National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Metformin Hydrochloride 500mg+Glibenclamide 5mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg metformin hydrochloride, equivalent to 390 mg metformin, and 5 mg glibenclamide.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

4. Clinical particulars

4.1 Therapeutic indications

Treatment of type 2 diabetes in adults, as replacement for previous combination therapy with metformin and glibenclamide in patients whose glycaemia is stable and well-controlled

4.2 Posology and method of administration

Posology

Oral route.

For use in adults only.

Adults with normal renal function (GFR≥ 90 mL/min)

As for all hypoglycaemic agents, the dosage should be adapted according to the individual metabolic response (glycaemia, HbA1c).

Initiation of treatment:

Treatment should be initiated with a dose of the combination product equivalent to previous individual doses of metformin and glibenclamide; the dose being gradually increased depending on results on glycaemic parameters.

Dose titration:

The dosage should be adjusted every 2 weeks or longer, by increments of 1 tablet, depending on glycaemia results.

A gradual increase in the dosage may aid gastrointestinal tolerance and prevent the onset of hypoglycaemia.

Maximum daily recommended dose:

 The maximum daily recommended dose is 6 tablets.

 The maximum daily recommended dose is 3 tablets.

 In exceptional cases, an increase up to 4 tablets may be recommended.

Dosage regimen:

The dosage regimen depends on the individual posology:

 Once a day, in the morning at breakfast, for a dosage of 1 tablet/day,

 Twice a day, morning and evening, for a dosage of 2 or 4 tablets/day,

 Three times a day, morning, noon and evening, for a dosage of 3, 5 or 6 tablets/day

The tablets should be taken with meals. The dosage regimen should be adjusted according to the individual eating habits. However, any intake must be followed by a meal with a sufficiently high carbohydrate content to prevent the onset of hypoglycaemic episodes.

Renal impairment A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months. The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin in patients with GFR

Combination with insulin therapy: No clinical data are available on the concomitant use of this product with insulin therapy. Elderly subjects: The dosage of metformin/glibenclamide should be adjusted depending on renal function parameters (start with 1 tablet of [Nationally completed name] 500 mg/2.5 mg); regular checks on the renal function are necessary (see section 4.4). Patients aged 65 years and older: starting and maintenance doses of glibenclamide must be carefully adjusted to reduce the risk of hypoglycaemia. Treatment should be started with the lowest available dose and increased gradually if necessary (see section 4.4). Paediatric patients: [Nationally completed name] is not recommended for use in children (see section 5.1).

4.3 Contraindications

This medicinal product must never be used in case of:

- hypersensitivity to the active substances, to other sulphonylurea(s) and sulphonamide(s) or to any of the excipients listed in section 6.1;
- type 1 diabetes (insulin-dependent diabetes),
- any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis),
- diabetic pre-coma;
- severe renal failure (GFR < 30 mL/min);
- acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock;
- 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;
- porphyria;

- lactation;
- in association with miconazole (see section 4.5).

4.4 Special warnings and precautions for use

Lactic acidosis

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended. Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5). Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Hypoglycaemia

As the medicinal product contains a sulphonylurea (glibenclamide), it exposes the patient to a risk of onset of hypoglycaemic episodes. After treatment initiation, a progressive dose titration may prevent the onset of hypoglycaemia. This treatment should only be prescribed if the patient adheres to a regular meal schedule (including breakfast). It is important that carbohydrate intake is regular since the risk of hypoglycaemia is increased by a late meal, insufficient or unbalanced carbohydrate intakes. Hypoglycaemia is more likely to occur in case of energy-restricted diet, after intensive or prolonged exercise, when alcohol intake or during the administration of a combination of hypoglycaemic agents. Diagnosis: The symptoms of hypoglycaemia are: headache, hunger, nausea, vomiting, extreme tiredness, sleep disorder, restlessness, aggression, impaired concentration and reactions, depression, confusion, speech impediment, visual disturbances, trembling, paralysis and paraesthesia, dizziness, delirium, convulsions, somnolence, unconsciousness, superficial breathing and bradycardia. Due to a counterregulation caused by the hypoglycaemia sweating, fear, tachycardia, hypertension, palpitations, angina and arrhythmia can occur. These latter symptoms can be absent when the hypoglycaemia is developed slowly, in case of autonomic neuropathy or when the patients take betablocking agents, clonidine, reserpine, guanethidine or sympathomimetics. Management of hypoglycaemia: Moderate hypoglycaemic symptoms without loss of consciousness or neurological manifestations should be corrected by the immediate intake of sugar. An adjustment to the dosage and/or changes to meal patterns should be ensured. Severe hypoglycaemic reactions with coma, seizures or other neurological signs are also possible and constitute a medical emergency requiring immediate treatment with intravenous glucose once the cause is diagnosed or suspected, prior to prompt hospitalisation of the patient. The careful selection of patients and dosage and adequate instructions for the patient are important to reduce the risk of hypoglycaemic episodes. If the patient encounters repeated episodes of hypoglycaemia, which are either severe or associated with unawareness of the situation,

