For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated: Please read carefully before using a new pack

Metformin Hydrochloride Sustained Release and Voglibose Tablet

Cetapin® V

Cetapin® V 0.2 mg
Each uncoated bilayered tablet contains:
Voglibose IP.....0.2 mg
Metformin hydrochloride IP (as sustained release)....500mg
Colour: Lake of Indigo Carmine

Cetapin® V 0.3 mg
Each uncoated bilayered tablet contains:
Voglibose IP.....0.3 mg
Metformin hydrochloride IP (as sustained release)....500mg
Colour: Lake of Erythrosine & Lake of Indigo Carmine

THERAPEUTIC INDICATIONS
Cetapin V is indicated as a second line treatment for type II diabetes mellitus when diet, exercise and single agent do not result in adequate glycemic control.

DOSAGE AND ADMINISTRATION
Dosage of Cetapin V must be individualized on the basis of both effectiveness and tolerance, while not exceeding the recommended daily dose.

The maximum recommended daily dose of metformin in adults is 2000 mg while the usual daily dose of voglibose is 0.6mg – 0.9mg.

Adults - 1 tablet to be given 2-3 times daily with heavy meals.

Special Populations

Paediatrics
Safety and effectiveness has not been established in children.

Geriatrics
Administration of Cetapin V should be initiated at a lower dose and should be carefully administered under close observation. Careful attention must be paid to the blood sugar level and the onset of any gastrointestinal symptoms. The initial and maintenance dosing of metformin should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of metformin.

Monitoring of renal function is necessary to aid in prevention of lactic acidosis, particularly in the elderly.

Dosage in Hepatic Insufficiency
The presence of liver disease is a risk factor for the development of lactic acidosis during metformin therapy and therefore combination of voglibose and metformin should be avoided in patients with hepatic insufficiency.

Dosage in Renal Failure
Due to the risk of lactic acidosis associated with metformin hydrochloride, the combination of voglibose and metformin hydrochloride is contraindicated in the presence of renal dysfunction, defined as serum creatinine greater than or equal to 1.5mg/dL (males), or 1.4mg/dL (females), or an abnormal creatinine clearance.

PREGNANCY
Cetapin® V should not be administered to pregnant women. Most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

LACTATION
Cetapin® V is contraindicated in lactation.

CONTRAINDICATIONS
- History of hypersensitivity to voglibose, metformin or to any other ingredient of this product.
- Severe infections, before or after operation or with severe trauma.
- Active liver disease
- Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.
- Should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.
- Excessive alcohol intake, acute or chronic
- Pregnancy and lactation
- Gastrointestinal obstruction or predisposed to it.

WARNINGS
For Metformin
- **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.

Diagnosis:
Lactic acidosis is characterized by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5mmol/L, and an increased anion gap and lactate/pyruvate ratio. If lactic acidosis is suspected, discontinue Cetapin V and institute general supportive measures in a hospital setting.. Prompt hemodialysis is recommended.

Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL..

Risk factors include renal impairment, concomitant use of certain drugs, age >65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment.

For Voglibose
The administration of Cetapin V should be limited to patients who have established diabetes as there are certain other disease conditions such as abnormal glucose tolerance and positive urinary sugar that represent diabetes-like symptoms (renal glycosuria, senile abnormal glucose tolerance, abnormal thyroid function, etc).

PRECAUTIONS
Cetapin V has to be administered carefully in following patients :
- who are receiving other antidiabetic drugs because hypoglycemia may occur.
- with a history of laparotomy or ileus
- with chronic intestinal disease accompanied by a disturbance in digestion and absorption.
- with Roemheld's syndrome, severe hernia or stenosis or ulceration of the large intestine,
- with serious hepatic dysfunction
- with serious renal dysfunction

Renal function: As metformin is excreted by the kidney, serum creatinine levels should be determined before initiating treatment and regularly thereafter:
- at least annually in patients with normal renal function,
- at least two to four times a year in patients with serum creatinine levels at the 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 an NSAID.

Administration of iodinated contrast agent: As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, metformin should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Surgery: Metformin hydrochloride should be discontinued 48 hours before elective surgery with general anaesthesia and should not be usually resumed earlier than 48 hours afterwards.
Regular monitoring of thyroid-stimulating hormone (TSH) levels is recommended in patients with hypothyroidism (see Adverse Reactions).

Long-term treatment with metformin has been associated with a decrease in vitamin B12 serum levels which may cause peripheral neuropathy. Monitoring of the vitamin B12 level is recommended (see Adverse Reactions).

Other precautions:
- All patients should continue their diet 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 hypoglycaemia, although caution is advised when it is used in combination with insulin or sulfonylureas

DRUG INTERACTIONS
For Voglibose
As voglibose is poorly absorbed after oral administration, its metabolism in liver and excretion though renal route is also negligible, so less likely to interact with co-administered drugs.

For Metformin
- *Glyburide:* In interaction studies in type 2 diabetes mellitus patients, co administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics.

- *Furosemide:* It is reported in a metformin-furosemide drug interaction study in healthy subjects that pharmacokinetic parameters of both compounds were affected by co-administration. No information is available about the interaction of metformin and furosemide when co-administered chronically.

