To be sold by retail on the prescription of Cardiologists only

Midotab 2.5

℞ Midodrine Hydrochloride Tablets USP 2.5 mg

WARNING: Because Midodrine hydrochloride can cause marked elevation of supine blood pressure; it should be used in patients whose lives are considerably impaired despite standard clinical care. The indication for use of Midodrine hydrochloride in the treatment of symptomatic orthostatic hypotension is based primarily on a change in a surrogate marker of effectiveness, an increase in systolic blood pressure measured one minute after standing, a surrogate marker considered likely to correspond to a clinical benefit. At present, however, clinical benefits of Midodrine hydrochloride, principally improved ability to carry out activities of daily living, have not been verified.

COMPOSITION

Each Uncoated Tablet Contains:

Midodrine Hydrochloride USP ..... 2.5 mg

Excipients ..... q.s.

PHARMACEUTICAL FORM

Uncoated Tablet

THERAPEUTIC INDICATION

It is indicated in the treatment of symptomatic orthostatic hypotension.

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Initial dose: 2.5 mg three times a day. Depending on the results of supine and standing blood pressure recordings, this dose may be increased weekly up to a dose of 10 mg three times a day. This is the usual maintenance dosage.

A careful evaluation of the response to treatment and of the overall balance of the expected benefits and risks needs to be undertaken before any dose increase and advice to continue therapy for long periods.

The last daily dose should be taken at least 4 hours before bedtime in order to prevent supine hypertension.

Special population:

Paediatric population

The safety and efficacy of midodrine in children have not been established. No data are available.

Elderly population

There is limited data on dosing in the elderly and there are no specific studies which have focused on a possible dose reduction in the elderly population. Cautious dose titration is recommended.

Patients with renal impairment

There are no specific studies that have focused on a possible dose reduction in patients with renal impairment. Typically, midodrine is contraindicated in patients with acute renal impairment and severe renal impairment.

Patients with hepatic impairment

There are no specific studies in this patient population.

Method of administration: For oral use only.

Patient should be advised to swallow the tablet whole, not to be chewed or crushed.

Do not exceed the stated dose.

Midodrine 2.5 mg tablets may be taken with food or as directed by the Physician.

CONTRAINDICATIONS

- Severe organic heart disease (e.g. bradycardia, heart attack, congestive heart failure, cardiac conduction disturbances or an aortic aneurysm).
- Hypertension.
- Serious obliterative blood vessel disease, cerebrovascular occlusions and vessel spasms.
- Acute kidney disease.
- Severe renal impairment (creatinine clearance of less than 30 ml/min).
- Serious prostate disorder.
- Urinary retention.
- Proliferative diabetic retinopathy.
- Pheochromocytoma.
- Hyperthyroidism.
- Narrow-angle glaucoma.
- Hypersensitivity to the active substance or to any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Severe orthostatic hypotension with supine hypertension

Regular monitoring of supine and standing blood pressure is necessary due to the risk of hypertension in the supine position, e.g. at night. Patients should be told to report symptoms of supine hypertension immediately such as chest pain, palpitations, shortness of breath, headache and blurred vision, and should be monitored for these side effects by the treating physician. Supine hypertension may often be controlled by an adjustment to the dose. If supine hypertension occurs, which is not overcome by reducing the dose, treatment with midodrine must be stopped.

The time of administration of the drug is important in this context. Avoid administration in the late evening. The last daily dose should be taken at least 4 hours before bedtime in order to prevent supine hypertension. The risk of supine hypertension occurring during the night can be reduced by elevating the head.

Severe disturbances of the autonomic nervous system

In patients suffering from a severe disturbance of the autonomic nervous system, administration of midodrine may lead to a further reduction of blood pressure when standing. If this occurs, further treatment with midodrine should be stopped.

Atherosclerotic disease

Caution must be observed in patients with atherosclerotic disease especially with symptoms of intestinal angina or claudication of the legs.

Prostate disorders

Caution is advised in patients with prostate disorders. Use of the drug may cause urinary retention.

Renal and hepatic function

This medicinal product is contraindicated in patients with acute renal impairment or severe renal impairment. Treatment with midodrine has not been studied in patients with hepatic impairment. It is therefore recommended to evaluate the renal and hepatic parameters before starting treatment with midodrine and on a regular basis.

