

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metformin 500mg Tablets BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains Metformin Hydrochloride 500mg equivalent to Metformin base 390mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White, round, biconvex film coated tablets embossed with '500' on one face and plain on the other.

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 film-coated tablets 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 film-coated 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

Monotherapy and combination with other oral anti-diabetic 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 is 3 g daily, taken as 3 divided doses.

If transfer from another oral anti-diabetic 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 is given at the usual starting dose of 500 mg or 850 mg 2-3 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

Metformin may be used in patients with moderate renal impairment, stage 3a (creatinine clearance [CrCl] 45– 59 mL/min or estimated glomerular filtration rate [eGFR] 45-59 mL/min/1.73m²) only in the absence of other conditions that may increase the risk of lactic acidosis and with the following dose adjustments:

The starting dose is 500 mg or 850 mg metformin hydrochloride, once daily. The maximum dose is 1000 mg daily, given as 2 divided doses. The renal function should be closely monitored (every 3-6 months).

If CrCl or eGFR fall <45 ml/min or <45 ml/min/1.73m² respectively, metformin must be discontinued immediately.

Paediatric population

Monotherapy and combination with insulin

- Metformin tablets can be used in children from 10 years of age and adolescents.
- The usual starting dose is one tablet of 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 is 2 g daily, taken as 2 or 3 divided doses.

Method of administration

For oral administration

4.3 Contraindications

- Hypersensitivity to metformin hydrochloride or to any of the excipients listed in section 6.1.
- Diabetic ketoacidosis, diabetic pre-coma.
- Moderate (stage 3b) and severe renal failure or renal dysfunction (CrCl < 45 ml/min or eGFR < 45 ml/min/1.73m²). Acute conditions with the potential to alter renal function such as:
 - dehydration
 - severe infection
 - shock
 - intravascular administration of iodinated contrast agents (see 4.4 Special warnings and precautions for use).
- Acute or chronic disease which may cause tissue hypoxia such as:
 - respiratory failure
 - recent myocardial infarction
 - shock
 - decompensated heart failure
- Hepatic insufficiency, acute alcohol intoxication, alcoholism

4.4 Special warnings and precautions for use

Lactic acidosis:

Lactic acidosis is a very rare, but serious (high mortality rate 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 impaired renal failure or acute worsening of renal function. Special caution should be paid to situations where renal function may become impaired, for example in case of dehydration (severe diarrhoea or vomiting), or when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID). In the acute conditions listed, metformin should be temporarily discontinued.

Other associated risk factors should be considered to avoid lactic acidosis such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia (such as decompensated cardiac failure, acute myocardial infarction) (see also section 4.3).

The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps, digestive disorders as abdominal pain and severe asthenia. Patients should be instructed to notify these signs immediately to their physicians if they occur, notably if patients had a good tolerance to metformin before. Metformin should be discontinued, at least temporarily, until the situation is clarified. Reintroduction of metformin should then be discussed taking into account the benefit/risk ratio in an individual basis as well as renal function.

Diagnosis:

Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5mmol/L, and an increased anion gap and lactate/pyruvate ratio. In case of lactic acidosis, the patient should be hospitalized immediately (see section 4.9).

Physicians should alert the patients on the risk and on the symptoms of lactic acidosis.

Renal function:

As metformin is excreted by the kidney, creatinine clearance (this can be estimated from serum creatinine levels by using the Cockcroft-Gault formula) or eGFR should be determined before initiating treatment and regularly thereafter:

- At least annually in patients with normal renal function.
- At least two or four times a year in patients with creatinine clearance at the lower limit of normal and in elderly subjects.

In case CrCl is <45 ml/min (eGFR < 45 ml/min/1.73m²), metformin is contraindicated (see section 4.3).

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 an NSAID (Non steroidal anti-inflammatory drug).

In these cases, it is also recommended to check renal function before initiating treatment with metformin.

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 agent:

The intravascular administration of iodinated contrast media in radiologic studies can lead to renal failure. This may induce metformin accumulation and may increase the risk for lactic acidosis. In patients with eGFR > 60 ml/min/1.73 m², metformin should be discontinued prior to, or at the time of the test and not reinstated until at least 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further (see section 4.5).

