For the use only of a Registered Medical Practitioner or hospital or a laboratory

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METFORMIN HYDROCHLORIDE PROLONGED RELEASE TABLETS IP

CETAPIN® XR

DESCRIPTION
Active Ingredient
Metformin Hydrochloride

Therapeutic or Pharmacological Class
Antidiabetic

Pharmaceutical Form(s)
Prolonged Release Tablets

COMPOSITION
Cetapin® XR 1000mg
Each uncoated prolonged release tablet contains:
Metformin hydrochloride I.P.…1000mg.
Excipients……q.s.

INDICATION
Cetapin® XR is to be used as an adjunct to diet and exercise to improve glycemic control in patients with Type II diabetes.

DOSAGE AND ADMINISTRATION
Posology

Adults with normal renal function (GFR≥ 90mL/min)

Monotherapy and combination with other oral antidiabetic agents:
• The usual starting dose is one tablet of Cetapin® XR 500 mg once daily.

• After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended dose is 4 tablets daily.

• Dosage increases should be made in increments of 500mg every 10-15 days, up to a maximum of 2000mg once daily with the evening meal. If glycaemic control is not achieved on Cetapin® XR 2000mg once daily, Cetapin® XR 1000 mg twice daily should be considered, with both doses being given with food. If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.

• In patients already treated with metformin tablets, the starting dose of Cetapin® XR should be equivalent to the daily dose of metformin immediate release tablets. In patients treated with metformin at a dose above 2000 mg daily, switching to Cetapin® XR is not recommended.

• If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate Cetapin® XR at the dose indicated above.

• Cetapin® XR 1000 mg are intended for patients who are already treated with metformin tablets (prolonged or immediate release).

• The dose of Cetapin® XR 1000 mg should be equivalent to the daily dose of metformin tablets (prolonged or immediate release), up to a maximum dose of 1500 mg or 2000 mg respectively, given with the evening meal.

Combination with insulin

Metformin and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose of Cetapin® XR is one 500 mg tablet once daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

For patients already treated with metformin and insulin in combination therapy, the dose of Cetapin® XR 1000 mg should be equivalent to the daily dose of metformin tablets up to a maximum of 2000 mg respectively, given with the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements.

Elderly patients

Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary (see Renal impairment below and section Warnings/ Precautions).

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

GFR ml/min	Total maximum daily dose (to be divided into 2-3 daily doses)	Additional considerations
60-89	3000 mg	Dose reduction may be considered in relation to declining renal function
45-59	2000 mg	Factors that may increase the risk of lactic acidosis (see section Warnings / Precautions) should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose
30-44	1000 mg.	
<30	-	Metformin is contraindicated

CONTRAINDICATIONS

Hypersensitivity to Metformin Hydrochloride or to any of the excipients.

- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis), diabetic pre-coma.
- Severe renal failure (GFR<30 mL/min).
- Acute conditions with the potential to alter renal function such as dehydration, severe infection, shock.
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism

WARNINGS/PRECAUTIONS

Lactic acidosis:

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections Contraindications and Interactions).

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Renal function:

GFR should be assessed before treatment initiation and regularly thereafter, (see section Dosage and Administration). Metformin is contraindicated in patients with GFR<30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function, (see section Contraindications).

Cardiac function:

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, metformin is contraindicated (see section Contraindications).

Administration of iodinated contrast agents:

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours

after, provided that renal function has been re-evaluated and found to be stable (see sections Dosage and Administration and Interactions).

Surgery:
Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

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 does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulfonylureas or meglitinides).
- Regular monitoring of thyroid-stimulating hormone (TSH) levels is recommended in patients with hypothyroidism (see section 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 section Adverse reactions).
- The tablet shells may be present in the faeces. Patients should be advised that this is normal.

INTERACTIONS
Concomitant use not recommended
Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition or hepatic impairment.
Iodinated contrast agents
Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections Dosage and Administration and Warnings / Precautions).

Combinations requiring precautions for use:
Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics)
More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation.

Medicinal products affecting renal function
Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Organic cation transporters (OCT)
Metformin is a substrate of both transporters OCT1 and OCT2.
Co-administration of metformin with
- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.

- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are coadministered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

Phenprocoumon
Metformin may decrease the anticoagulant effect of phenprocoumon. Therefore, a close monitoring of the INR is recommended

Levothyroxine
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.

REPRODUCTION
Pregnancy
Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality.

A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or post-natal development (see section Contraindication).

When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with metformin but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the foetus.

Lactation
Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breast-feeding is not recommended during metformin treatment. A decision on whether to discontinue breast-feeding should be made, taking into account the benefit of breast-feeding and the potential risk to adverse effects on the child.

Fertility
Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

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 (e.g. sulfonylureas, insulin or meglitinides).

ADVERSE REACTIONS
The following CIOMS frequency rating is used, when applicable

Very common ≥ 10%; Common ≥ 1 and < 10%; Uncommon ≥ 0.1 and < 1%;

Rare ≥ 0.01 and < 0.1%; Very rare < 0.01%; Not known (cannot be estimated from available data).

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take metformin in 2 or 3 daily doses and to increase slowly the doses.

The following adverse reactions may occur under treatment with metformin.
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Blood and lymphatic system disorders

Not known:

- Hemolytic anemia.

Metabolism and nutrition disorders

Very rare:

- Lactic acidosis (see section Warnings / Precautions).
- Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

Not known:

- Cases of peripheral neuropathy in patients with vitamin B12 deficiency have been reported in postmarketing experience (see section Warnings/Precautions).

Nervous system disorders

Common:

- Taste disturbance.

Not known:

- Encephalopathy.

Gastrointestinal disorders

Very common:

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

Hepatobiliary disorders

Very rare:

- Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders

Very rare:

- Skin reactions such as erythema, pruritus and urticaria.

Not known:
- Photosensitivity.

Investigations
Not known:
- Reduction of thyrotropin level in patients with hypothyroidism.
- Hypomagnesemia in the context of diarrhea.

Paediatric population
In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10 - 16 years treated during 1 year, adverse event reporting was similar in nature and severity to that reported in adults.

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

MODE OF ACTION
Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:
- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- and delay of 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 (GLUT).

STORAGE
Store below +25°C in a dry place. Protected from light.

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Windlas Biotech Limited (Plant-IV), Plot No. 183 & 192, Mohabewala Industrial Area, Dehradun-248110, Uttarakhand (India)

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