Heart rate

Slowing of the heart rate may occur after midodrine administration, due to vagal reflex. Caution is advised when midodrine is used concomitantly with cardiac glycosides (such as digitalis preparations) and other agents that directly or indirectly reduce heart rate. Patients should be monitored for signs or symptoms suggesting bradycardia.

DRUG INTERACTION

Sympathomimetics and other vasopressor agents

Concomitant treatment with sympathomimetics and other vasoconstrictive substances such as reserpine, guanethidine, tricyclic antidepressants, antihistamines, thyroid hormones and MAO-inhibitors, including treatments that are available without prescription, should be avoided as a pronounced increase in blood pressure may occur.

Alpha-adrenergic antagonists

As with other specific α-adrenergic agonists, the effect of midodrine is blocked by α-adrenergic antagonists such as prazosin and phentolamine.

Heart rate reducing drugs

Monitoring is recommended if midodrine is combined with other drugs that directly or indirectly reduce the heart rate.

Glycosides

Simultaneous use of digitalis preparations is not recommended, as the heart rate reducing effect may be potentiated by midodrine and heart block may occur.

Corticosteroid preparations

Midodrine may potentiate or enhance the 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.

Potential pharmacokinetic interactions

The potential for pharmacokinetic interaction is limited as the metabolic pathways do not involve cytochrome P450 enzymes. However, decreased clearance of medicinal products metabolised by CYP2D6 (e.g. promethazine) has been reported.

Potential effect of other drugs on midodrine

No studies to evaluate the effect of other drugs on the pharmacokinetics of midodrine or the active metabolite desglymidodrine have been conducted. In vitro data indicate that desglymidodrine is a substrate of CYP2D6. Concomitant administration of drugs that inhibit this enzyme (e.g. quinidine, paroxetine, fluoxetine and bupropion) may cause increased plasma levels of desglymidodrine with a potential risk of increased adverse events.

Potential effect of midodrine on other drugs

Midodrine is an inhibitor of CYP2D6 and may affect the metabolism of other drugs. This may be of clinical relevance for active substances that are mainly metabolized by CYP2D6, e.g. tricyclic antidepressants, beta blockers, selective serotonin reuptake inhibitors (SSRI), antiarrhythmics (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-inhibitors) type B, especially if the active substance also has a narrow therapeutic index.

Falsely elevated plasma metanephrine

Patients taking midodrine may have falsely elevated plasma metanephrine as a result of analytical interference when measured by HILIC-based HPLC-MS/MS. This potential for interference should be considered in cases where patients taking midodrine require biochemical investigation for potential phaeochromocytomas and paragangliomas.

USE IN SPECIFIC POPULATIONS

Pregnancy

There are no data from the use of midodrine hydrochloride in pregnant women. Studies in animals have shown reproductive toxicity at maternally toxic doses.

Midodrine 2.5 mg tablets are not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding

It is unknown whether midodrine and its metabolites are excreted in human milk.

A risk to newborns/infants cannot be excluded. Midodrine 2.5 mg tablets should not be used during breastfeeding.

Fertility

Animal studies are insufficient with respect to the assessment of fertility.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Midodrine 2.5 mg tablets 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.

UNDESIRABLE EFFECTS

Summary of the Safety Profile

The most frequent and very common adverse reactions related to Midodrine hydrochloride therapy are piloerection, pruritus of the scalp and dysuria.

Adverse effects have been ranked under headings of frequency using the following convention: 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); frequency not known (cannot be estimated from the available data).

Psychiatric disorders: Uncommon: Sleep disorders, Insomnia. Not known: Anxiety, Confusional state.

Nervous system disorders: Common: Paraesthesia, Paraesthesia of the scalp, and Headache. Uncommon: Restlessness, Excitability, and Irritability.

Cardiac disorders: Uncommon: Reflex bradycardia. Rare: Tachycardia, Palpitations.

Vascular disorders: Common: Supine hypertension (dose dependent effect).

Gastrointestinal disorders: Common: Nausea, Dyspepsia, and Stomatitis. Not known: Abdominal pain, Vomiting and Diarrhoea.

Hepatobiliary disorders: Rare: Abnormal hepatic function, Raised liver enzymes.

