SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metformin 500 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg metformin hydrochloride

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

A white coloured, caplet shaped film coated tablet, marked with M500 on one side and plain on other with approximate length of 16 mm and width of 8 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Non insulin dependent (NIDDM, type II) and, in particular in obese patients, when adequate dietary treatment has failed.

Metformin 500 mg film-coated tablets can be given alone as initial therapy, or can be administered in combination with sulfonylureas after careful assessment of the contra-indications.

4.2 Posology and method of administration

Posology

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

Dosage

Usual dosage:

The required daily dose ranges from 500mg to 3g. Therapy should be initiated with a low dose of one 500mg tablet three times a day or one 850 mg tablet twice a day. Depending on the metabolic state the dose can be increased stepwise at intervals of a few days up to two weeks until the therapeutically required dose has been reached.

The daily dose should be divided and taken with or after meals in order to minimise the gastro-intestinal side effects. Generally, daily doses of 1000mg to 1700mg are sufficient.
If diabetic control is incomplete a cautious increase in dosage to a maximum of 2 to 3g daily is justified. No additional benefit can usually be achieved by use of doses exceeding 3g daily. Once control has been achieved it may be possible to reduce the daily dose.
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 maxium daily dose (to be divided into 2-3 daily doses)	Additional considerations
60-89	3000mg	Dose reduction may be considered in relation to declining renal function
45-59	2000mg	Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin. The staring dose is at most half of the maximum dose.
30-44	1000mg	
<30	-	Metformin is contraindicated

In cases of metabolic decompensation:
The metformin hydrochloride dosage may be reduced in cases of metabolic decompensation. If only small daily doses are administered an omission of one metformin hydrochloride dose should be tried. This is of importance in elderly patients to reduce the risk of lactic acidosis.

Children and juveniles:
Metformin 500 mg film-coated tablets are not recommended for use in children.

Elderly patients:
Metformin 500 mg film-coated tablets are indicated for use in the elderly.

Further dosage information
Combination with sulfonylureas:
Metformin 500 mg film-coated tablets may be used in combination with sulfonylureas if monotherapy with metformin hydrochloride does not lead to a satisfactory response. However, it should be noted that metformin hydrochloride and sulfonylureas have a different mode of action and therefore an additive or potentiating effect of these drugs might cause a hypoglycaemic shock.
Substitution for sulfonylureas:
Metformin 500 mg film-coated tablets may be used instead of sulfonylureas in patients who formerly have been treated with sulfonylureas.

Method of administration
Metformin 500 mg film-coated tablets should be taken whole with a glass of water during or after meals. They should not be chewed.

Monitoring advice
See special warnings and special precautions for use.

4.3 Contraindications

- Hypersensitivity to metformin hydrochloride or to any of the excipients listed in section 6.1.
- In patients with non-insulin-dependent diabetes (NIDDM, type II), if sulphonylurea therapy has completely failed.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).
- Diabetic precoma, coma and ketoacidosis.
- Impaired renal function of any degree.
- Chronic liver disease.
- Severe cardiovascular impairment.
- Cardiac failure and recent myocardial infarction.
- Severe peripheral vascular disease.
- Severe renal failure (GFR < 30 mL/min)

- Acute sever disorders, example infections with fever, pancreatitis or trauma.
- Dehydration.
- History of or conditions associated with lactic acidosis such as shock or pulmonary insufficiency, alcoholism (acute or chronic), and conditions associated with hypoxaemia.
- Reduced diet (< 1000 kcal or 4200 kJ per day).

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.

Patients with known or suspected mitochondrial diseases:

In patients with known mitochondrial diseases such as Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome and Maternal inherited diabetes and deafness (MIDD), metformin is not recommended due to the risk of lactic acidosis exacerbation and neurologic complications which may lead to worsening of the disease.

In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of metformin, treatment with metformin should be withdrawn immediately and prompt diagnostic evaluation should be performed.

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 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 reevaluated and found to be stable (see section 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.

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 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 anaemia 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.

