

Metformin Hydrochloride and Voglibose Tablets

METADOZE® V - 0.2/0.3

Q100TAB 0.2/0.3

METADOZE® V - 0.2

COMPOSITION

Each uncoated bi-layered tablet contains Metformin Hydrochloride IP 500 mg Voglibose 0.2 mg

METADOZE® V - 0.3

COMPOSITION

Each uncoated bi-layered tablet contains Metformin Hydrochloride IP 500 mg Voglibose 0.3 mg

PHARMACEUTICAL FORM

Tablet

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Mechanism of Action

Voglibose

Voglibose is an alpha-glucosidase inhibitor which reduces intestinal absorption of starch, dextrin, and disaccharides by inhibiting the action of α -glucosidase in the intestinal brush border. Inhibition of this enzyme halts the decomposition of disaccharides into monosaccharides and slows the digestion and absorption of carbohydrates; the post-prandial rise in plasma glucose is blunted in both normal and diabetic subjects resulting in improvement of post-prandial hyperglycemia and various disorders caused by hyperglycemia. α -glucosidase inhibitors do not stimulate insulin release and therefore do not result in hypoglycemia. These agents may be considered as monotherapy in elderly patients or in patients with predominantly post prandial hyperglycemia. α -glucosidase inhibitors are typically used in combination with other oral antidiabetic agents and/or insulin. Voglibose should be administered at the start of a meal as it is poorly absorbed.

Clinical Efficacy:

In a randomized double-blind trial comprising 1780 Japanese individuals with impaired glucose tolerance, who were treated for an average of 48.1 weeks (standard deviation, SD =36.3). Ruzyo Kawamori et al reported voglibose to be better than placebo (p=0.0026). It was noted that voglibose, in addition to lifestyle modification, can reduce the development of type 2 diabetes in high risk Japanese individuals with impaired glucose tolerance.

Kazuhsa Takami et al examined the effects of dietary modification/restriction alone and dietary modification/restriction with voglibose or glyburide on abdominal adiposity and metabolic abnormalities in 26 Japanese patients with type 2 diabetes. In newly diagnosed patients who were relatively lean but had excess visceral adipose tissue area (VAT), dietary modification/restriction (with or without voglibose or glyburide) effectively reduced VAT. Decrease in VAT was closely associated with improvement of glycemic control through diet. Additional use of voglibose or low-dose glyburide had no detrimental effects on abdominal adiposity and had beneficial effects on insulin sensitivity and the acute insulin response.

In another trial, treatment with voglibose in diabetes mellitus patients demonstrated improved post prandial blood glucose levels, a significant decline in triglyceride level, and an elevation of high density lipoprotein (HDL) cholesterol and apolipoprotein A-1. As compared to acarbose, voglibose was more effective and had fewer side effects.

In a meta-analysis comparing miglitol and voglibose, no significant differences in post prandial glucose were observed between the 2 groups.

Metformin

Metformin is a biguanide with antihyperglycemic effects, lowering both basal and post-prandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia.

Metformin may act via 3 mechanisms:

1. By reducing hepatic glucose production through inhibition of gluconeogenesis and glycogenolysis.
2. By increasing insulin sensitivity in muscle, improving peripheral glucose uptake and utilization.
3. By delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUTs), known till date. In humans, independently of its action on glycemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long term clinical studies: Metformin reduces total cholesterol, low density lipoprotein (LDL) cholesterol, and triglycerides levels.

Clinical Efficacy:

The prospective randomized UKPDS trial established long-term benefit of intensive blood glucose control in type 2 diabetes.

Analysis of the results of overweight patients treated with metformin after failure of diet alone showed:

- A significant reduction of the absolute risk of any diabetes-related complications in the metformin group (29.8 events/1000 patient-years), the group with diet alone (44.3 events/1000 patient-years, p=0.0023) and the combined sulfonylurea and insulin monotherapy group (40.1 events/1000 patient-years, p=0.0034).
- A significant reduction of the absolute risk of the diabetes-related mortality: metformin, hydrochloride 7.5 events/1000 patient-years; diet alone, 12.7 events/1000 patient-years, p=0.017.
- A significant reduction of the absolute risk of overall mortality: metformin hydrochloride 13.5 events/1000 patient-years; versus diet alone 20.6 events/1000 patient-years (p=0.011), and the combined sulfonylurea and insulin monotherapy group 18.9 events/1000 patient-years (p=0.021).
- A significant reduction in the absolute risk of myocardial infarction: metformin group, 11 events/1000 patients-years, diet alone 18 events/1000 patients years (p=0.01).