In patients with moderate renal impairment (eGFR between 45 and 60 ml/min/1.73m²), metformin must be discontinued 48 hours before administration of iodinated contrast media and not be reinstated until at least 48 hours afterwards and only after renal function has been re-evaluated and has not deteriorated further (see section 4.5).

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.

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 pre-pubescent 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 metformin efficacy and safety 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, although caution is advised when it is used in combination with insulin or other oral anti-diabetics (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:

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 agents may lead to renal failure, resulting in metformin accumulation and an increased risk of lactic acidosis.

In patients with $eGFR > 60 \text{ ml/min/1.73m}^2$, metformin must be discontinued prior to, or at the time of the test and not be reinstated until at least 48 hours afterwards, and only after renal function has been reevaluated and has not deteriorated further (see section 4.4).

In patients with moderate renal impairment ($eGFR$ between 45 and 60 ml/min/1.73m^2), metformin should be discontinued prior to, or at the time of the test and not reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further..

Combinations requiring precautions for use:

Glucocorticoids (systemic and local routes), beta-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 anti-diabetic drug during therapy with the other drug and upon its discontinuation.

ACE-inhibitors:

They 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.

Diuretics, especially loop diuretics:

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

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, embryonal or foetal development, parturition or postnatal development (see also section 5.3).

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.

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 anti-diabetic agents (sulphonylureas, insulin, 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. To prevent them, it is recommended to take metformin in 2 or 3 daily doses and to increase slowly the doses.

The following adverse reactions may occur under treatment with metformin. Frequencies are defined as follows: very common: $\geq 1/10$; common $\geq 1/100$, $< 1/10$; uncommon $\geq 1/1,000$, $< 1/100$; rare $\geq 1/10,000$, $< 1/1,000$; very rare $< 1/10,000$ and isolated reports.

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

Metabolism and nutrition disorders:

Very rare: Lactic acidosis (see Section 4.4.).

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:

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. 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.

Hepatobiliary disorders:

Very rare: Isolated reports liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders:

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

Paediatric population:

In published and post and post marketing data and in controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year, adverse event reporting was similar in nature and severity to that reported in adults

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

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

Pharmacotherapeutic group: Blood glucose lowering drugs. Biguanides. ATC code: A10BA02

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 (GLUTs) known to date.

Pharmacodynamic effects

In clinical studies, use of metformin was associated with either a stable body weight or modest weight loss.

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.

Clinical efficacy

The prospective randomised study (UKPDS) has established the long-term benefit of intensive blood glucose control in adult patients with type 2 diabetes.

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 sulfonylurea 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 sulfonylurea 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 sulfonylurea, 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.

Paediatric population

Controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year demonstrated a similar response in glycaemic control to that seen in adults.

5.2 Pharmacokinetic properties

Absorption

After an oral dose of metformin, maximum plasma concentration (c_{\max}) is reached in 2.5 hours (t_{\max}). Absolute bioavailability of a 500 mg or 850 mg

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

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of time to peak plasma concentration were observed. The clinical relevance of these decreases 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 (V_d) 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 500 mg, paediatric patients have shown similar pharmacokinetics 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

Sodium starch glycollate
Povidone
Colloidal anhydrous silica
Maize starch
Magnesium stearate

Film-coat

Hypromellose
Titanium dioxide (E171)
Macrogol 6000
Propylene glycol
Purified talc

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

Blisters : Do not store above 25°C. Store in the original package.

Keep the blister in the outer carton

Bulk : Do not store above 25°C. Store in the original container.

Keep the container tightly closed.

6.5 Nature and contents of container

Blisters of aluminium (20 μ) and clear transparent PVC (250 μ) coated with PVDC (60 gsm) in pack sizes of 14, 28, 56 or 84 tablets.

White opaque HDPE tablet containers in pack sizes of 100, 250, 300 or 500 tablets.

6.6 Special precautions for disposal

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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23/09/2015