

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1 NAME OF THE MEDICINAL PRODUCT**

Metformin hydrochloride 500 mg film-coated tablets

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each 500 mg film-coated tablet contains 500 mg metformin hydrochloride equivalent to metformin base 390 mg.

For the full list of excipients, see section 6.1.

### **3. PHARMACEUTICAL FORM**

Film-coated tablet.

White, round, normal convex, film-coated tablets plain on both sides. Diameter about 12.0 mm.

### **4 CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

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

- In adults, Metformin hydrochloride 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 hydrochloride 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 with normal renal function (GFR ≥ 90 mL/min):**

*Monotherapy and combination with other oral antidiabetic agents:*

- The usual starting dose is one tablet of 500 mg or 850 mg metformin 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.

In patients receiving a high metformin dose (2 to 3 grams per day), it is possible to replace two Metformin hydrochloride 500 mg film-coated tablets with one Metformin hydrochloride 1000 mg film-coated tablet.

The maximum recommended dose of metformin is 3 g daily, taken as 3 divided doses.

If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate metformin at the dose indicated above.

*Combination with insulin:*

Metformin and insulin may be used in combination therapy to achieve better blood glucose control. Metformin is given at the usual starting dose of one tablet of 500 mg or 850 mg metformin, 2 or 3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

**Renal impairment:**

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

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

**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).

**Paediatric population:**

*Monotherapy and combination with insulin*

- Metformin hydrochloride film-coated 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 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.

### 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)
- Diabetic pre-coma
- Severe renal failure (GFR  $\leq$  30 mL/min)
- Acute conditions with the potential to alter renal function such as:
  - dehydration
  - severe infection
  - shock.
- 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.

### 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 functioning 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 ( $> 5\text{mmol/L}$ ) and an increased anion gap and lactate/pyruvate ratio.

If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalised immediately (see section 4.9).

**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

D

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

#### **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*

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.5.

#### *Surgery*

Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or

resumption of oral nutrition and provided that renal function has been re-evaluated and found

to be stable.

#### **Children and adolescents:**

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.

**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 anemia 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. sulfonylureas or meglitinides).

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

## **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.

Avoid consumption of alcohol and alcohol-containing medicinal products.

#### *Iodinated contrast agents*

Intravascular administration of iodinated contrast media 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 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 functioning of renal function is necessary.

*Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics)*

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation.

*Organic cation transporters (OCT)*

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin

#### **4.6 Fertility, Pregnancy and lactation**

##### Pregnancy

Uncontrolled 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 fetoneonatal 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**

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 (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 slowly the doses.

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

|                                     |
|-------------------------------------|
| Metabolism and nutrition disorders: |
|-------------------------------------|

|  |  |
|--|--|
| <i>Common:</i>                                 | VitaminB12 decrease/deficiency   |
| <i>Very rare:</i>                              | Lactic acidosis (see section 4.4)  |
| <u>Nervous system disorders:</u>               |  |
| <i>Common:</i>                                 | Taste disturbance  |
| <u>Gastrointestinal disorders:</u>             |  |
| <i>Very common:</i>                            | 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. |
| <u>Hepatobiliary disorders:</u>                |  |
| <i>Very rare:</i>                              | Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.  |
| <u>Skin and subcutaneous tissue disorders:</u> |  |
| <i>Very rare:</i>                              | 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](http://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 of metformin or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

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.

Mechanism of action

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 and safety

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

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

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

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

#### Distribution:

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution ( $V_d$ ) ranged between 63-276 L.

#### Biotransformation:

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 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**

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core:

Povidone K-30

Magnesium stearate

#### Film-coating:

Hypromellose

Hydroxypropyl cellulose

Macrogol 400 and 8000

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

Blister pack: 3 years  
HDPE bottle: 3 years.

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

Metformin hydrochloride tablets are packed in blister packs (PVC Aluminium) containing 10, 15, 20, 28, 30, 40, 50, 56, 60, 84, 90, 100, 120 and 180 tablets and bottles (high density polyethylene) with caps (polypropylene) containing 30,100,180, 200, 300, 400,500 and 1000 tablets. Metformin hydrochloride 850 mg and 1000 mg film-coated tablets are also available in blister multipacks containing 180 (2 packs of 90) tablets.

### **6.6 Special precautions for disposal**

No special requirements for disposal.

## **7 MARKETING AUTHORISATION HOLDER**

Generics [UK] Ltd. T/A Mylan  
Station Close  
Potters Bar  
Herts  
EN6 1TL  
United Kingdom

## **8 MARKETING AUTHORISATION NUMBER(S)**

PL 04569/1135

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

31/12/2012

**10 DATE OF REVISION OF THE TEXT**

21/01/2023