# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Metformin EQL 500 mg film-coated tablet
Metformin EQL 850 mg film-coated tablet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains metforminhydrochloride 500 mg and 850 mg respectively corresponding to 390 mg and 662,9 mg metformin base.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet
Metformin EQL 500 mg: White, round film-coated tablets with a diameter of 11 mm, 6,0 mm height and marked 500 on one side.
Metformin EQL 850 mg: White, round, film-coated tablets with a diameter of 13,5 mm, 7.1 mm height and marked 850 on one side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of type 2 diabetes mellitus, especially in obese patients, where diet and exercise alone does not result in adequate glycaemic control. In adults, Metformin EQL can be used as monotherapy or in combination with other oral antidiabetic agents or with insulin.

- In children from 10 years of age and older, Metformin EQL can be used as monotherapy or in combination with insulin.

A reduction in diabetic complications has been demonstrated in overweight adult patients with type 2 diabetes treated with metformin as a first-line preparation 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 500 mg or 850 mg metformin hydrochloride 2 to 3 times daily during or after meals.
After 10 to 15 days, the dose should be adjusted based on the measurement of blood sugar. A slow increase in dose may result in improved gastrointestinal tolerance.
The recommended maximum dose of metformin is 3 g daily, divided into 3 daily doses.

If transition from another oral antidiabetic agent is planned: Stop treatment with the other agent and start metformin hydrochloride at the dose indicated above.

*Combination with insulin*

Metformin and insulin can be used as combination therapy to achieve better blood sugar control. Metformin hydrochloride is given at the usual starting dose of 500 mg or 850 mg 2 - 3 times daily, while the insulin dose is adjusted based on blood glucose measurement.

*Elderly*

Due to the potential for impaired renal function in elderly patients, the metformin dose should be adjusted based on renal function. Regular monitoring of renal function is necessary (see section 4.4).

*Impaired renal function*

GFR should be assessed before starting treatment with metformin containing drugs and at least every year thereafter. In patients with increased risk of further deterioration of renal function and in the elderly, renal function should be assessed more frequently, eg. every third to every sixth months.

| GFR ml/min | Total maximum daily dose (should be divided on 2 - 3 daily doses) | To consider |
|---|---|---|
| 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 assessed before starting treatment. The starting dose is at most half the maximum dose |
| 30 - 44 | 1000 mg | |
| <30 | - | Metformin is contraindicated. |

*Paediatric population*

**Monotherapy and combination with insulin**

- Metformin EQL can be used in children from 10 years of age and adolescents.
- The usual starting dose is 500 mg or 850 mg metformin hydrochloride daily during or after meals.

After 10 to 15 days, the dose should be adjusted based on the measurement of blood sugar. A slow increase in dose may result in improved gastrointestinal tolerance. The recommended maximum daily dose of metformin hydrochloride is 2 g divided into 2-3 times

## 4.3 Contraindications

- Hypersensitivity to metformin or to any of the excipients listed in section 6.1.
- All types of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma.
- Severe renal impairment (GFR <30 ml / min).
- Acute conditions that may affect kidney function, such as: dehydration, severe infection, shock.
- Disease that can cause tissue hypoxia (especially acute disease or impaired chronic disease) such as decompensated heart failure, respiratory failure, recent myocardial infarction, shock.
- Hepatic insufficiency, acute alcohol toxicity, alcoholism.

## 4.4 Special warnings and precautions for use

Lactic acidosis

Lactic acidosis, a very rare but serious metabolic complication, often occurs in acute renal function impairment, cardiovascular disease or sepsis. Metformin is accumulated in acute renal function impairment, which increases the risk of lactic acidosis.

In case of dehydration (severe diarrhea or vomiting, fever or reduced fluid intake), metformin treatment should be temporarily discontinued and it is recommended to contact the healthcare.

Medicines that may cause acute renal impairment (eg blood pressure lowering drugs, diuretics and NSAIDs) should be administered with caution in patients treated with metformin. Other risk factors for lactic acidosis are high alcohol intake, hepatic impairment, non-controlled diabetes, ketosis, prolonged fasting and all conditions associated with hypoxia, as well as concomitant use of drugs that may cause lactic acidosis (see sections 4.3 and 4.5).

