Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Metformin Germania 850 mg Film coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 850 mg metformin hydrochloride, corresponding to 662,9 mg metformin base.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet.

White, circular and biconvex film coated tablets, marked with a score on one side.

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.

Metformin may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

A reduction of diabetic complications has been shown in overweight type 2 diabetic patients treated with metformin as first-line therapy after diet failure (see 5.1. Pharmacodynamic properties).

4.2 Posology and method of adminstration

Monotherapy and combination with other oral antidiabetic agents

- The usual starting dose is one tablet 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.
- The maximum recommended dose of metformin is 3 g daily.
- 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 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 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 data, metformin 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 (e.g. serum creatinine levels > 135 µmol/L in males and > 110 µmol/L in females)
- Acute conditions with the potential to alter renal function such as:
- Dehydration
- severe infection
- shock
- intravascular administration of iodinated contrast agents (see 4.4. Special warnings and special precautions for use).
- 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 special 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 Overdose).

Renal function:

As metformin 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 or 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 be usually 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

Inadvisable combinations

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

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.

Associations 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

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 patients plan 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.

Metformin is excreted into milk in lactating rats. Similar data is 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

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, repaglinide).

4.8 Undesirable effects

Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite (> 10 %) are very common: these occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent these gastrointestinal symptoms, 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.

- Metallic taste (3 %) is common.

- Mild erythema has been reported in some hypersensitive individuals. The incidence of such effects is regarded as very rare (< 0.01 %)

- A decrease of vitamin B12 absorption with decrease of serum levels has been observed in patients treated long-term with metformin and appears generally to be without clinical significance (< 0.01 %).

- Lactic acidosis (0.03 cases/1000 patient-years) is very rare (see 4.4. Special warnings and special precautions for use).

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 or concomitant risks of metformin 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: Oral blood glucose lowering drugs
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) 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 (GLUT).

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:

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in 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)

For metformin used as a second-line therapy, in combination with a sulfonylurea, benefit regarding the 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 metformin, T_{max} is reached in 2.5 hours. 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 usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 µg/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC (area under the curve) and a 35 minute prolongation of time to peak plasma concentration were observed. The clinical relevance of these decreases 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 V_d 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 of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Povidone
Magnesium stearate

Film-coat:
Talcum
Hypromellose
Povidone
Titanium dioxide (E 171)
Stearic Acid

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

3 years

6.4 Special precautions for storage

No special precautions for storage

6.5 Nature and contents of container

Strip of 10 or 15 tablets (blister PVC-aluminium). Packs of 30 and 100 tablets

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Germania Pharmazeutika GesmbH
Schuselkagasse 8
A-1150 Vienna
Austria

8 MARKETING AUTHORISATION NUMBER

PA 929/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

May 2004