Metformin alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulphonylureas 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), 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 OCT 2.

Co-administration of metformin with

• Inhibitors of OCT 1 (such as verapamil) may reduce efficacy of metformin.

• Inducers of OCT 1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.

• Inhibitors of OCT 2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.

• Inhibitors of both OCT 1 and OCT 2 (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 hyperglycaemia in the periconceptional phase and during pregnancy is associated with increased risk of congenital abnormalities, pregnancy loss, pregnancy-induced hypertension, preeclampsia, and perinatal mortality.

It is important to maintain blood glucose levels as close to normal as possible throughout pregnancy, to reduce the risk of adverse hyperglycaemia-related outcomes to the mother and her child.

Metformin crosses the placenta with levels that can be as high as maternal concentrations.

A large amount of data on pregnant women (more than 1000 exposed outcomes) from a register-based cohort study and published data (meta-analyses, clinical studies, and registries) indicates no increased risk of congenital abnormalities nor feta/neonatal toxicity after exposure to metformin in the periconceptional phase and/or during pregnancy.

There is limited and inconclusive evidence on the metformin effect on the long-term weight outcome of children exposed in utero. Metformin does not appear to affect motor and social development up to 4 years of age in children exposed during pregnancy although data on long term outcomes are limited.

If clinically needed, the use of metformin can be considered during pregnancy and in the periconceptional phase as an addition or an alternative to insulin.

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

When used as monotherapy metformin hydrochloride does not influence the ability to drive or operate machinery. In cases of combined therapy with sulphonylureas or other drugs with blood glucose lowering effects, hypoglycaemia may occur and, hence, such combinations may produce minor or moderate adverse effects. Patients undergoing such combination therapy should be warned about the possible adverse effects of hypoglycaemia.

4.8 Undesirable effects

Summary of the safety profile

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.

List of adverse reactions

The following adverse reactions may occur under treatment with metformin. Frequencies are defined as follows: very common ≥1/10; common ≥1/100, <1/10; uncommon ≥1/1,000, <1/100; rare ≥1/10,000, <1/1,000; very rare <1/10,000, not known (cannot be estimated from available data).

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

Metabolism and nutrition disorders:	
Common:	Vitamin B12 decrease/deficiency (see section 4.4)
Very rare:	Lactic acidosis (see section 4.4).
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 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 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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Human experience

Intoxication with metformin hydrochloride does not lead to hypoglycaemia but lactic acidosis may develop. Hypoglycaemia can occur when metformin hydrochloride is given concomitantly with sulphonylureas, alcohol or insulin.

Management of overdosage in man

In cases of metformin hydrochloride overdosage, for example in attempted suicide, or if signs of lactic acidosis are shown, patients must be admitted to a hospital as an emergency. The diagnosis of lactic acidosis should be confirmed by determination of lactate and metformin hydrochloride concentrations.

Haemodialysis is the most effective measure to eliminate lactate and metformin hydrochloride. Symptomatic treatment includes circulatory stabilisation, compensation of acidosis and elimination of hypoxia. The metformin hydrochloride concentration in erythrocytes is a good indicator for accumulation and can be used to decide whether repeated haemodialysis is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood glucose lowering drugs, Biguanide; ATC Code; A10B A02

Mechanism of action

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 glusose production by inhibiting gluconeogenesis and glycogenolysis.
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
- 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 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 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).

Benefit regarding clinical outcome has not been shown for metformin used as second-line therapy, in combination with a sulfonylurea.

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 (Cmax) is reached in approximately 2.5 hours (tmax). 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 hydrochloride 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 (Cmax) 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 and 276 litres.

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).

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

Core

Sodium starch glycollate

Maize starch

Povidone

Colloidal anhydrous silica

Magnesium stearate

Film-coating

Hypromellose

Titanium dioxide E 171

Propylene glycol

Macrogol 6000

Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Blister packs consisting of 250µm clear PVC and 20µm hard temper aluminium foil contained in a carton.

Pack Sizes: 28, 84, 504 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special precautions are required.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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