antidiabetic treatment options other than [Nationally completed name] should be taken into consideration.

Concomitant use of glibenclamide with other medicinal products

The concomitant use of glibenclamide with alcohol, phenylbutazone or danazol is not recommended (see section 4.5). Surgery Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable. 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. Regular physical exercise is as necessary as taking [Nationally completed name]. The usual laboratory tests for diabetes monitoring (glycaemia, HbA1c) should be performed regularly. Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since glibenclamide belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combination

Related to glibenclamide Miconazole (systemic route, oromucosal gel): Increase in the hypoglycaemic effect with possible onset of hypoglycaemic manifestations, or even coma (see section 4.3). Concomitant use not recommended

Related to sulphonylurea(s) Alcohol: Antabuse effect (intolerance to alcohol), notably for chlorpropamide, glibenclamide, glipizide, tolbutamide. Increase of the hypoglycaemic reaction (inhibition of compensation reactions), which may facilitate the onset of a hypoglycaemic coma (see section 4.4). Avoid consumption of alcohol and alcohol-containing medications. Phenylbutazone (systemic route): Increase in the hypoglycaemic effect of sulphonylurea(s) (displacement of sulphonylurea(s) from protein-binding sites and/or decrease in their elimination). Preferably use another anti-inflammatory agent exhibiting fewer interactions, or else warn the patient and step up self-monitoring; if necessary, adjust the dosage during treatment with the anti-inflammatory agent and after its withdrawal.

Related to all antidiabetic agents Danazol: If the combination cannot be avoided, warn the patient and step up self-monitoring of blood glucose. Possibly adjust the dosage of the antidiabetic treatment during treatment with danazol and after its withdrawal.

Related to metformin Alcohol Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

Fluconazole:

Increase in the half-life of sulphonylurea with possible onset of hypoglycaemic manifestations. Warn the patient and step up blood glucose self-monitoring, and possibly adjust the dosage of the antidiabetic treatment during treatment with fluconazole and after its withdrawal. Bosentan: Risk of decreased hypoglycaemic effect of glibenclamide because bosentan reduces the plasma concentration of glibenclamide. An increased risk of liver enzyme elevations was reported in

patients receiving glibenclamide concomitantly with bosentan. Warn the patient, set-up monitoring of glycaemia and liver enzymes and adjust the dosage of the antidiabetic treatment if necessary. Bile acid binding agents: Concomitant use may cause a decrease in plasma concentration of glibenclamide, which could lead to a reduced hypoglycaemic effect. This effect was not observed when glibenclamide was taken at an earlier time than the other medicinal product. It is recommended that glibenclamide/metformin is taken at least 4 hours before the intake of a bile acid agent.

Other interaction: combination to be taken into account: Related to glibenclamide Desmopressin: Reduction in antidiuretic activity.

4.6 Pregnancy and Lactation

Pregnancy No preclinical and clinical data on exposed pregnancies are available for [Nationally completed name]. Risk related to diabetes When uncontrolled, diabetes (gestational or permanent) gives rise to an increase in congenital abnormalities and perinatal mortality. Diabetes must be controlled as far as possible during the period of conception in order to reduce the risk of congenital abnormalities. Risk related to metformin (see section 5.3) Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development. Limited amount of data from the use of [Nationally completed name] in pregnant women indicate no increased risk of congenital abnormalities.

