PACKAGE INSERT

METFORMIN 250MG TABLET

Each tablet contains:-
Metformin HCl 250mg

Product Description: Round, convex, white, film-coated tablet with single score on one side only.

Pharmacodynamics:
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). In humans, independently of its action on glycaemia, 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, LDL cholesterol and triglyceride levels.

Pharmacokinetics:
After an oral dose of metformin, T_{max} is reached in 2.5 hours. Absolute bioavailability of a 500mg or 850mg metformin tablet is approximately 50-60% in healthy subjects. Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Indication:
It is used in the treatment of maturity on-set diabetes mellitus not responsive to diet alone or diet plus the treatment with a sulphonylurea.

Recommended Dosage:
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 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.

**The text " to be divided 2-3 daily doses" should be omitted for extended release product containing metformin as single agent*

Route of Administration: Oral

Contraindications:
Metformin hydrochloride should not be given to patients with impaired hepatic or renal function, cardiovascular collapse, congestive heart failure, acute myocardial infarction or other conditions leading to hypotension or to hypoxaemia. It should not be given to patients with diabetes mellitus complicated by acidosis or gangrene or during pregnancy or during surgery.
• Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).
• Severely reduced kidney function (GFR < 30/min). Acute conditions with the potential to alter renal function such as: dehydration, severe infection,shock.

Warning 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.

Medical product that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factor 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 renal function [See Section Contraindications].

Administration of Iodinated Contrast Agent:
As the intravascular administration of iodinated materials in radiologist 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.

Children and Adolescents:
The diagnosis of Type II diabetes mellitus should be confirmed before treatment with metformin is initiated. A careful follow-up of the effect of metformin on growth and puberty in metformin-treated children, especially pre-pubescent children, is recommended. Although metformin efficacy and safety in children aged 10 -12 years did not differ from efficacy and safety in older children, particular caution is recommended when prescribing to children aged between 10 and 12 years.

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 sulphonylureas.
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 contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

Interaction with other Medicaments:
It is reported that metformin reduces the absorption of vitamin B12. The serum level of vitamin B12 is not affected.
Tetracycline may precipitate metformin induced lactic acidosis.

Concomitant use not recommended.

Alcohol
Increased risk of lactic acidosis in acute alcohol, particularly in case of fasting or malnutrition and hepatic insufficiency.
Avoid consumption of alcohol-containing medications.

Iodinated Contrast Agents
See Warning and Precautions.

Combinations Requiring Precautions for Use:
Glucocorticoids (systemic and local routes), B_2-agonists and diuretics have intrinsic hyperglycaemic activity whereas 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 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 are not available in humans and a decision should be made whether to discontinue nursing or to discontinue metformin, taking into account the importance of the drug to the mother.

Side Effects:
Anorexia, nausea, vomiting and diarrhoea are not uncommon; occasionally a metallic taste, loss of weight, weakness, lassitude or skin rashes may occur. Lactic acidosis possibly heralded by vomiting, abdominal pain, hyperventilation and diminished consciousness may occur.

Metabolism and nutrition disorders:
Common: Vitamin B12 decrease/deficiency (see Warnings and Precautions).
Very rare: Lactic acidosis (see Warnings and Precautions).

Symptoms and Treatment of Overdose:
The symptoms are nausea and vomiting, anorexia, weight loss, low epigastric pain, unconsciousness, and pulmonary oedema.
In the treatment of lactic acidosis, sodium bicarbonate is given promptly by infusion to correct the acidosis. It may be necessary to give diuretics to avoid sodium overload. Peritoneal dialysis or haemodialysis have been reported to be successful.

Effects on Ability to Drive and Use Machine: Not known.

Storage Conditions: Store at or below 30°C.

Pack Size: Blister pack : 100 x 10, 50 x 10, 10 x 10 tablet per strip.
Pack Size (export only): 1000 tablets.

Shelf-life: 3 Years

FURTHER INFORMATION CONCERNING THIS DRUG CAN BE OBTAINED FROM YOUR FAMILY PHYSICIAN / LOCAL GENERAL PRACTITIONER / PHARMACIST.

Manufacturer & Product Registration Holder:
SUNWARD PHARMACEUTICAL SDN. BHD.
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