

SUMMARY OF PRODUCT CHARACTERISTICS

METFORMIN HYDROCHLORIDE EXTENDED RELEASE TABLETS USP 500 & 1000 mg

1. NAME OF THE MEDICINAL PRODUCT

Metformin hydrochloride extended release tablets USP 500 / 1000 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated extended release tablet contains

Metformin Hydrochloride USP 500 / 1000 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Metformin hydrochloride extended release tablets USP 500 mg:

White to off white colored, oval shaped, biconvex uncoated tablets with plain surface on both sides.

Metformin hydrochloride extended release tablets USP 1000 mg:

White to off white colored, oval shaped, biconvex uncoated tablets debossed with 1000 on one side and plain surface on other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS:

Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. Metformin hydrochloride extended release tablets may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Monotherapy and combination with other oral antidiabetic agents:

- The usual starting dose is one tablet of Metformin hydrochloride extended release tablets 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 of Metformin hydrochloride extended release tablets 500 mg 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. If glycaemic control is not achieved on Metformin

hydrochloride extended release tablets 2000 mg once daily, Metformin hydrochloride extended release tablets 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 Metformin hydrochloride extended release tablets 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 Metformin hydrochloride extended release tablets are not recommended.
- If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate Metformin hydrochloride extended release tablets at the dose indicated above.
- Metformin hydrochloride extended release tablets 750 mg and Metformin hydrochloride extended release tablets 1000 mg are intended for patients who are already treated with metformin tablets (prolonged or immediate release).
- The dose of Metformin hydrochloride extended release tablets 750 mg or Metformin hydrochloride extended release tablets 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 Metformin hydrochloride extended release tablets 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 Metformin hydrochloride extended release tablets 750 mg or Metformin hydrochloride extended release tablets 1000 mg should be equivalent to the daily dose of metformin tablets up to a maximum of 1500 mg or 2000 mg respectively, given with the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements.

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 (see section 4.4).

Children: In the absence of available data, Metformin hydrochloride extended release tablets should not be used in children.

4.3 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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:

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 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalised immediately (see section 4.9).

Renal function:

As metformin is excreted by the kidney, creatinine clearance (this can be estimated from serum creatinine levels using the Cockcroft-Gault formula) 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 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 a non-steroidal anti-inflammatory drug (NSAID).

Administration of iodinated contrast media:

The intravascular administration of iodinated contrast media in radiological studies can lead to renal failure. This may lead to metformin accumulation and risk of lactic acidosis. Metformin must 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 (see section 4.5).

Surgery:

Metformin should be discontinued 48 hours before elective surgery with general spinal or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition provided normal renal function has been established.

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 other oral antidiabetics (e.g. sulphonylureas or meglitinides).

The tablet shells may be present in the faeces. Patients should be advised that this is normal.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Concomitant use not recommended

Alcohol

Acute alcohol intoxication is associated with an 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 media

Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis.

Metformin hydrochloride must 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 (see section 4.4).

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 other drug and upon its discontinuation.

Diuretics, especially loop diuretics

They may increase the risk of lactic acidosis due to their potential to decrease renal function

4.6 PREGNANCY AND LACTATION

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 fetal development, parturition or postnatal development (see section 5.3).

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, breastfeeding 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 effect 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.

4.7 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. sulphonylureas, insulin, or meglinitides).

4.8 UNDESIRABLE EFFECTS

In post marketing data and in controlled clinical studies, adverse event reporting in patients treated with Metformin hydrochloride extended release tablets was similar in nature and severity to that reported in patients treated with Metformin hydrochloride immediate release.

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, which resolve spontaneously in most cases.

The following adverse reactions may occur with Metformin hydrochloride extended release tablets.

Frequencies are defined as follows: very common: $>1/10$; common $\geq 1/100$, $<1/10$; uncommon $\geq 1/1,000$, $<1/100$; rare $\geq 1/10,000$, $<1/1,000$; very rare $<1/10,000$.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders

very rare: Lactic acidosis (see 4.4. Special warnings and precautions for use).

Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such an aetiology is recommended if a patient presents with megaloblastic anaemia.

Nervous system disorders

Common: Taste disturbance

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. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders

Isolated Liver function tests abnormalities or hepatitis resolving upon metformin reports: discontinuation.