Patients and/or caregivers should be informed of the risk of lactic acidosis. Lactic acidosis is characterized 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), elevated lactate levels in plasma (<5 mmol/l), an increased anion gap and an increased 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 is initiated and regularly thereafter, see section 4.2. Metformin is contraindicated in patients with GFR <30 ml/min and should be temporarily discontinued for conditions that alter renal function, see section 4.3.

Cardiac function

Patients with heart failure are at greater risk for hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used if cardiac and renal function are monitored regularly.

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 cause contrast-induced nephropathy leading to accumulation of metformin and increased risk of lactic acidosis. Metformin should be discontinued before or at the time of image diagnostics and should not be reintroduced until at least 48 hours thereafter, provided that renal function has been evaluated and shown to be stable, see sections 4.2 and 4.5.

Surgery

Metformin must be discontinued during surgery during anesthesia, spinal anesthesia or epidural anesthesia. Treatment should not be reinstated until at least 48 hours after surgery or after resuming oral nutrition, provided that renal function has been evaluated and shown to be stable.

Pediatric population

The diagnosis for type 2 diabetes should be confirmed before starting treatment with metformin.

No effect of metformin on growth and puberty has been demonstrated in controlled clinical trials lasted less than 1 year, but no long-term data are available. Therefore, a careful follow-up of metformin is recommended concerning growth and puberty in children treated with metformin and especially in children pre-puberty.

**Children between 10 and 12 years**

Only 15 people aged 10 to 12 years participated in the controlled clinical study in children and adolescents. Although metformin's efficacy and safety in these children did not appear to be different from that in older children and adolescents, special care is recommended when metformin is administered to children between 10 and 12 years of age.

Other precautions

All patients should continue their diets with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their low-energy diets.

Usual laboratory tests for monitoring diabetes should be performed regularly.

Metformin as monotherapy does not cause hypoglycaemia but caution should be exercised when used with insulin or other oral antidiabetic agents (eg sulphonylureas or meglitinides).

## 4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use is not recommended:

*Alcohol*

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition and impaired liver function.

Iodinated contrast agents:

Metformin must be discontinued before or at the time of image diagnostics and should not be reintroduced until at least 48 hours thereafter, provided that renal function has been evaluated and shown to be stable, see sections 4.2 and 4.4.

Combinations requiring caution

Some medicinal products may impair renal function, which may increase the risk of lactic acidosis, eg. NSAIDs, including selective cyclooxygenase II inhibitors (COX II inhibitors), ACE inhibitors, angiotensin II receptor antagonists and diuretics, particularly loop diuretics. When such drugs are administered in combination with metformin, close monitoring of renal function is required

*Drugs with an inherent hyperglycemic action (eg glucocorticoids (systemic and local treatment) and sympathomimetics)*

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, the metformin dose must be adjusted during treatment with the respective drug and upon discontinuation of such treatment.

Organic Cation Transporters (OCT)

Metformin is the substrate for both carrier OCT1 and OCT2.

Concomitant administration of metformin with:
• OCT1 inhibitors (such as verapamil) may reduce the effect of metformin.
• OCT1 inducers (such as rifampicin) may increase gastrointestinal absorption and the effect of metformin.
• OCT2 inhibitors (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may reduce the renal excretion of metformin, thus leading to increased metformin plasma concentrations.
• Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter the effect and renal excretion of metformin.

Therefore, caution is recommended, especially in patients with renal impairment, if these medicines are administered concomitantly with metformin, as metformin plasma concentrations may increase. If necessary, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the effect of metformin.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

Uncontrolled diabetes during pregnancy (gestational diabetes or permanent diabetes) is associated with an increased risk of congenital malformations and perinatal mortality.

The limited data available for the use of metformin in pregnant women does not indicate an increased risk of congenital malformations. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see section 5.3).
If the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with metformin but with insulin to maintain blood sugar levels as close to normal as possible to reduce the risk of fetal malformations.

