SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metfil (Metformin Tablets BP 500 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Metformin Hydrochloride BP 500 mg.

For the full list of excipients, please refer to section 6.1.

3. PHARMACEUTICAL FORM

White, circular, slightly biconvex film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Metformin Hydrochloride is a biguanide hypoglycaemic agent. It is given by mouth in the treatment of non-insulin-dependent diabetes mellitus. Metformin is indicated in:

1. Type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM).
2. Type 1 diabetes (insulin-dependent diabetes mellitus, IDDM) as adjuvant therapy in combination with insulin.
3. Obesity and hyperinsulinaemia.
4. Hyperlipoproteinaemia.

4.2 Posology and Method of Administration

It is important that Metfil tablets be taken in divided doses with meals.

Adults: Initially one 500 mg tablet three times a day with or after food. After 10 to 15 days the dose should be adjusted, or increased to 850 mg or 1000 mg twice daily. A

slow increase in dose may improve gastrointestinal tolerability. If control is incomplete, a cautious increase in dosage to a maximum of 3 g daily is justified. Once control has been obtained it may be possible to reduce the dosage of Metfil.

Children: Metformin Tablets BP 500 mg is not recommended for use in type 1 diabetes mellitus.

Elderly: Metformin Tablets BP 500 mg is indicated in the elderly, but not when renal function is impaired.

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 500 mg or 850 mg, 2 or 3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

Method of Administration: Oral.

4.3 Contraindications

Hypersensitivity to metformin hydrochloride or any of the excipients;

Diabetic ketoacidosis, diabetic pre-coma, or the history thereof;

Impaired renal function; pancreatitis; chronic liver disease;

History of or states associated with lactic acidosis such as shock or pulmonary insufficiency;

Cardiac failure and recent myocardial infarction;

Conditions associated with hypoxia;

Hepatic insufficiency; acute alcohol intoxication; alcoholism.

Safety in pregnancy and lactation has not been established.

In children, safety and efficacy have not been established.

4.4 Special Warnings and Precautions for Use

Lactic Acidosis: Lactic acidosis is a rare but serious (high mortality in the absence of prompt treatment) metabolic complication that can occur due to metformin hydrochloride accumulation. Reported cases of lactic acidosis in patients on metformin hydrochloride have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

Diagnosis: The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps with digestive disorders, abdominal pain and severe asthenia. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/l, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin hydrochloride should be discontinued and the patient hospitalised immediately.

Renal Function: As metformin hydrochloride is excreted by the kidney, serum creatinine levels 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 serum creatinine levels at the upper limit of normal and in elderly subjects. Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired.

Administration of Iodinated Contrast Agent: As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, metformin hydrochloride must be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Surgery: Metformin hydrochloride must be discontinued 48 hours before elective surgery under general, spinal or peridural anaesthesia. Therapy may be restarted no

earlier than 48 hours following surgery or resumption of oral nutrition and only if normal renal function has been established.

Children and Adolescents: The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin hydrochloride is initiated. No effect of metformin hydrochloride 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. A careful follow-up is recommended, especially in pre-pubescent children.

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 hydrochloride alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or sulfonylureas.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Alcohol: Increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of fasting, malnutrition or hepatic insufficiency. Avoid consumption of alcohol and alcohol-containing medicinal products.

Iodinated Contrast Agents: Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin hydrochloride accumulation and an increased risk of lactic acidosis. Metformin hydrochloride must be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Combinations Requiring Precautions for Use: Glucocorticoids (systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. Inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, adjust the dosage of the antidiabetic medicinal product during therapy with the other medicinal product and upon its discontinuation.

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

4.6 Fertility, Pregnancy and Lactation

Use in Pregnancy: To date, no relevant epidemiological data are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or foetal development, parturition or postnatal development. When a woman plans to become pregnant and during pregnancy, diabetes should not be treated with metformin hydrochloride; insulin should be used to maintain blood glucose levels as close to normal as possible.

Use in Lactation: Metformin hydrochloride is contra-indicated during lactation. Metformin hydrochloride is excreted into milk in lactating rats. Similar data are not available in humans and a decision should be made whether to discontinue breast-feeding or to discontinue metformin hydrochloride, taking into account the importance of the medicinal product to the mother.

4.7 Effects on Ability to Drive and Use Machines

Metformin hydrochloride 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 hydrochloride is used in combination with other antidiabetic agents (sulfonylureas, insulin, repaglinide).

4.8 Undesirable Effects

The following undesirable effects may occur under treatment with metformin hydrochloride. Frequencies are defined as: 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 hydrochloride 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. Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin hydrochloride. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

Hepatobiliary disorders: Not known: Isolated reports of liver function test abnormalities or hepatitis resolving upon metformin hydrochloride discontinuation.

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.

Health care professionals are asked to report any suspected adverse reactions via the https://pv.pharmacyboardkenya.org

4.9 Overdose

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin hydrochloride 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 hydrochloride is haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Blood glucose lowering drugs, excl. insulins; biguanides.

ATC Code: A10BA02

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; and (3) delay of intestinal glucose absorption.

Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase. It 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, reducing total cholesterol, LDL cholesterol and triglyceride levels.

Clinical Efficacy: 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 significant reductions in the absolute risk of any diabetes-related complication, diabetes-related mortality and overall mortality. A significant reduction in the absolute risk of myocardial infarction was also demonstrated.

5.2 Pharmacokinetic Properties

Absorption: After an oral dose of metformin hydrochloride, Tmax is reached in 2.5 hours. Absolute bioavailability of a 500 mg or 850 mg tablet is approximately 50–60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces

was 20–30%. Food decreases the extent and slightly delays the absorption of metformin hydrochloride.

Distribution: Plasma protein binding is negligible. Metformin hydrochloride partitions into erythrocytes. The mean volume of distribution (Vd) ranged between 63–276 L.

Metabolism: 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.

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

Microcrystalline Cellulose, Povidone, Purified Talc, Magnesium Stearate, Colloidal Anhydrous Silica, Croscarmellose Sodium, Purified Water, Hypromellose, Macrogol 6000, Propylene Glycol, Polysorbate 80, Titanium Dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 months.

6.4 Special Precautions for Storage

Store below 30°C in a dry place. Protect from light.

6.5 Nature and Contents of Container

10 strips of 10 tablets each packed in a carton along with a product literature. 3 strips of 10 tablets each packed in a carton along with a product literature. 1 strip of 10 tablets packed in a carton along with a product literature.

6.6 Special Precautions for Disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

390

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

07 April 2009.

10. DATE OF REVISION OF THE TEXT

29 July 2025.