Skin and subcutaneous tissue disorders

very rare: Skin reactions such as erythema, pruritus, urticaria

4.9 OVERDOSE

Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ORAL ANTI-DIABETICS

(A10BA02: Gastrointestinal tract and metabolism)

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:

- (1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- (2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation

(3) 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 clinical studies, the major non glycaemic effect of metformin is either weight stability or modest weight loss.

In humans, independently of its action on glycaemia, immediate release metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: immediate release metformin reduces total cholesterol, LDL cholesterol and triglyceride levels. A similar action has not been demonstrated with the prolonged release formulation, possibly due to the evening administration, and an increase in triglycerides may occur.

Clinical efficacy :

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in overweight type 2 diabetic patients treated with immediate release metformin as first-line therapy after diet failure. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/ 1000 patient-years) versus diet alone (43.3 events/ 1000 patient-years), $p=0.0023$, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/ 1000 patient-years), $p=0.0034$.
- a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/ 1000 patient-years, $p=0.017$;
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/ 1000 patient-years versus diet alone 20.6 events/ 1000 patient-years ($p=0.011$), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/ 1000 patient-years ($p=0.021$);
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/ 1000 patient-years, diet alone 18 events/ 1000 patient-years ($p=0.01$)

For metformin used as second-line therapy, in combination with a sulphonylurea, benefit regarding clinical outcome has not been shown.

In type 1 diabetes, the combination of metformin and insulin has been used in selected patients, but the clinical benefit of this combination has not been formally established.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After an oral dose of the prolonged release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a T_{max} at 7 hours (T_{max} for the immediate release tablet is 2.5 hours).

At steady state, similar to the immediate release formulation, C_{max} and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000mg of metformin prolonged release tablets is similar to that observed after administration of 1000mg of metformin immediate release tablets b.i.d.

Intrasubject variability of C_{max} and AUC of metformin prolonged release is comparable to that observed with metformin immediate release tablets.

When the prolonged release tablet is administered in fasting conditions the AUC is decreased by 30% (both C_{max} and T_{max} are unaffected).

Mean metformin absorption from the prolonged release formulation is almost not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000mg of metformin as prolonged release tablets.

Following a single oral administration of 1500 mg of Metformin hydrochloride extended release tablets 750 mg, a mean peak plasma concentration of 1193 ng/ml is achieved with a median value of 5 hours and a range of 4 to 12 hours.

Metformin hydrochloride extended release tablets 750 mg was shown to be bioequivalent to Metformin hydrochloride extended release tablets 500 mg at a 1500 mg dose with respect to C_{max} and AUC in healthy fed and fasted subjects.

Following a single oral administration in the fed state of one tablet of Metformin hydrochloride extended release tablets 1000 mg, a mean peak plasma concentration of 1214 ng/ml is achieved with a median time of 5 hours (range of 4 to 10 hours).

Metformin hydrochloride extended release tablets 1000 mg was shown to be bioequivalent to Metformin hydrochloride extended release tablets 500 mg at a 1000 mg dose with respect to C_{max} and AUC in healthy fed and fasted subjects.

When the 1000 mg prolonged release tablet is administered in fed conditions the AUC is increased by 77% (C_{max} is increased by 26% and T_{max} is slightly prolonged by about 1 hour).

Distribution

Plasma protein binding is negligible. 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 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 > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 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.

5.3 PRECLINICAL SAFETY DATA:

Preclinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity reproduction.

6. PHARMACEUTICAL PARTICULARS**6.1 LIST OF EXCIPIENTS:**

Microcrystalline cellulose, hydroxypropyl methyl cellulose, povidone K 90, colloidal silicon dioxide and magnesium stearate.

6.2 INCOMPATIBILITIES:

Not applicable

6.3 SHELF LIFE:

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE:

Do not Store above 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER:

10 tablets of Metformin hydrochloride extended release tablets USP 500/1000 mg are sealed with PVC/PVdC blister foil on one side and Aluminium blister foil on the other side in the form of a blister pack and such 3 blister packs are further packed in a printed carton along with instructions for use.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL:

Any unused product or waste material should be disposed off in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER:

MSN LABORATORIES PRIVATE LIMITED

MSN House, Plot No. : C-24, Industrial Estate,
Sanath Nagar, Hyderabad – 500 018
Telangana, India.

8. DATE OF REVISION OF THE TEXT:

February 2017