values were comparable to those observed in adults, suggesting that there may be no essential difference in the pharmacokinetics of midodrine between children and adults.

6. Effects of meals

When a single 2-mg oral dose of midodrine hydrochloride was administered to healthy adults either after meals or during fasting, no significant differences were found in the pharmacokinetics of the drug.

CLINICAL STUDIES

The results of double-blind and open-label clinical trials are as follows:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total efficacy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential hypotension</td>
<td>58.2% (89/153)</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>66.7% (336/504)</td>
</tr>
</tbody>
</table>

PHARMACOLOGY

1. Effects on blood pressure in experimental animals

(1) Elevation of blood pressure

1) Midodrine induced a constriction of the peripheral blood vessels mainly in skeletal muscle and the vasculature of the gastrointestinal tract and consequently increased the total peripheral vascular resistance, resulting in elevation of blood pressure (in dogs and monkeys). It showed no direct action on the heart (in dogs).

2) In dogs, oral administration of midodrine hydrochloride (2 and 5 mg/kg) produced a gradual and sustained pressor response.

(2) Pressor effect in animal models of orthostatic hypotension

1) In baroreceptor-denervated rabbits, in which the denervation was accomplished by bilateral sectioning of the carotid sinus, aortic depressor, and vagus nerves, midodrine reduced the decrease in blood pressure induced by 30-degree passive head-up tilt.

2) In hexamethonium-treated dogs, midodrine reduced the decreases in blood pressure, cardiac output, and cerebral blood flow with 30-degree passive head-up tilt.

3) In monkeys, midodrine reduced the decrease in cerebral blood flow during acute hemorrhagic hypotension.

2. Effects on blood pressure in human subjects

(1) Midodrine hydrochloride significantly increased the blood pressure in the supine, sitting, and standing positions in patients with essential hypotension or orthostatic hypotension upon oral treatment with 4 mg per day (in 2 divided doses) to 6 mg per day (in 3 divided doses) for 2 to 8 weeks.

(2) Midodrine hydrochloride significantly reduced the orthostatic blood pressure fall (from supine to standing position) in patients with orthostatic hypotension upon oral treatment with 4 mg per day (in 2 divided doses) for 1 week.

(3) In healthy male adults, midodrine hydrochloride did not affect blood pressure even after oral administration of 8 mg per day (in 2 divided doses) for 1 week.

3. Mechanism of action

The active moiety, desglymidodrine, of the prodrug midodrine is a selective alpha2-agonist and causes constriction of the peripheral blood vessels via activation of alpha-adrenergic receptors. This is supported by the following findings:

- Midodrine produces an increase in blood pressure in vitro (in rats and cats), which can be strongly blocked by an alpha2-antagonist, but only weakly by an alpha1-antagonist.
- Desglymidodrine induces contraction of the smooth muscle in isolated blood vessel preparations in vitro (e.g., rabbit thoracic aorta, dog femoral artery, dog femoral vein, human saphenous vein), which can be strongly blocked by an alpha1-antagonist, but only weakly by an alpha2-antagonist. Midodrine shows no (or only weak) activity in vitro.
- Midodrine and desglymidodrine have neither agonistic nor antagonistic effects on beta-adrenergic receptors.

DESCRIPTION

Generic name: Midodrine hydrochloride
Chemical name: (±)-2-Amino-N-(β-hydroxy-2,5-dimethoxyphenethyl)-acetamide hydrochloride
Structural formula:

![Molecular formula](image)

Molecular formula: C_{12}H_{19}N_{2}O_{4}·HCl
Molecular weight: 290.74
Physicochemical properties: Midodrine hydrochloride is a white crystalline powder. It is freely soluble in formic acid, soluble in water, slightly soluble in 95% ethanol, and practically insoluble in acetone/ethyl. Its aqueous solution (1 → 25) shows no optical rotation.

Melting point: Approx. 200 °C (decomposition)

PACKAGING

<table>
<thead>
<tr>
<th>METLIGINE</th>
<th>Pack with 100, 500, 700, or 1000 tablets (PTP/ blister pack)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets 2 mg</td>
<td>Pack with 500 tablets (loose)</td>
</tr>
</tbody>
</table>
REFERENCES

2) Nagata K et al.: *Yakuri to Chiryou*, 15(3), 1225 (1987)
9) Ishii K et al.: *Progress in Medicine*, 7(3), 598 (1987)
14) Data on file, Taisho (available in Japanese only)
15) Tsuchida K et al.: *Yakuri to Chiryou*, 15(1), 89 (1987)

For Medical Information (including requests for literature):
Customer Service Section
Taisho Toyama Pharmaceutical Co., Ltd.
Tel: +81-(0)3-3985-5599

Manufactured and Marketed by:
Taisho Pharmaceutical Co., Ltd.
24-1, Takada 3-chome, Toshima-ku, Tokyo 170-8633, Japan

Distributed by:
Taisho Toyama Pharmaceutical Co., Ltd.
25-1, Takada 3-chome, Toshima-ku, Tokyo 170-8635, Japan

Revised in June 2009: No changes to the CONTRAINDICATIONS or PRECAUTIONS sections