Pharmacokinetic Properties

Voglibose:

Absorption:

Voglibose is poorly absorbed after oral dosing. Plasma concentrations after oral doses have usually been undetectable. After an 80 mg dose (substantially higher than the recommended dose), peak plasma levels of about 20 ng/ml were observed in 1 to 1.5 hours.

When voglibose tablets were repeatedly administered to healthy male adults (6 subjects) in a single dose of 0.2 mg, 3 times a day for 7 consecutive days, voglibose was not detected in plasma or urine. Similarly, when voglibose was administered to healthy male adults (10 subjects) as a single dose of 2 mg, voglibose was not detected in plasma or urine.

Distribution:

After ingestion of voglibose (and other glucosidase inhibitors), the majority of active unchanged drug remains in the lumen of the gastrointestinal tract to exert its pharmacological activity.

Metabolism

Voglibose is metabolized by intestinal enzymes and by the microbial flora.

Elimination:

Voglibose is excreted in the urine and feces.

In a study in which a single dose of 1 mg/kg of C14-voglibose was administered to rats, the transfer of voglibose to the fetus and to mother's milk was observed, and the rates of excretion into urine and feces were about 5% and 98%, respectively.

Metformin

Absorption:

After an oral dose of metformin, time to peak plasma concentration (T_{max}) is reached in 2.5 hours. Absolute bioavailability of a 500 mg or 850 mg metformin tablet is approximately 50% to 60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in feces was 20% to 30%. After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and the dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 µg/ml. In controlled clinical trials, peak plasma concentration (C_{max}) of metformin did not exceed 4 µg/ml, even at maximum doses. Food decreases the extent of absorption and slightly delays absorption. Following administration of a dose of 850mg, a 40% lower C_{max}, a 25% decrease in area under the curve (AUC) and a 35-minute prolongation of T_{max} were observed. The clinical relevance of these findings is unknown.

Distribution:

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean V_d ranges between 63 to 276 L.

Metabolism

Metformin is excreted unchanged in urine. No metabolites have been identified in humans.

Elimination:

Renal clearance of metformin is >400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Children and Adolescents:

Single-dose study: After single doses of metformin 500 mg, pediatric patients have shown a similar pharmacokinetic profile to that observed in healthy adults.

Multiple-dose study: Data are restricted to 1 study. After repeated doses of 500 mg BID for 7 days in pediatric patients the C_{max} and systemic exposure (AUC₀₋₁) were reduced by approximately 33% and 40%, respectively, compared to diabetic adults who received repeated doses of 500 mg BID for 14 days. As the dose is individually titrated based on glycemic control, this is of limited clinical relevance.

Preclinical Safety Data

No animal studies have been conducted with the combined products in METADOZE® V - 0.2/0.3 mg. The following data are findings in studies performed with metformin individually.

Voglibose

No animal studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development have been conducted with voglibose.

Metformin

Preclinical data suggests no special hazards for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and reproductive toxicity.

CLINICAL PARTICULARS

Therapeutic Indications

As a second-line treatment of type 2 diabetes mellitus when diet, exercise, and the single agent do not result in adequate glycemic control.

Posology and Method of Administration

One tablet, 3 times daily before meals, or as prescribed by the physician

Voglibose

Normal Adult Dose

Usually, voglibose tablets are orally administered in a single dose of 0.2 mg, 3 times a day, before each meal. If the effect is not sufficient, the quantity of a single dose may be increased up to 0.3 mg.

Dosage in Renal Failure

Voglibose is poorly absorbed after oral doses and renal excretion is negligible, suggesting that no dose adjustment is required. However, pharmacokinetic studies in patients with renal insufficiency are not available.

Pediatrics

The safety and effectiveness of voglibose in children has not been established.

Geriatrics

Since elderly patients generally have a physiological hypofunction, it is desirable that such caution be taken as starting the administration at a low dose (eg, 0.1 mg at a time). Furthermore, this drug should be carefully administered under close observation through the course of the disease condition, with careful attention to the blood sugar level and the onset of gastrointestinal symptoms.