Skin and subcutaneous tissue disorders: Very common: Piloerection (goosebumps), Pruritus of the scalp. Common: Pruritus, Chills, Flushing and Rash.

Renal and Urinary disorders: Very common: Dysuria. Common: Urinary retention. Uncommon: Urinary urgency.

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. Kindly report any suspected adverse reactions to pharmavigil@jbcpl.com

OVERDOSE

The symptoms of overdose are the same as experienced with side effects. The following in particular may occur: hypertension, piloerection (goosebumps) and feeling cold, bradycardia (reflex bradycardia) and urinary retention.

Treatment: In addition to the main general "life support" measures, induced vomiting and the administration of an α-sympatholytic agent (e.g. nitroprusside, phentolamine, nitroglycerine) is recommended, based on the pharmacology of the drug.

Bradycardia and bradycardic conduction disturbances can be blocked by atropine.

The active metabolite desglymidodrine is dialysable.

CLINICAL PHARMACOLOGY

Pharmacodynamic properties

Midodrine is the rapidly absorbed pro-drug of the pharmacologically active constituent desglymidodrine. Desglymidodrine is a sympathomimetic agent with a direct and selective effect on the peripheral α1-adrenergic receptors. This α1-stimulative effect induces vasoconstriction of the venous system (causing a reduction in venous pooling). The α1-adrenergic effects of desglymidodrine are almost wholly attributable to the (-) enantiomer of desglymidodrine. After taking midodrine, which is a racemic mixture, (+) desglymidodrine is also present, though this contributes almost nothing to the desired effect.

Desglymidodrine increases the peripheral arterial resistance, resulting in an increase in arterial blood pressure.

Only limited data is available on the long-term effects of taking midodrine.

Stimulation of the α-adrenergic receptors of the bladder and the ureter increases the sphincter muscle tone.

Desglymidodrine has no β-adrenergic effects.

Pharmacokinetic properties

Absorption

After oral administration, midodrine is rapidly absorbed. Peak plasma concentrations are reached after approximately 30 minutes, and the plasma concentration of the active metabolite, desglymidodrine, peaks after approximately 1 hour.

AUC and C_{max} increase proportionally to the dose across a dosage range of 2.5 – 22.5 mg. Administration with food increases the AUC by approximately 25%, and the C_{max} decreases by approximately 30%. The pharmacokinetics of desglymidodrine are not affected.

Distribution

Neither midodrine nor desgylmidodrine are bound to plasma proteins to any significant extent (less than 30%). Desglymidodrine diffuses poorly across the blood-brain barrier. Diffusion across the placenta has been reported. It is not known whether this drug is excreted in human milk.

Metabolism

Midodrine is partially hydrolysed before absorption (in the intestines), and partially after absorption (in plasma) by the separation of glycine, herewith generating the active metabolite, desglymidodrine. The elimination of desglymidodrine is primarily caused by an oxidating metabolism, followed by (partial) conjugation.

Excretion

Midodrine (8%), desglymidodrine (40%), and their degradation products (55%) are excreted in the urine by more than 90% within 24 hours in conjugated or non-conjugated forms. The plasma elimination half-life for midodrine is approximately 30 minutes, and is approximately 3 hours for desglymidodrine. Elimination of the active (-) enantiomer of desglymidodrine is slower than the elimination of the inactive (+) enantiomer.

Special Population

A study with 16 patients undergoing hemodialysis demonstrated that Midodrine hydrochloride is removed by dialysis.

INCOMPATIBILITY

Not applicable.

DESCRIPTION

Midodrine hydrochloride is a vasopressor/antihypotensive agent. It is chemically described as: (1) Acetamide, 2-amino-*N*-[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]-monohydrochloride, (±)- ; or (2) (±)-2-amino-*N*-(ß-hydroxy-2,5-dimethoxyphenethyl) acetamide monohydrochloride. Midodrine hydrochloride's molecular formula is $C_{12}H_{18}N_2O_4HCl$, its molecular weight is 290.7

PACKAGING INFORMATION

Blister of 20 tablets and 4 Tablets.

STORAGE INSTRUCTIONS

Store protected from light & moisture, at a temperature not exceeding 25°C.

Keep all medicines out of reach of children.

Marketed by :
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road,
Worli, Mumbai - 400 030. India.

*Trade Mark under Registration

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Note: This prescribing information is applicable for India Market only.