SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metabet SR 500mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release tablet contains;

Metformin Hydrochloride 500 mg corresponding to 390 mg metformin base

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged release tablet

Off-white coloured, oval, biconvex, film coated tablets plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycemic control. Metabet SR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

4.2 Posology and method of administration

Adults

Monotherapy and combination with other oral antidiabetic agents

The usual starting dose is one tablet of Metabet SR 500 mg tablet once daily.

After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended dose is 4 tablets of Metabet SR 500 mg tablet daily.

Dosage increases should be made in increments of 500 mg every 10-15 days, up to a maximum of 2000 mg once daily with the evening meal. If glycaemic control is not achieved on 2000 mg of Metabet SR once daily, of 1000 mg of Metabet SR twice daily should be considered, with both doses being given with food. If glycaemic

control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.

In patients already treated with metformin tablets, the starting dose of Metabet SR should be equivalent to the daily dose of metformin immediate release tablets. In patients treated with metformin at a dose above 2000 mg daily, switching to Metformin sustained release tablets is not recommended.

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

Combination with insulin:

Metformin and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose of Metabet SR is one 500 mg tablet once daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

For patients already treated with metformin and insulin in combination therapy, the dose of metformin 750mg prolonged release tablets or metformin 1000 mg prolonged release tablets should be equivalent to the daily dose of metformin tablets upto a maximum of 1500 mg or 2000 mg respectively, given with the evening meal, 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 dosage should be adjusted based on renal function. Regular assessment of renal function is necessary (see section 4.4).

Children: In the absence of available data, Metabet SR should not be used in children.

4.3 Contraindications

• Hypersensitivity to metformin hydrochloride or to any of the excipients.

• Diabetic ketoacidosis, diabetic pre-coma.

• Renal failure or renal dysfunction (creatinine clearance < 60mL/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

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 accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

Diagnosis:

Lactic acidosis is characterised by acidotic dyspnea, 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 should be discontinued and the patient should be hospitalised immediately (see section 4.9).

Renal function:

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

* 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, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with an NSAID.

Administration of iodinated contrast agent

As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, metformin should 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 should be discontinued 48 hours before elective surgery with general anaesthesia and should not usually be resumed earlier than 48 hours afterwards.

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 never causes hypoglycaemia, although 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

Concomitant use not recommended

Alcohol

Increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:

- fasting or malnutrition
- hepatic insufficiency

Avoid consumption of alcohol and alcohol-containing medications.

Iodinated contrast agents (see section 4.4)

Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis.

Metformin should 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 drug during therapy with the other drug and upon its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

4.6 Pregnancy and lactation

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 (see also section 5.3)

When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with metformin but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels.

Lactation

Metformin is excreted into milk in lactating rats. Similar data are not available in humans and a decision should be made whether to discontinue nursing or to discontinue metformin, taking into account the importance of the compound to the mother.

4.7 Effects on ability to drive and use machines

Metabet SR 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, repaglinide).

4.8 Undesirable effects

The following undesirable effects 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)

Metabolism and nutrition disorders

Very rare: Decrease of 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 megaloblastic anaemia.
Very rare: Lactic acidosis (see section 4.4.).

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. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders:
Isolated reports: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

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

4.9 Overdose

Hypoglycaemia has not been seen with metformin doses of up to 85g, 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, excluding Insulins 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.

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) 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 (GLUT).

In humans, independently of its action on glycaemia, immediate release metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: immediate release metformin reduces total cholesterol, LDL cholesterol and triglyceride levels. A similar action has not been demonstrated with the prolonged release formulation, possibly due to the evening administration, and an increase in triglycerides may occur

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 in patients treated with immediate release metformin as first line therapy after diet failure.

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)

For metformin used as second-line therapy, in combination with a sulfonylurea, benefit regarding clinical outcome has not been shown.

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.

5.2 Pharmacokinetic properties

Absorption:

After an oral dose of the prolonged release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a Tmax at 7 hours (Tmax for the immediate release tablet is 2.5 hours).

At steady state, similar to the immediate release formulation, Cmax and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000mg of metformin prolonged release tablets is similar to that observed after administration of 1000mg of metformin immediate release tablets b.i.d.

Intrasubject variability of Cmax and AUC of metformin prolonged release is comparable to that observed with metformin immediate release tablets.

When the prolonged release tablet is administered in fasting conditions the AUC is decreased by 30% (both Cmax and Tmax are unaffected).

Mean metformin absorption from the prolonged release formulation is almost not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000mg of metformin as prolonged release tablets.

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 Vd ranged between 63-276 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 is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin 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, toxicity reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Stearic Acid

Shellac (Refined bleached)

Povidone K-30

Silica, colloidal anhydrous

Magnesium Stearate

Film-Coating

Hypromellose

Hydroxy Propyl cellulose

Titanium dioxide

Propylene Glycol

Macrogol 6000

Talc

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

PVC/PVDC/Aluminium blister- Blister packs of 7, 10, 14, 20, 28, 30, 56, 60, 84, 90, 100 and 112 film coated tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Morningside Healthcare Ltd

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LE3 0PA

United Kingdom

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PL 20117/0173

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