SUMMARY OF PRODUCT CHARACTERISTICS

1  NAME OF THE MEDICINAL PRODUCT
   Metformin 500mg Tablets

2  QUALITATIVE AND QUANTITATIVE COMPOSITION
   One film-coated tablet contains metformin hydrochloride 500 mg.
   For the full list of excipients, see section 6.1

3.  PHARMACEUTICAL FORM
   Film-coated tablets
   White coloured, film-coated, round, biconvex tablets.

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

   Paediatric population
   Metformin is indicated in children above 10 years and adolescents, adults (see
   section 4.2)

4.2  Posology and method of administration

   Posology

   Adults with normal renal function (\(GFR \geq 90\) mL/min):

   [Text continues]
Monotherapy and combination with other oral antidiabetic agents:

The usual starting dose is one tablet 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 hydrochloride at the dose indicated above.

Combination with insulin:

Metformin hydrochloride and insulin may be used in combination therapy to achieve better blood glucose control. Metformin hydrochloride is given at the usual starting dose of one tablet 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 hydrochloride dosage should be adjusted based on renal function. Regular assessment of renal function is necessary (see section 4.4)

Paediatric Population

Monotherapy and combination with insulin

- Metformin film-coated tablets 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 meals 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.

In cases of metabolic decompensation:

The metformin 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.

Patients with renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at 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.

<table>
<thead>
<tr>
<th>GFR</th>
<th>Total maximum daily dose</th>
<th>Additional considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>


<table>
<thead>
<tr>
<th>mL/min</th>
<th>(to be divided into 2-3 daily doses)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>60-89</td>
<td>3000 mg</td>
<td>Dose reduction may be considered in relation to declining renal function.</td>
</tr>
<tr>
<td>45-59</td>
<td>2000 mg</td>
<td>Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin.</td>
</tr>
<tr>
<td>30-44</td>
<td>1000 mg</td>
<td>The starting dose is at most half of the maximum dose.</td>
</tr>
<tr>
<td>&lt;30</td>
<td>-</td>
<td>Metformin is contraindicated.</td>
</tr>
</tbody>
</table>

**Method of administration**

Metformin 500mg 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 precautions for use.

### 4.3 Contraindications

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

- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).

- Renal failure or renal dysfunction.

- Severe renal failure (GFR <30 mL/min)

- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, intravascular administration of iodinated contrast agents (see section 4.4).

- Acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, shock

- Hepatic insufficiency, acute alcohol intoxication, alcoholism

- Lactation

### 4.4 Special warnings and precautions for use

**Warnings**

- In patients with impaired liver function, lactate clearance may be restricted.

**Lactic acidosis:**

Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure.
Lactic acidosis, a very rare 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, reduced fluid intake) metformin should be temporarily discontinued and contact with a health care professional is recommended.

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

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 patients should stop taking metformin and seek immediate medical attention (see section 4.9).

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:**

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

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

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).

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, diuretic therapy or when starting therapy with a non-steroidal anti-inflammatory drug (NSAID).

**Administration of iodinated contrast agent**

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 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 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).

Applies only to film-coated tablet and powder for oral solution formulations:

**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 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.

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**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 cases of fasting, malnutrition or hepatic impairment.

Avoid consumption of alcohol and alcohol-containing medicinal products.
Iodinated contrast agents (see section 4.4)

Intravascular administration of iodinated contrast agents may lead to renal failure, 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 re-evaluated and found to be stable, see section 4.2 and 4.4.

Combinations requiring precautions for use

- Medicinal products with intrinsic hyperglycaemic activity as glucocorticoids (systemic or by local route) 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 products.

- **ACE-inhibitors** may decrease the blood glucose levels. Therefore, dose adjustment of metformin may be necessary during and after addition or discontinuation of such medicinal products.

- Cationic medicinal products that are eliminated by renal tubular secretion (e.g., cimetidine) may interact with metformin by competing for common renal tubular transport systems. A study conducted in seven normal healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased metformin systemic exposure (AUC) by 50 % and Cmax by 81 %. Therefore, close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are co-administered.

- Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclooxygenase (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.

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 new-borns/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, taken 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 has negligible influence on the ability to drive and use machines. Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines. However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (e.g. sulphonylureas, insulin or meglitinides.)

### 4.8 Undesirable effects

All medicines can cause allergic reactions although serious allergic reactions are very rare.

The following adverse reactions may occur under treatment with metformin.

Frequencies are defined as follows:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>very common (≥1/10), common (≥1/100 to &lt;1/10), uncommon (≥1/1000 to &lt;1/100), rare (≥1/10000 to &lt;1/1000), very rare (&lt;1/10000), not known (cannot be estimated from the available data)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>System</th>
<th>Adverse reactions</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Taste disturbance</td>
<td>Common</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, vomiting</td>
<td>Very common</td>
</tr>
</tbody>
</table>
diarrhoea, abdominal pain and loss of appetite

Skin and subcutaneous tissue disorders
Skin reaction erythema, pruritus, urticaria
Very rare

Metabolism and nutrition disorders
Lactic acidosis (see section 4.4). Decrease of vitamin B12 absorption (long term use) may lead to Megaloblastic anaemia
Very rare

Hepatobiliary disorders
Liver function tests abnormalities or hepatitis which resolve after discontinuation of Metformin
Very rare

Gastrointestinal adverse reaction mentioned above occur most frequently during initiation of therapy and resolve spontaneously in most cases.

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 at: www.mhra.gov.uk/yellowcard

4.9 Overdose
Symptoms:
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.
Management:
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

Mechanism of action:
Metformin hydrochloride 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 hydrochloride 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.

Pharmacodynamic effects:
Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin hydrochloride increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

In humans, independently of its action on glycaemia, metformin hydrochloride has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical efficacy and safety:

The prospective randomised (UKPDS) study 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 hydrochloride after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride used as second-line therapy, in combination with a sulfonylurea.

In type 1 diabetes, the combination of metformin hydrochloride 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, Tmax is reached in 2.5 hours. Absolute bioavailability of a 500mg or 850mg 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 hydrochloride absorption are non-linear.

At the recommended metformin hydrochloride 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 hydrochloride plasma levels (Cmax) did not exceed 4 microgram/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin hydrochloride. 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 the time to peak plasma concentration were observed. The clinical relevance of these decreases is unknown.

Distribution:
Plasma protein binding is negligible. Metformin hydrochloride 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.

**Biotransformation:**

Metformin hydrochloride is excreted unchanged in the urine. No metabolites have been identified in humans.

**Elimination:**

Renal clearance of metformin hydrochloride is $>400$ ml/min, indicating that metformin hydrochloride 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 hydrochloride in plasma.

**Paediatric population:**

Single dose study: After single doses of metformin 500 mg, paediatric patients have shown a 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

Non-clinical 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

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

**Film-coating**
- Hypromellose
- Titanium dioxide E 171
- 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.
Store in original package in order to protect from light.

### 6.5 Nature and contents of container
PVC/PVDC/Aluminium blister packs in outer cardboard cartons.
Contents: 28 and 84 film-coated tablets.
Not all pack sizes may be marketed.

### 6.6. Special precautions for disposal
No special requirement for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

### 7 MARKETING AUTHORISATION HOLDER
Mercury Pharmaceuticals Ltd
8. MARKETING AUTHORISATION NUMBER

PL 12762/0081

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/03/2009

10. DATE OF REVISION OF THE TEXT

14/02/2017