SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Formetic 850 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 850 mg metformin hydrochloride equivalent to 662,8 mg of metformin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White, oblong film-coated tablet, with scoreline on one side and deep breakline on the other.

The tablet can be divided into equal doses.

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 hydrochoride 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 hydrochoride 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 hydrochloride as first-line therapy after diet failure (see section 5.1).

- Pre-diabetic state: impaired fasting glycaemia (IFG) and/or impaired glucose tolerance (IGT), when dietary management and exercise alone does not result in adequate glycaemic control.

4.2 Posology and method of administration

Posology

For the different dose regimens Formetic is available as 500 mg, 850 mg or 1000 mg film-coated tablets. In patients receiving a high metformin hydrochloride dose (2 to 3 grams per day), it is possible to replace two 500 mg film-coated tablets with one 1000 mg film-coated tablet.

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

Adults:
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 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 the 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, the other agent should be discontinued and metformin initiated at the dose indicated above.

Combination with insulin
Metformin and insulin may be used in combination therapy to achieve better blood glucose control. Metformin hydrochloride is given at the usual starting dose of 500 mg or 850 mg metformin hydrochloride 2 to 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 patients, the metformin hydrochloride dosage should be adjusted based on renal function. Regular assessment of renal function is therefore necessary (see section 4.4).

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. The starting dose is at most half of the maximum dose.
30-44	1000 mg	
<30	-	Metformin is contraindicated.

Children and adolescents:
Monotherapy and combination with insulin
Formetic 500 mg, 850 mg and 1000 mg 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 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.

Pre-diabetic state: impaired fasting glycaemia (IFG) and/or impaired glucose tolerance (IGT)

The usual starting dose is 500 mg (1 film-coated tablet Formetic 500 mg or ½ film-coated tablet Formetic 1000 mg) daily. Dose should be adjusted according to the clinical effect up to 1700 mg daily, taken as 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 <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 function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Renal function

GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2. Metformin is contraindicated in patients with GFR<30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function, see section 4.3.

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.

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 sections 4.2 and 4.5.

Surgery

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

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 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.

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 agent

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

Medicinal products with intrinsic hyperglycaemic activity (as 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 the therapy with the respective medicinal product.

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

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 fetal development, parturition or post-natal development.

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. sulphonylureas, insulin, or meglitinides).

4.8 Undesirable effects

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

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.

Skin and subcutaneous tissue disorders:

Very rare:
Skin reactions such as erythema, pruritus and urticaria

Metabolism and nutrition disorders:

Very rare:
- Lactic acidosis (see section 4.4).
- Decrease in 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 megaloplastic anaemia.

Hepatobiliary disorders:

Very rare:
- Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Paediatric population
In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10 to 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 national reporting system listed in Appendix V*.

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, excl. insulines. Biguanides
ATC code: A10BA02

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial blood glucose levels. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin probably acts via three 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) 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.

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 demonstrated at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical efficacy:
A 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 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 7.5 events/1000 patient-years versus 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 sulphonylurea and insulin monotherapy groups 18.9 events/1000 patient-years (p=0.021);
- a significant reduction of 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 sulphonylurea.

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

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

At the recommended doses and usual 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 dose of 850 mg tablet metformin hydrochloride, a 40% lower peak plasma 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 significance 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 probably represent a secondary compartment of distribution. The mean volume of distribution (V_d) ranged between 63 and 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 decreases in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased concentrations of metformin in plasma.

Paediatric population
Single dose study: After single doses of metformin hydrochloride 500 mg, peadiatric 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 (BID) 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 BID 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

Tablet core:
Hypromellose (15,000 mPas)
Povidone (K 25)
Magnesium stearate

Tablet coating:
Hypromellose (5 mPas)
Macrogol 6000
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/aluminium blister

Packages with 30 film-coated tablets
Packages with 60 film-coated tablets

Packages with 90 film-coated tablets
Packages with 120 film-coated tablets
Packages with 180 film-coated tablets

Packages for hospital use only with 600 (20x30) film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

POLPHARMA SA
19 Pelplińska Street
83-200 Starogard Gdański
Poland
Telefon: ++48 58/563 16 00
Telefax: ++48 58/563 23 53

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

{DD/MM/YYYY}
[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

17.10.2022