SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Metformin 500mg Tablets BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
1 film-coated tablet contains metformin hydrochloride 500 mg
For excipients see 6.1

3 PHARMACEUTICAL FORM
Film-coated tablets
White coloured, film-coated, round, biconvex tablets
OR
White coloured, film-coated, round, biconvex tablets embossed ‘M500’ on one side and plain on the other side.

4 CLINICAL PARTICULARS

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

- Metformin 500mg Tablets BP can be given alone as initial therapy, or can be administered in combination with sulphonylureas after careful assessment of the contra-indications.

4.2 Posology and method of administration
Dosage
Usual dosage:
The required daily dose ranges from 0.5 to 3 g. The usual starting dose is one 500mg tablet three times a day or one 850mg tablet twice a day. The daily dose should be divided and taken with or after meals in order to minimise the gastro-intestinal side effects. If diabetic control is incomplete a cautious increase in dosage to a maximum of 3g daily is justified. No additional benefit can usually be achieved by use of doses exceeding 3 g daily. Once control has been achieved it may be possible to reduce the daily dose.

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 500mg Tablets BP are not recommended for use in children.

Elderly patients:

Metformin 500mg Tablets BP are indicated for use in the elderly.

Further dosage information

Combination with sulphonylureas:

Metformin 500mg Tablets BP may be used in combination with sulphonylureas if monotherapy with metformin hydrochloride does not lead to a satisfactory response. However, it should be noted that metformin hydrochloride and sulphonylureas have a different mode of action and therefore an additive or potentiating effect of these drugs might cause a hypoglycaemic shock.

Substitution for sulphonylureas:

Metformin 500mg Tablets BP may be used instead of sulphonylureas in patients who formerly have been treated with sulphonylureas.

Method of administration

Metformin 500mg Tablets BP 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
- 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.
- 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 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 5 mmol/L, an increased anion gap and lactate/pyruvate ratio. In case of lactic acidosis, the patient should be hospitalised 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 to 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 in case of dehydration, or when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID). 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 media**

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 must be discontinued prior to, or at the time of the test and not be re instituted 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 re instituted 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 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
Acute alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting or malnutrition and hepatic insufficiency. Avoid consumption of alcohol and alcohol-containing medicinal products.

Iodinated contrast media
Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and an increased risk of lactic acidosis. In patients with eGFR > 60 ml/min/1.73m², metformin must be discontinued prior to, or at the time of the test and not be reinstituted until at least 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further (see section 4.4).
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 reinstituted until at least 48 hours afterwards and only after renal function has been re-evaluated and has not deteriorated further.

Combinations requiring precaution 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 respective medicinal product 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, 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. To prevent them, it is recommended to take metformin in 2 or 3 daily doses and to
increase the doses slowly.

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 \( < 1/10,000 \).
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 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

Paediatric population
In published 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, website www.mhra.gov.uk/yellowcard.

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.

5.1 Pharmacodynamic properties

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

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 glucose 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.

**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 hydrochloride tablet, maximum plasma concentration ($C_{\text{max}}$) is reached in approximately 2.5 hours $t_{\text{max}}$. 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 ($C_{\text{max}}$) 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.

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\text{max}) and systemic exposure (\text{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

Core
- Sodium starch glycollate
- Maize starch
- Povidone
- Colloidal anhydrous silica
- Magnesium stearate

Film-coating
- Hypermellose
- Titanium dioxide E171
- Propylene glycol
- Macrogol 6000
- Purified talc

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container

PVC/Aluminium blister packs in outer cardboard cartons.

Packs : 28 or 84 film-coated tablets.
Calendar Packs : 28, 84

Securitainer (LDPE) with tamper-proof closures (HDPE) containing 500 tablets.
A desiccant is included in the pack.

6.6 Special precautions for disposal
No special precautions are required.
MARKETING AUTHORISATION HOLDER
Medley Pharma Limited
Unit 2A,
Olympic Way
Sefton Business Park
Liverpool L30 1RD
UK

MARKETING AUTHORISATION NUMBER(S)
PL 43870/0004

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
31/07/2001 / 19/02/2009

DATE OF REVISION OF THE TEXT
31/07/2017