

PART I B SUMMARY OF PRODUCT CHARACTERISTICS

PRODUCT SUMMARY

1. TRADE NAME OF THE MEDICINAL PRODUCT

METFORMIN 500mg TABLETS BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg Metformin Hydrochloride.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White, circular, biconvex, film-coated tablets, impressed "C" on one face and the identifying letters "MF" on the reverse.

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 glycaemic 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 Administration

Monotherapy and combination with other oral antidiabetic agents

Adults: The usual starting dose is one tablet 2 or 3 times daily with or after food. 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 3g 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

Adults: 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 2-3 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.

For oral use.

4.3. Contra-indications

- Known 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 >110µmol/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. 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 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 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 should be discontinued and the patient should be hospitalised immediately (see section 4.9).

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 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 reinstated 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 sulphonylureas.

4.5. Interactions 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 reinstated 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 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.

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 (sulphonylureas, insulin, repaglinide).

4.8. Undesirable Effects

Metabolism and nutrition disorders: 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 Warnings and special precautions for use).

Gastrointestinal disorders: 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.

Skin and subcutaneous tissue disorders: Mild erythema has been reported in some hypersensitive individuals. The incidence of such effects is regarded as very rare (<0.01%).

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 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

Oral anti-diabetics

(A10B A02: Gastrointestinal tract and metabolism)

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 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, 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 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 sulphonylurea, 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 metformin, T_{max} is reached in 2.5 hours. Absolute bioavailability of a 500mg or 850mg 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 $1\mu\text{g/ml}$. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed $4\mu\text{g/ml}$, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850mg, 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 Vd ranged between 63-276L.

Metabolism:

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination:

Renal clearance of metformin is >400ml/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. Pre-clinical Safety Data

Preclinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity in reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

The tablets contain: povidone (E1201), stearic acid, colloidal anhydrous silica.

The coating contains: methylhydroxypropylcellulose (E464), titanium dioxide (E171), polyethylene glycol.

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

Three years.

6.4. Special Precautions for Storage

Do not store above 25°C.

6.5. Nature and Contents of Container

The product tablet containers are rigid injection moulded polypropylene tablet containers with polyfoam wad or polyethylene ullage filler and snap-on polyethylene lids.

The product may also be supplied in blister packs and cartons:

- a) Carton: Printed carton manufactured from white folding box board.
- b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil with 6-8g/M² PVC and PVdC compatible heat seal lacquer on the reverse side.

Pack sizes: 28s, 30s, 50s, 56s, 60s, 84s, 90s, 100s, 112s, 120s, 168s, 180s, 250s, 300s, 500s, 1000s.

Not all pack sizes may be marketed.

6.6. Instructions for use and handling and disposal

Not applicable.

Administrative Data

7. MARKETING AUTHORISATION HOLDER

Actavis UK Limited (Trading style: Actavis)
Whiddon Valley
BARNSTAPLE
N Devon EX32 8NS

8. MARKETING AUTHORISATION NUMBER(S)

PL 0142/0505

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 April 2001

10. DATE OF REVISION OF THE TEXT

May 2007