180 mm

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Provision For Pharmacode
Size : 10 x 7 mm

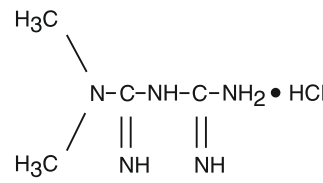
240 mm

Package insert

METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS 500 MG

PROGLUTROL 500

Product Description:
PROGLUTROL 500 (Metformin hydrochloride extended release tablets) is oral anti hyperglycemic drugs used in the management of type 2 diabetes. The chemical name is N,N-dimethylimidodicarbonimidic diamide hydrochloride. The emperical formula is $C_4H_{11}N_5 \cdot HCl$ and the molecular weight is 165.63
The structural formula is:



Composition:
PROGLUTROL 500
Each uncoated extended-release tablet contains:
Metformin Hydrochloride ..... 500 mg
Excipients ..... q.s.

Product Description
PROGLUTROL 500
White to off white capsule shaped tablet plain on both sides and blister packed in Aluminium foil and clear PVC/PVDC.

Inactive Ingredients:
Hypromellose, Sodium carboxy methyl cellulose, Methacrylic acid copolymer Dispersion, Macrogol, Povidone, Magnesium stearate, Purified water

Pharmacodynamics/Pharmacokinetics:
Pharmacodynamics
Metformin hydrochloride is an anti hyperglycemic agent, which improves glucose tolerance in NIDDM (type 2 diabetes mellitus) subjects, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from those of sulfonylureas. Metformin decreases hepatic glucose and improves insulin sensitivity (increases peripheral glucose uptake and utilization). Unlike sulfonylureas, metformin does not produce hypoglycemia in either diabetic or nondiabetic subjects and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacokinetics
Following a single oral dose of sustained release Metformin, Cmax is achieved with a median value of 7 hours and a range of 4 hours to 8 hours. After repeated administration of a sustained release formulation, Metformin does not accumulate in plasma. Although the extent of absorption of the sustained release Metformin increases by approximately 50% when given with food, there is no effect of food on Cmax and Tmax of Metformin.
The apparent volume of distribution (V/F) of Metformin following single oral doses of 850 mg averaged 654 ± 357 L. Metformin is negligibly bound to plasma proteins. Metformin partitions erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules, steady state plasma concentrations of Metformin are reached within 24 -48 hours and are generally < 1 mg/ml.
Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism or biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of Metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Indication:
Treatment of type 2 diabetes mellitus in adults, when dietary management and exercise alone does not result in adequate glycaemic control. PROGLUTROL 500 may be used as monotherapy or in combination with other oral antidiabetic agents or with insulin.

Recommended Dosage:
Monotherapy and Combination with Other Oral Antidiabetic Agents: Usual Starting Dose: 1 tab once daily.
After 10-15 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 is 4 tabs daily.
Dosage increases should be made in increments of 500 mg every 10-15 days, up to a maximum of 2000 mg once daily with the evening meal. In patients already treated with metformin tablets, the starting dose of PROGLUTROL 500 should be equivalent to the daily dose of metformin immediate-release tablets. If transfer from another oral antidiabetic agent is intended, discontinue the other agent and initiate PROGLUTROL 500 at the dose indicated previously.
Combination with Insulin: Metformin and insulin may be used in combination therapy to achieve better blood glucose control. Usual Starting Dose: 1 tab once daily, while insulin dosage is adjusted on the basis of blood glucose measurements.
Children: In the absence of available data, PROGLUTROL 500 should not be used in children.
Elderly: 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.

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	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 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.

Mode of Administration: The route of administration is oral.