Metformin:

Adults:

- The usual starting dose for fixed-dose combination of voglibose 0.2/0.3 mg and metformin hydrochloride 500 mg is 1 tablet, 2 or 3 times daily, given during or after meals. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose of metformin is 3 g daily, taken as 3 divided doses. Do not exceed 0.9 mg voglibose and 2500 mg metformin daily.

- If transfer from another oral antidiabetic is intended, discontinue the other agent and initiate metformin at the dose indicated above.

Dose in Renal Failure

Metformin has the potential for decreased renal function in elderly subjects, therefore the combination of metformin and voglibose is contraindicated in the presence of renal

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METADOZE® V-0.2/0.3

THE TABLET V-02/0.3

dysfunction. Regular assessment of renal function is necessary (for details see "Special Warnings and Precautions for Use").

Pediatrics:

Metformin can be used in children from 10 years of age and adolescents. The safety and effectiveness of voglibose and metformin combination has not been established in children.

Contraindications

- Hypersensitivity to metformin, voglibose, or to any of the excipients.
- Diabetic ketoacidosis, diabetic pre-coma.
- Severe infection, before and after operation or with serious trauma.
- Gastrointestinal obstruction or predisposed to it.
- Renal failure or renal dysfunction (creatinine clearance <60 mL/min)
- Acute conditions with the potential to alter renal function such as:
 - dehydration
 - severe infection
 - shock
 - intravascular administration of iodinated contrast agents (see "Special Warnings and Precautions for Use").
- Acute or chronic disease which may cause tissue hypoxia such as:
 - cardiac or respiratory failure
 - recent myocardial infarction
 - shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism
- Lactation.

Special Warnings and Precautions for Use

Lactic Acidosis:

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly-controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency, and any condition associated with hypoxia. The risk of lactic acidosis must be considered in the event of non-specific signs, such as muscle cramps with digestive disorders as abdominal pain and severe asthenia. Lactic acidosis is characterised by acidotic dyspnea, abdominal pain, and hypotension followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If lactic acidosis is suspected, metformin should be discontinued and patient should be hospitalised immediately (for more details see "Overdose").

Renal Function:

As metformin is excreted by the kidneys, serum creatinine levels should be determined before initiating treatment and regularly thereafter:

- At least annually in patients with normal renal function.
- At least 2 to 4 times a year in patients with serum creatinine levels at the upper limit of normal and in elderly subjects.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID).

Other Precautions:

- In patients who are being managed with lifestyle modifications (diet and/or exercise), this drug must be given only when the 2-hour post prandial blood glucose levels are ≥ 200 mg/dL.
- Voglibose tablets should be administered with caution to the following patients: patients with history of laparotomy or ileus; patients with chronic intestinal disease accompanied by disturbance in digestion and absorption; patients with aggravating symptoms due to increased generation of intestinal gas (eg. Roemheld syndrome, severe hernia, and stenosis and ulcer of the large intestine) and patients with serious hepatic or renal disorders.
- All patients should continue their dietary restriction with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy restricted diet.
- The usual laboratory tests for diabetes monitoring should be performed regularly.
- Metformin alone never causes hypoglycemia, although caution is advised when it is used in combination with insulin and sulfonylureas.
- Patients should be instructed and explained to recognize hypoglycemic symptoms and its management.
- When patients with diabetes are exposed to unusual stress such as fever, trauma, infection, or surgery, a temporary loss of control of blood glucose may occur. At such times insulin therapy may be necessary for some time.

Drug Interactions

Voglibose

When voglibose is used in combination with derivative(s) of sulfonylurea, sulfonylurea or biguanide, or with insulin, hypoglycemic symptoms may occur. Therefore, when used in combination with any of these drugs, care should be taken, such as starting the administration at a low dose.

When voglibose is administered concomitantly with drugs that enhance or diminish the hypoglycemic action of antidiabetic drugs, caution should be taken as this might additionally delay the action of voglibose on the absorption of carbohydrates. Examples of drugs enhancing the hypoglycemic action of antidiabetic drugs: β blockers, salicylic acid preparations, monamine oxidase inhibitors and fibrates derivatives. Examples of drugs diminishing the hypoglycemic action of antidiabetic drugs: epinephrine, adrenocortical hormone, and thyroid hormone.