- *Nifedipine:* Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

- *Cationic Drugs:* Cationic drugs (e.g. amiloride, digoxin, morphine, procainamide, quinidine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion, theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Therefore, careful patient monitoring and dose adjustment of metformin or the interfering drug is recommended in patients who are taking cationic medications that are excreted via renal tubular secretion.

- *Other:* Other drugs tend to produce hyperglycemia and may lead to a loss of blood sugar control. These include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, estrogen plus progestogen, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to patients receiving metformin, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving metformin, the patient should be observed closely for hypoglycemia.

In healthy volunteers, the pharmacokinetics of propranolol and ibuprofen were not affected by metformin when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to sulfonylureas, which are extensively bound to serum proteins.

Inadvisable combinations:
Alcohol
Increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:
• fasting or malnutrition,
• hepatic insufficiency.

Avoid consumption of alcohol and alcohol-containing medications.

Iodinated contrast agents
Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis.
Metformin should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal

Associations requiring precautions for use:
Glucocorticoids (systemic and local routes), **beta-2-agonists**, and **diuretics** have intrinsic hyperglycaemic activity. Inform the patient and perform **more frequent blood glucose monitoring**, especially at the beginning of 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.

Metformin may decrease the anticoagulant effect of phenprocoumon. Therefore, a close monitoring

of the INR is recommended.

Levothyroxine can reduce the hypoglycemic effect of metformin. Monitoring of blood glucose levels is recommended, especially when thyroid hormone therapy is initiated or stopped, and the dosage of metformin must be adjusted if necessary

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS

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

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

OVERDOSAGE

No cases of overdosage have been reported with Cetapin® V. In the event of overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Hypoglycemia has not been seen with ingestion upto 85gms of metformin hydrochloride, although lactic acidosis has occurred in such circumstances. Metformin is dialyzable with a clearance of upto 70 ml/min under good hemodynamic conditions. Therefore, hemodialysis maybe useful for removal of accumulated metformin from patients in whom metformin overdosage is suspected. **Pancreatitis may occur in the context of a metformin overdose**

ADVERSE REACTIONS:

For Voglibose

- Gastrointestinal adverse effects like diarrhea, loose stools, abdominal pain, constipation, anorexia, nausea, vomiting and heartburn may occur with the use of voglibose. Abdominal swelling, increased flatus, etc, may occur and intestinal obstruction-like symptom due to an increase in intestinal gas, etc, may also occur. Serious hepatic dysfunction accompanied with jaundice, increased AST, ALT may occur. When voglibose is administered to patients with serious liver cirrhosis, hyperammonemia may worsen with the development of constipation, etc, followed by disturbance of consciousness. Elevation of GOT (glutamate oxaloacetate), GPT (glutamate pyruvate transaminase), LDH (lactate dehydrogenase), aGPT (aglutamate pyruvate) or alkaline phosphatase may infrequently occur.

  When voglibose is used in combination with other antidiabetic drugs, hypoglycemia may occur. Further hypoglycemia has been reported to occur even when other antidiabetic drug was not concomitantly used with this drug.

  Hypersensitivity: Rash and pruritus may rarely occur.

  Psychoneurologic: Headache may rarely occur.

  Hematologic: Anemia; thrombocytopenia, and leucopenia may rarely occur.

Others: Numbness, edema of face, blurred vision, hot flushes, malaise, weakness, hyperkalemia, increased serum amylase, decreased HDL cholesterol, diaphoresis or alopecia,and perspiration.

For Metformin

- Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite (>10%) are very common: these occur most frequently during initiation of therapy and resolve spontaneously in most cases.
- Metallic taste (3%) is common.
- Mild erythema has been reported in some hypersensitive individuals. The incidence of such effects is regarded as very rare (<0.01%).
- A decrease of vitamin B12 absorption with decrease of serum levels has been observed in patients treated long-term with metformin and appears generally to be without clinical significance (<0.01%).

However, **cases of peripheral neuropathy in patients with vitamin B12 deficiency** have been reported in post-marketing experience (frequency not known)(see Precautions)

- Lactic acidosis (0.03 cases/1000 patient-years) is very rare.
- **Hemolytic anemia (frequency unknown)**
- **Reduction of thyrotropin level in patients with hypothyroidism (see Precautions) (frequency unknown)**
- **Hypomagnesemia in the context of diarrhea (frequency unknown)**
- **Encephalopathy (frequency unknown)**
- **Photosensitivity (frequency unknown)**

STORAGE :
Store in a cool and dry place. Protect from light.

Manufactured by :
Inventia Healthcare Pvt. Ltd.,
F1-F1/1, Additional Ambernath MIDC
Ambernath (East) 421506

Marketed by:
Sanofi India Limited
Sanofi House, CT Survey No 117-B, L&T Business Park, Saki Vihar Road, Powai, Mumbai 400072

Updated : April 2021

Source: CCDS Version version 8 dated 23rd June 2016 for Glimepiride plus Metformin Fixed Dose Combination
Metformin GLU ver 1 dated March 2015 and version 2 dated July 2015
Glucophage XR pack insert dated May 2018

VOLICOSE - 0.2/0.3 mg Prescribing Information, Mfg by Biocon Ltd accessed on 09th April 2021