Breast-feeding

Metformin is excreted into breast milk. No adverse effects have been observed in newborn/infants who are breastfeeding. However, since only limited data are available, breast-feeding is not recommended during treatment with metformin. When assessing whether breast-feeding should be discontinued, the benefit of breast-feeding and the possible risk of adverse reactions in the child should be considered.

Fertility

Fertility in male and female rats was not affected by metformin when given at doses up to 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface comparison.

## 4.7 Effects on ability to drive and use machines

Metformin as monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive and use machines.

However, patients should be warned of the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (eg sulfonylureas, insulin or meglitinides).

## 4.8 Undesirable effects

At the beginning of treatment, the most common side effects are nausea, vomiting, diarrhea, stomach pain and loss of appetite that cease spontaneously in most cases. To prevent these side effects, it is recommended that the metformin dose be taken 2 or 3 times daily and to increase slowly the doses.

The following side effects may occur during treatment with metformin. The frequencies are defined as follows: Very common ≥1 / 10, common ≥1 / 100, <1/10; uncommon ≥1 / 1,000, <1/100, rare ≥1 / 10,000, <1/1000, very rare <1/10,000.

Adverse reactions are presented within each frequency range by decreasing severity.

Metabolism and nutrition disorders

*Very rare*
- Lactic acidosis (see section 4.4).
- A decrease in the absorption of vitamin B12 with decreased serum levels has been observed in patients treated with metformin for a long time. B12 deficiency should be considered when finding megaloblastic anaemia.

Nervous system disorders

*Common*
- Taste disturbance

Gastrointestinal disorders

*Very common*
- Gastrointestinal symptoms such as nausea, vomiting, diarrhea, abdominal pain and loss of appetite. These side effects usually occur when starting treatment and resolve spontaneously in most cases. To prevent these gastrointestinal symptoms, it is recommended that metformin be taken two to three times daily during or after meals. A gradual increase in the dose may also improve gastrointestinal tolerance.

Hepatobiliary disorders:

*Very rare*
- Isolated reports show abnormal liver function values or hepatitis resolving upon discontinuation of metformin.

Skin and subcutaneous tissue disorders

*Very rare*
- Skin reactions such as erythema, pruritus, urticaria.

**Paediatric population**

In published data and post-marketing data and in controlled clinical trials in a limited group of children and adolescents 10-16 years treated for one year, the adverse reaction profile was similar to that observed 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 national reporting system listed in Appendix V.*

### 4.9 Overdose

Hypoglycaemia has not been observed with metformin hydrochloride doses up to 85 g, although lactic acidosis has occurred under these conditions. High overdose or associated risks with metformin may result in lactic acidosis. Lactic acidosis is a medical emergency state and must be treated in hospitals. The most effective method for removing lactate and metformin is hemodialysis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood glucose-lowering drugs, excl insulins. Biguanides, ATC code: A10BA02

Mechanism of action

Metformin is a biguanide with antihyperglycaemic effects, which lowers both the basal and postprandial levels of plasma glucose. It does not stimulate insulin secretion and therefore does not cause hypoglycaemia.
Metformin has 3 mechanisms of action:

- reduction of liver production of glucose by inhibiting gluconeogenesis and glycogenolysis.
- Increasing insulin sensitivity, improving peripheral glucose uptake and muscular glucose utilization.
- delay in intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthetase.
Metformin increases the transport capacity of all the hitherto known types of membrane fluid transporters (GLUT).

Pharmacodynamic effects
The use of metformin in clinical trials has been associated with a stable body weight or a slight weight loss.

Positive effects on lipid metabolism have been observed in humans regardless of its effect on blood sugar levels. This has been demonstrated at therapeutic doses in controlled clinical trials. Metformin reduces total cholesterol, LDL cholesterol and triglyceride levels

Clinical efficacy and safety

The prospective, randomized (UKPDS) study has established the long-term positive effect of intensive blood sugar control in adults with type 2 diabetes.

