PACKAGE INSERT TEMPLATE FOR METFORMIN TABLET

Brand or Product Name
[Product name] Tablet 250mg
[Product name] Tablet 500mg
[Product name] Tablet 850mg
[Product name] Tablet 1000mg

Name and Strength of Active Substance(s)
Metformin Hydrochloride ….mg equivalent to metformin 250mg
Metformin Hydrochloride ….mg equivalent to metformin 500mg
Metformin Hydrochloride ….mg equivalent to metformin 850mg
Metformin Hydrochloride ….mg equivalent to metformin 1000mg

Product Description
[Visual description of the appearance of the product (eg colour, markings etc)
eg White, circular flat beveled edge tablets marked '500' on one side]

Pharmacodynamics

Metformin is a biguanide derivative of guanidine, used for treating type II diabetes mellitus. It has antihyperglycaemic effects, which lowers both basal and postprandial plasma glucose. It does not increase insulin secretion and hence, does not cause hypoglycaemia.

Metformin acts via 3 mechanisms:

(1) reduction in hepatic glucose production,

(2) reduction in intestinal glucose absorption, and

(3) increased insulin sensitivity (improved peripheral glucose uptake and utilization).

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUTs).

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism.

Unlike sulfonylureas and insulin, metformin does not cause weight gain.

Pharmacokinetics
Absorption:
After an oral dose of metformin hydrochloride tablet, maximum plasma concentration (Cmax) is reached in approximately 2.5 hours (tmax).
Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract.
It is assumed that the pharmacokinetics of metformin absorption is non-linear.
Bioavailability for oral metformin is approximately 50-60% in healthy subjects.
Dose proportionality is lacking due to decreasing absorption with increasing doses.

Steady state plasma concentrations for metformin are reached within 24 to 48 hours and are generally less than 1 microgram/ml at recommended doses and dosing schedules.

Food decreases the extent and delays the time to achieve maximum absorption. The plasma peak concentration may be 40% lower with food administration.

Distribution:
Protein binding in plasma is negligible.
Metformin crosses the placenta and is distributed into breast milk in small amounts.

Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged between 63-276 L.

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

Elimination:
Renal clearance of metformin is 450 to 540 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion.
The plasma elimination half-life is approximately 2 to 6 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.
Hemodialysis effectively removes metformin and corrects metabolic acidosis induced by metformin.

Indication
Treatment of type 2 diabetes mellitus, when dietary management and exercise alone does not result in adequate glycaemic control.
- In adults, metformin may be used as monotherapy or in combination with other oral anti-diabetic agents or with insulin.
- In children from 10 years of age and adolescents, metformin may be used as monotherapy or in combination with insulin.
A reduction of diabetic complications has been shown in overweight type 2 diabetic adult patients treated with metformin as first-line therapy after diet failure.
In Type I diabetes, metformin may be given as an adjuvant to patients whose diabetic are poorly controlled.

Recommended Dosage
Adults:
Monotherapy and combination with other oral antidiabetic agents:
- The usual starting dose is one tablet (500mg or 850mg) 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.
- In patients receiving a high meformin hydrochloride dose (2 to 3grams per day), it is possible to replace two Metformin 500mg tablets with one Metformin 1000mg tablet.
- The maximum recommended dose of metformin hydrochloride is 3 g daily, taken as 3 divided doses.
- If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate metformin at the dose indicated above.

Combination with insulin:
Metformin and insulin may be used in combination therapy to achieve better blood glucose control. Metformin hydrochloride is given at the usual starting dose of one tablet (500mg or 850mg) 2 or 3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

Children and adolescents:

Monotherapy and combination with insulin
- Metformin can be used in children from 10 years of age and adolescents.
- The usual starting dose is 500 mg or 850 mg metformin hydrochloride once 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 hydrochloride is 2 g daily, taken as 2 or 3 divided doses.

Mode of Administration
Oral

Contraindications
- Hypersensitivity to metformin or to any of the excipients.
- Diabetic ketoacidosis, diabetic pre-coma.
- 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.
- 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.

Warnings and Precautions
Lactic acidosis
Lactic acidosis is a rare, but serious metabolic complication that can occur due to metformin accumulation during treatment with metformin hydrochloride; when it occurs, it is fatal in approximately 50% of cases.

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:
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. This can be followed by acidotic dyspnea, abdominal pain, hypothermia and coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5mmol/l, and an increased anion gap and lactate/ pyruvate ratio.

