

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Metsafe 500 film coated tablets

2. Qualitative and quantitative composition

Each film coated tablet contains:

Metformin hydrochloride 500 mg corresponding to 390 mg metformin base.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film coated tablet

White colored, round shaped, biconvex film coated tablets with plain surface on both sides

4. Clinical particulars

4.1 Therapeutic indications

Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

- In adults, Metformin Hydrochloride Tablets may be used as monotherapy or in combination with other oral antidiabetic agents or with insulin.
- In children from 10 years of age and adolescents, Metformin Hydrochloride Tablets 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 (see section 5.1).

4.2 Posology and method of administration

Posology

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

Monotherapy and combination with other oral antidiabetic agents

The usual starting dose is 500 mg or 850 mg metformin hydrochloride 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.

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 500 mg or 850 mg 2 or 3 times daily, 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).

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	2000 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 4.4) 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.

Paediatric population

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.

4.3 Contraindications

- Hypersensitivity to metformin or to any of the excipients listed in section 6.1.
- 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

4.4 Special warnings and precautions for use

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 4.3 and 4.5).

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 4.2. 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 4.3.

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 4.3).

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 4.2 and 4.5.

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.

Paediatric population

The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin is initiated.

No effect of metformin on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially prepubescent children, is recommended.

Children aged between 10 and 12 years

Only 15 subjects aged between 10 and 12 years were included in the controlled clinical studies conducted in children and adolescents. Although efficacy and safety of metformin in these children did not differ from efficacy and safety in older children and adolescents, 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 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).

4.5 Interaction with other medicinal products and other forms of interaction

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 4.2 and 4.4.

Combinations requiring precautions for use

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.

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.

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, trimethoprim, 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 co-administered 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.

4.6 Fertility, 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 foetal 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.

Breast-feeding

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.

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. sulfonylureas, insulin or meglitinides).

4.8 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.

The following adverse reactions may occur with metformin.

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

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, urticaria

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the TMDA ADR reporting tool; website: <https://imis.tmda.go.tz/arrt> or search for TMDA Adverse Reactions Reporting Tool in the Google Play Store.

4.9 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.

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.

Mechanism of action

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).

Pharmacodynamic effects

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:

Reduction in the risk or delay of type 2 diabetes mellitus

The **Diabetes Prevention Program (DPP)** was a multicenter randomised controlled clinical trial in adults assessing the efficacy of an intensive lifestyle intervention or metformin to prevent or delay the development of type 2 diabetes mellitus. Inclusion criteria were age ≥ 25 years, BMI

≥ 24 kg/m² (≥ 22 kg/m² for Asian-Americans), and impaired glucose tolerance plus a fasting plasma glucose of 95 – 125 mg/dl (or ≤ 125 mg/dl for American Indians). Patients were either treated with intensive lifestyle intervention, 2x850 mg metformin plus standard lifestyle change, or placebo plus standard lifestyle change.

The mean baseline values of the DPP participants (n=3,234 for 2.8 years) were age 50.6 \pm 10.7 years, 106.5 \pm 8.3 mg/dl fasted plasma glucose, 164.6 \pm 17.0 mg/dl plasma glucose two hours after an oral glucose load, and 34.0 \pm 6.7 kg/m² BMI. Intensive lifestyle intervention as well as metformin significantly reduced the risk of developing overt diabetes compared to placebo, 58% (95% CI 48-66%) and 31% (95% CI 17-43%), respectively.

The advantage of the lifestyle intervention over metformin was greater in older persons.

The patients who benefited most from the metformin treatment were aged below 45 years, with a BMI equal or above 35kg/m², a baseline glucose 2 h value of 9.6-11.0 mmol/l, a baseline HbA_{1c} equal or above 6.0% or with a history of gestational diabetes.

To prevent one case of overt diabetes during the three years in the whole population of the DPP, 6.9 patients had to participate in the intensive lifestyle group and 13.9 in the metformin group. The point of reaching a cumulative incidence of diabetes equal to 50% was delayed by about three years in the metformin group compared to placebo.

The **Diabetes Prevention Program Outcomes Study (DPPOS)** is the long-term follow-up study of the DPP including more than 87% of the original DPP population for long-term follow up.

Among the DPPOS participants (n=2776), the cumulative incidence of diabetes at year 15 is 62% in the placebo group, 56% in the metformin group, and 55% in the intensive lifestyle intervention group. Crude rates of diabetes are 7.0, 5.7 and 5.2 cases per 100 person-years among the placebo, metformin, and intensive lifestyle participants, respectively. Reductions in the diabetes risk were of 18% (hazard ratio (HR) 0.82, 95% CI 0.72–0.93; p=0.001) for the metformin group and 27% (HR 0.73, 95% CI 0.65–0.83; p<0.0001) for the intensive lifestyle intervention group, when compared with the placebo group. For an aggregate microvascular endpoint of nephropathy, retinopathy and neuropathy, the outcome was not significantly different between the treatment groups, but among the participants who had not developed diabetes during DPP/DPPOS, the prevalence of the aggregate microvascular outcome was 28% lower compared with those who had developed diabetes (Risk Ratio 0.72, 95% CI 0.63–0.83; p<0.0001). No prospective comparative data for metformin on macrovascular outcomes in patients with IGT and/or IFG and/or increased HbA_{1c} are available.

Published risk factors for type 2 diabetes include: Asian or black ethnic background, age above 40, dyslipidaemia, hypertension, obesity or being overweight, age, 1st degree family history of diabetes, history of gestational diabetes mellitus, and polycystic ovary syndrome (PCOS).

Consideration must be given to current national guidance on the definition of prediabetes.

Patients at high risk should be identified by a validated risk-assessment tool.

Treatment of type 2 diabetes mellitus

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 metformin hydrochloride tablet, maximum plasma concentration (C_{max}) is reached in approximately 2.5 hours (t_{max}). Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.

At the recommended metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 5 microgram/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following oral administration of a 850 mg tablet, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these findings is unknown.

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 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 > 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.

Characteristics in specific groups of patients

Renal impairment

The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations (see section 4.2).

Paediatric population

Single dose study: After single doses of metformin hydrochloride 500 mg paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (C_{max}) and systemic exposure (AUC_{0-t}) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

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 and reproductive toxicity.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core

Povidone K 30,

Povidone K-90,

Magnesium Stearate

Film-coating

Opadry White 02B580001.

6.2 Incompatibilities

None

6.3 Shelf life

2 years (24 months)

6.4 Special precautions for storage

Keep out of reach of children, Protect form light and moisture, Store below 30°C in a dry place

6.5 Nature and contents of container

10 tablets of Metsafe 500 (Metformin hydrochloride tablets USP) 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 3 such blister packs are further packed in a printed carton along with instructions for use.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. Marketing authorisation holder

7.1 Marketing Authorization Holder

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

7.2 Manufacturing site

MSN Laboratories Private Limited
Formulations Division,
Plot No.: 42, ANRICH Industrial Estate,
Bollaram, Medak District, Pin Code – 502325, Telangana,
India.

8. Marketing authorisation number(s)

TZ19H0039

9. Date of first authorisation/renewal of the authorisation

December 31, 2018

10. Date of revision of the text

June 2020