Voglibose does not affect the pharmacokinetics of warfarin, hence it can be safely administered along with warfarin.

Metformin

Concomitant use with alcohol is not recommended. Increased risk of lactic acidosis in acute intoxication, particularly in case of:

- fasting or malnutrition
 - hepatic insufficiency
- Concomitant consumption of alcohol-containing medications should be avoided.

Combinations Requiring Precautions for Use

Glucocorticoids (systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycemic activity. Inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of the treatment. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

Pregnancy and Lactation

To date, no relevant epidemiological data are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or fetal development, parturition or post natal development, therefore the drug should be given to pregnant women or women suspected of being pregnant only when the potential benefits outweigh the possible hazards.

When the patient plans pregnancy and during pregnancy, diabetes should not be treated with metformin but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of fetal malformations associated with abnormal blood glucose levels.

Metformin is excreted into milk in lactating rats. Similar data is not available in humans and a decision should be made whether to discontinue nursing or to discontinue metformin, taking into account the benefit of using the compound in the mother.

Animal studies (rats) have revealed a suppressive action of voglibose on body weight increase in newborns presumably due to suppression of milk production in mother animals resulting from suppression of carbohydrate absorption. Therefore, it is desirable not to give voglibose to women during lactation. When the administration is unavoidable, nursing should be avoided.

Effects on Ability to Drive and Use Machines

Metformin monotherapy does not cause hypoglycemia and therefore has no effect on the ability to drive or to use machines.

However, patients should be alerted to the risk of hypoglycemia when metformin is used in combination with other antidiabetic agents (sulfonylureas, insulin, repaglinide).

Undesirable Effects

Gastrointestinal disorders such as diarrhea, loose stools, abdominal pain, constipation, anorexia, nausea, vomiting, diarrhoea, abdominal pain, and loss of appetite may occur with the combination of voglibose and metformin. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin hydrochloride be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Skin and subcutaneous tissue disorders: very rarely skin reactions such as erythema, pruritus, urticaria have been seen. In such a case, voglibose tablets should be discontinued.

Metabolism and nutrition disorders: decrease of vitamin B-12 absorption with decrease in serum levels may occur during long term use of metformin. Consideration of this etiology is recommended if a patient on metformin presents with megaloblastic anemia. There are isolated reports of liver-function-test abnormalities or hepatitis resolving upon metformin discontinuation. Serious hepatic dysfunction accompanied with jaundice, increased AST or ALT may also occur.

When voglibose is used in combination with other antidiabetic drugs, hypoglycemia may occur (0.1% to <5%).

Overdose

Hypoglycemia has not been seen with metformin doses up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in a hospital. The most effective method to remove lactate and metformin is hemodialysis.

Voglibose competitively and reversibly inhibits the α -glucosidase enzymes (glucoamylase, sucrase, maltase, and isomaltase) in the brush border of the small intestine, which delays the hydrolysis of complex carbohydrates. The combination is unlikely to produce hypoglycemia in overdose, but abdominal discomfort and diarrhea may occur.

PHARMACEUTICAL PARTICULARS

List of Excipients:

- Microcrystalline cellulose
- Sodium starch glycolate
- Povidone K-30
- Starch
- Purified talc
- Microcrystalline cellulose
- Magnesium stearate
- Quinoline yellow (METADOZE® V-0.2 mg)
- Tartarize (METADOZE® V-0.3 mg)
- Isopropyl alcohol
- Colloidal silicon dioxide

Incompatibilities: None reported.

Shelf Life: 24 months.

Storage and Precautions

Store in a cool, dry place. Protect from light. Keep the medicine out of reach of children.

Special Precautions for Disposal and Other Handling

No special requirements.

THE TABLET SHOULD BE SWALLOWED AS A WHOLE AND NOT TO BE CRUSHED OR CHEWED

Nature and Contents of Container
Aluminum blister pack of 3x10 tablets in a carton

MANUFACTURED BY: Biocon Limited
at Kharsa No. 587/588
Jharmajri, Baddi, Tehsil Nalagarh, Dist. Solan, Himachal Pradesh - 173205.

MARKETED BY: Biocon Limited
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