Lactic acidosis is a medical emergency that must be treated in a hospital setting where metformin should be discontinued immediately and general supportive measures promptly instituted.

Renal function:
Creatinine clearance 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 creatinine clearance at the lower 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).

Surgery
Metformin must be discontinued 48 hours before elective surgery under general, spinal or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and only if normal renal function has been established.

Administration of iodinated contrast media:
The intravascular administration of iodinated contrast media in radiologic studies can lead to possible acute alteration of renal function resulting in increased risk of lactic acidosis. Metformin must be discontinued prior to, or at the time of the test and not be reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Children and adolescents:
The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin is initiated. Careful follow-up, especially in prepubescent children, is recommended.
Particular caution is recommended when prescribing to children aged between 10 and 12 years.

Elderly:
The metformin dosage should be adjusted based on renal function. Careful monitoring of renal function is required for this group of patients.

Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin hydrochloride, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism.

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 concurrently with insulin or other oral antidiabetics (e.g. sulfonylureas or meglitinides).

Effects on ability to drive and use machines
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).

Interactions with Other Medicaments

Concurrent use of metformin and alcohol may result in an increased risk of lactic acidosis, particularly in case of: fasting or malnutrition, hepatic insufficiency.

Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be temporarily stopped 48 hours before the examination, and withheld until normal renal function is confirmed.

Concomitant use of medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics with metformin may require more frequent blood glucose monitoring, especially at the beginning of treatment.
If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation.

Concurrent use of metformin and diuretics, especially loop diuretics may result in an increased risk of lactic acidosis due to their potential to decrease renal function.

Concurrent use of metformin and fluoroquinolones (e.g. ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin) and may result in changes in blood glucose and increased risk of hypoglycemia or hyperglycemia.

Concurrent use of metformin and acetazolamide may result in an additive risk of lactic acidosis.

Concurrent use of metformin and beta-blockers (e.g. atenolol, bisoprolol, carvedilol) may result in hypoglycemia, hyperglycemia, or hypertension.

Concurrent use of metformin and cephalexin may result in an increase in metformin plasma levels and may increase risk of metformin side effects (nausea, vomiting, diarrhea, asthenia, headache).

Concurrent use of metformin and danazol may result in an increased blood glucose levels.

Concurrent use of metformin and the following may result in an increase in metformin plasma concentrations:

- Amiloride
- Cimetidine
- Digoxin
- Glycopyrrolate
- Morphine
- Morphine Sulfate Liposome
- Quinidine
- Quinine
- Ranitidine
- Vancomycin
- Enalapril Maleate

Concurrent use of metformin and enalapril may result in hyperkalemic lactic acidosis.

Concurrent use of metformin and the following may result in reduced antidiabetic agent: effectiveness:

- Glucosamine
- Levothyroxine
- Thyroid

Concurrent use of metformin and the following may result in excessive hypoglycemia, CNS depression, and seizures:

- Linezolid
- Moclobemide
- Selegiline

Concurrent use of metformin and nidfedipine may result in an increased absorption of metformin.

Concurrent use of metformin and topiramate may result in an additive risk of metabolic acidosis.

Concurrent use of metformin and trimethoprim may result in an increased metformin exposure.

Statement on Usage During Pregnancy and Lactation

Pregnancy

Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality.There are limited data to suggest that metformin does not increase the risk of congenital abnormalities and does not adversely affect pregnancy outcome in diabetic women. Insulin is generally preferred for treatment of diabetes in women planning on becoming pregnant and during pregnancy to maintain blood glucose levels
as close to normal as possible, to reduce the risk of malformations of the foetus.

Lactation

Metformin may be distributed into breast milk, and that the possible effects on the infant should be considered if women wish to breastfeed while receiving the drug.
Since 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 breastfeeding 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.

Adverse Effects / Undesirable Effects

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 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.

Gastrointestinal disorders: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, malabsorption syndrome

Metabolism and nutrition disorders: Lactic acidosis, 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.

Nervous system disorders: Taste disturbance, asthenia, headache

Skin and subcutaneous tissue disorders: Skin reactions such as erythema, pruritus, urticaria

Overdose and Treatment

Symptoms

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.

Treatment
Symptomatic and supportive care is the mainstay of treatment in patients who present with mild to moderate biguanide toxicity. Activated charcoal can be considered after large ingestions.
Hemodialysis is the most effective method in removing lactate and metformin.

Storage Conditions
Store below ….°C

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]