Analysis of the results for obese patients treated with metformin following diet failure as a single treatment showed:

- a significant reduction in the absolute risk of any type of diabetes-related complication in the metformin group (29.8 cases / 1000 patient-years) compared to diet alone (43.3 cases / 1000 patient-years), p = 0.0023, and the combined groups as received sulphonylurea and insulin as monotherapy (40.1 cases / 1000 patient years), p = 0.0034.
- a significant reduction in absolute risk of diabetes-related mortality: metformin 7.5 cases / 1000 patient-years, diet alone 12.7 cases / 1000 patient-years, p = 0.017;
- a significant reduction in the absolute risk of total mortality: metformin 13.5 cases / 1000 patient years compared to diet alone 20.6 cases / 1000 patient years (p = 0.011), and the combined groups receiving sulphonylurea and insulin monotherapy 18, 9 cases / 1000 patient years (p = 0.021);
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 cases / 1000 patient years, diet alone 18 cases / 1000 patient years (p = 0.01).

When metformin was used as second-line therapy, in combination with a sulphonylurea, a positive effect on clinical outcome has not been demonstrated.
In type 1 diabetes, the combination of metformin and insulin has been used in selected patients, but the clinical benefits of this combination have not been formally established.

Paediatric population
In clinical trials in a limited group of children and adolescents 10 to 16 years of age treated for 1 year, a similar response to blood glucose control as in adults was shown.

## 5.2 Pharmacokinetic properties

Absorption

Following an oral dose of metformin hydrochloride as a tablet, peak plasma concentrations (Cmax) are achieved within about 2,5 hours ($t_{max}$). 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 the faeces was 20-30%.

After oral administration, absorption of metformin is saturable and incomplete. It is assumed that metformin's absorption pharmacokinetics are non-linear.
At recommended metformin doses and dosing intervals, steady-state plasma concentrations are reached within 24 to 48 hours and are generally below 1 microgram / ml. In controlled clinical trials, maximum metformin plasma levels ($C_{max}$) did not exceed 5 micrograms / ml, even at maximum doses.

Food intake decreases the extent, and delays, the absorption of metformin. Following oral administration of a 850 mg tablet, 40% lower Cmax, 25% decrease in AUC and 35 minutes prolongation of Tmax were observed. The clinical relevance of these findings is unknown.

Distribution

Plasma protein binding rate is insignificant. Metformin penetrates erythrocytes. $C_{max}$ in blood is lower than $C_{max}$ in plasma and occurs approximately simultaneously. The red blood cells are likely to be a secondary volume of distribution. Average $V_d$ was between 63 - 276 liters.

Biotransformation

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

Elimination

The renal clearance of metformin is> 400 ml / min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. After an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

If renal function is impaired, renal clearance is reduced relative to the clearance of creatinine and thus the elimination half-life is prolonged, leading to increased metformin plasma levels.

Special patient groups

Impaired renal function

Available data from subjects with moderate renal insufficiency are limited and no reliable evaluation of systemic exposure of metformin in this subgroup compared to subjects with normal renal function can be done. Dose adjustment should therefore be based on clinical efficacy/tolerance considerations (see section 4.2).

Pediatric population

Single dose study: Metformin hydrochloride 500 mg in children and adolescents has shown similar pharmacokinetic profile to that of healthy adults.

Repeated Dose Study: Data only available from one study. After repeated doses of 500 mg twice daily for 7 days in children and adolescents, plasma concentrations of Cmax and systemic exposure were reduced by approximately 33% and 40%, respectively, compared to adult diabetics receiving 500 mg twice daily for 14 days. Since the dose is individually titrated on glycemic control, this has limited clinical relevance.
Characteristics of specific patient groups

### 5.3 Preclinical safety data

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core
Sodium starch glycolate
Povidone
Maize starch
Colloidal anhydrous silica
Magnesium stearate

Tablet coat
Hypromellose
Titanium dioxide (E171)
Talc
Macrogol
Propylene glycol

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

4 years

## 6.4 Special precautions for storage

No special storage conditions.

## 6.5 Nature and contents of container

*500 mg*
Bottle of high-density polyethylene, with child-protecting cap of polypropylene: 105, 300, 330 and 400 tablets

850 mg
Bottle of high-density polyethylene, with cap of polypropylene: 105 and 210 tablets.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

# 7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

# 8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

# 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2018-11-01

# 10. DATE OF REVISION OF THE TEXT

2025-03-04