

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gerformin 500mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 500mg metformin hydrochloride corresponding to 390 mg metformin base.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, circular convex film-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

- In adults, Gerformin 500mg film-coated tablets may be used as monotherapy or in combination with other oral anti-diabetic agents or with insulin.
- In Children from 10 years of aged and adolescents, Gerformin 500mg film-coated tablets 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, Pharmacodynamic properties*).

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, Pharmacodynamic properties*).

4.2 Posology and method of administration

Adults:

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 hydrochloride is 3 g daily, taken as 3 divided doses.

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

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 one tablet 2 or 3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements, 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 hydrochloride dosage should be adjusted based on renal function. Regular assessment of renal function is necessary (*see section 4.4, Special warnings and precautions for use*).

Children and adolescents:

Monotherapy and combination with insulin

- Gerformin 500 mg film-coated tablets 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.

4.3 Contraindications

- Hypersensitivity to metformin hydrochloride or to any of the excipients.
- Diabetic ketoacidosis, diabetic precoma.
- Renal failure or renal dysfunction (creatinine clearance < 60 ml/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, Special warnings and 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 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 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:

The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps with digestive disorders as abdominal pain and severe asthenia.

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 hydrochloride should be discontinued and the patient should be hospitalised immediately (*see section 4.9, Overdose*).

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.

Decrease renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations when renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug.

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 be reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (*see section 4.5, Interaction with other medicinal product and other forms of interaction*).

Surgery:

Metformin hydrochloride must be discontinued 48 hours before elective surgery under general, spinal or peri-dural 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. Therefore, a careful follow-up of the effect of metformin hydrochloride on these parameters in metformin hydrochloride-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 hydrochloride 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.

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 interactionConcomitant 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 medicinal product.

Iodinated contrast agents (see section 4.4, Special warnings and precautions for use):

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 be reinstated 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 diuretic:

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

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 section 5.3, Preclinical safety data*).

When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with metformin hydrochloride 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 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 follows: very common: $\geq 1/10$; common $\geq 1/100$, $< 1/10$; uncommon $\geq 1/1,000$, $< 1/100$; rare $\geq 1/10,000$, $< 1/1,000$; very rare $< 1/10,000$, not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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, urticaria

Metabolism and nutrition disorders:

Very rare:

Lactic acidosis (*see section 4.4, Special warnings and precautions for use*).

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 tests abnormalities or hepatitis resolving upon metformin hydrochloride discontinuation.

In published and post marketing data and in controlled clinical studies in a limited paediatric population ages 10-16 years treated during 1 year. Adverse event reporting was similar in nature and severity to that reported in adults.

4.9 Overdose

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85g, 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. 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 utilization.
- 3) and delay of intestinal glucose absorption.

Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin hydrochloride 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. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical efficacy:

The 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 hydrochloride after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride used as second-line therapy, in combination with a sulfonylurea.

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 formally established.

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, T_{max} is reached in 2.5 hours. 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 faeces was 20-30%.

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

At the recommended metformin hydrochloride doses and 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 hydrochloride plasma levels (C_{max}) did not exceed 4 microgram/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin hydrochloride. 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 the time to peak plasma concentration were observed. The clinical relevance of these findings is unknown.

Distribution:

Plasma protein binding is negligible. Metformin hydrochloride 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 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.

Children and adolescents:

Single dose study: After single doses of metformin hydrochloride 500 mg paediatric 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 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 twice daily 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***Core*

Povidone

Magnesium stearate

Coating

Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

1 (x100), 9, 20, 21, 30, 40, 50, 56, 60, 84, 90, 100, 120, 200, 500, 600 or 1000 tablets in blister packs (PVC - aluminium).

21, 30, 40, 50, 60, 100, 120, 300, 400, 500, 600 or 1000 tablets in plastic bottles (high density polyethylene) with caps (polypropylene).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Limited (t/a Gerard Laboratories),
35-36 Baldoyle Industrial Estate,
Grange Road,
Dublin 13.

8 MARKETING AUTHORISATION NUMBER

PA 0577/039/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 February 2001

Date of last renewal: 23 February 2006

10 DATE OF REVISION OF THE TEXT

April 2008