5 mm | 5 mm

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Product Name : **PROGLUTROL 500 (Malaysia) (For Submission purpose)**	
Packaging Material : Pack Insert (Front & Back Side)	
Location : Ambernath	Version No.:
Size : 180 x 240 mm (As per Drawing)	
No. of Colour : 01 ■ Black	
Artwork No.:	SAP Code:
Substrate : White rectangular piece of Maplitho paper.	
Drawing No. : PGB195200304 LF	
Specification : 60 GSM	
Pharmacode :	
Any other Requirement : Unfolded & Transparency required	
Change History : CC - 1. Text added 2. Addition of Plot from "F1-F1/1 to F1-F1/1-F75/1" in Inventia address 3. Date of Revision of Package Insert changed from “Apr. 2021" to “Mar. 2024" 4. Pharmacode changed	

Font Style - Switzerland Condensed
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Contraindications:
Renal or hepatic failure, alcoholism, NIDDM complicated by severe ketosis and acidosis, diabetic precoma and coma, patients undergoing surgery, after severe trauma or during infections, chronic obstructive pulmonary disease, coronary heart disease, cardiac failure, peripheral vascular disease, hypoglycemia and known hypersensitivity to Metformin.
It is also contraindicated in:

- Severely reduced kidney function (GFR<30 mL/min)
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)

Warnings and 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 antihypertensive, 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.
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 there after [See Section Recommended Dosage]. Metformin is contraindicated in patients with GFR < 30 mL/min and should be temporarily discontinued in the presence of conditions that alter function [See Section Contraindications]
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 hrs afterwards, and only after renal function has been re-evaluated and found to be normal.
Surgery: Metformin HCl should be discontinued 48 hrs before elective surgery with general anaesthesia and should not be usually resumed earlier than 48 hrs afterwards.

Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

Others: 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 sulphonylureas. The tablet shells may be present in the faeces. Patients should be advised that this is normal.
Effects on the Ability to Drive or Operate Machinery: PROGLUTROL500 monotherapy does not cause hypoglycaemia and therefore, has no effect on the ability to drive or use machines. However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (sulphonylureas, insulin, repaglinide).

Interactions with other Medicaments:
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 hrs afterwards, and only after renal function has beenre-evaluated and found to be normal.
Associations Requiring Precautions for Use: Glucocorticoids (systemic and local routes), ~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.
Incompatibilities: None.

Pregnancy and Lactation:
To date, no relevant epidemiological data are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or foetal development, parturition or postnatal development.
When the patient plans to become pregnant 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 foetal 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 importance of PROGLUTROL 500 to the mother.

Undesirable effects:
-lactic acidosis
In post-marketing data and in controlled clinical studies, adverse event reporting in patients treated with PROGlUTROl 500 was similar in nature and severity to that reported in patients treated with Metformin Hydrochloride immediate release.
The following undesirable effects may occur under treatment with metformin. Frequencies are defined as follows: Very common (>1/10); common (>1/100, <1110); uncommon (>1/1000, <11100); rare (>1/10,000, <1/1000); very rare «1/1 0,000); and isolated reports.
Metabolism and nutrition disorders : Common: Vitamin B12 decrease/deficiency
Nervous System Disorders: Common: Taste disturbance.
Gastrointestinal Disorders: Very Common: 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. A slow increase of the dose may also improve gastrointestinal tolerability.
Hepatobiliary Disorders: Isolated Reports: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.
Skin and Subcutaneous Tissue Disorders: Very Rare: Skin reactions eg, erythema, pruritus, urticaria.

Overdosage and Treatment:
Hypoglycaemia has not been seen with metformin HCl doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin HCl 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 HCl is haemodialysis.

STORAGE CONDITION:
Store below 30°C. Protect from light and moisture. Keep out of reach of children.

Shelf Life: 36 months

Dosage forms and packaging available
PROGLUTROL 500 tablets are available in strength of 500 mg 10 tablets in a Blister .
• 100 tablets in a box.

Manufactured by:
inventia
Inventia Healthcare Limited,
F1-F1/1-F75/1 Additional Ambernath M.I.D.C.,
Ambernath (East), Thane, Maharashtra State,
Ambernath, 421506, India

Product Registration Holder
HEALOL PHARMACEUTICALS SDN. BHD., 74-3, Jalan Wangsa Delima 6, KLSC, Wangsa Maju, 53300 Kuala Lumpur, Malaysia.

Date of Revision of Package Insert:
Mar. 2024

Space For Artwork Code

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