Studies in animals have shown no evidence of teratogenic activity. In the absence of a teratogenic effect in animals, foetal malformation in humans is not to be expected since to date, substances known to cause malformation in humans have proved to be teratogenic in well-conducted animal studies in two species. In clinical practice, there are currently no relevant data on which to base an evaluation of potential malformation or fetotoxicity due to glibenclamide when administered during pregnancy. Management Adequate blood glucose control allows pregnancy to proceed normally in this category of patients. [Nationally completed name] must not be used for the treatment of diabetes during pregnancy. It is imperative that insulin be used to achieve adequate blood glucose control. It is recommended that the patient be transferred from oral antidiabetic therapy to insulin as soon as she plans to become pregnant or if pregnancy is exposed to this medicinal product. Neonatal blood glucose monitoring is recommended. Breast-feeding Metformin is excreted in human breast milk. No adverse effects were observed in breastfed newborns/infants of mothers treated with metformin alone. However, in the absence of data concerning passage of glibenclamide into breast milk, and in view of the risk of neonatal hypoglycaemia, this medicinal product is contraindicated in the event of breast-feeding. Fertility Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparison. Fertility of male or female rats was not affected by glibenclamide, administered orally in doses of 100 to 300 mg/kg/day.

4.7 Effects on ability to drive and use machines

Patients should be alerted to the symptoms of hypoglycaemia and should be advised to exercise caution when driving or using machines.

4.8 Undesirable effects

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take [Nationally completed name] in 2 or 3 daily doses and to increase

slowly the doses. At the start of treatment, transient visual disturbances may occur due to a decrease in glycaemia levels.

The following undesirable effects may occur under treatment with [Nationally completed name]. Frequencies are defined as follows: very common (≥1/10), common (≥1/100 to

Blood and lymphatic system disorders: These are reversible upon treatment discontinuation. Rare: leukopenia, thrombocytopenia. Very rare: agranulocytosis, haemolytic anaemia, bone marrow aplasia and pancytopenia. Metabolism and nutrition disorders: Hypoglycaemia (see section 4.4). Uncommon: crises of hepatic porphyria and porphyria cutanea. Very rare: lactic acidosis (see section 4.4). 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. Disulfiram-like reaction with alcohol intake. Nervous system disorders: Common: taste disturbance. Eye disorders: Transient visual disturbances may occur at the start of treatment due to a decrease in glycaemia levels. Gastrointestinal disorders: Very common: gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur more frequently during treatment initiation and resolve spontaneously in most cases. To prevent them, it is recommended that [Nationally completed name] be taken in 2 or 3 daily doses. A slow increase of the dose may also improve gastrointestinal tolerability. Hepatobiliary disorders: Very rare: liver function test abnormalities or hepatitis requiring treatment discontinuation Skin and subcutaneous tissue disorders: Rare: skin reactions such as pruritus, urticaria, maculopapular rash. Very rare: cutaneous or visceral allergic angiitis, erythema multiforme, exfoliative dermatitis, photosensitization, urticaria evolving to shock. A cross reactivity to sulphonamide(s) and their derivatives may occur. Investigations: Uncommon: average to moderate elevations in serum urea and creatinine concentrations. Very rare: hyponatremia.

4.9 Overdose

Overdose may precipitate hypoglycaemia due to the presence of the sulphonylurea (see section 4.4). High overdose or the existence of concomitant risk factors may lead to lactic acidosis due to the presence of metformin (see section 4.4). Lactic acidosis is a medical emergency and must be treated in hospital. The most effective treatment is to remove lactate and metformin by haemodialysis. The plasma clearance of glibenclamide may be prolonged in patients suffering from liver disease. Since glibenclamide is extensively bound to proteins, it is not eliminated by dialysis

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Metformin and sulfonamides. ATC code: A10BD02 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) by reducing hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis (2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation (3) and by delaying 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. In clinical trials conducted so far with combination therapy with metformin and glibenclamide, these favourable

effects on lipid metabolism have not been shown. Glibenclamide is a second generation sulphonylurea with a medium half-life: it causes acute lowering of blood glucose by stimulating the release of insulin by the pancreas, this effect being dependent on the presence of functioning beta cells in the islets of Langerhans.

The stimulation of insulin secretion by glibenclamide in response to a meal is of major importance. The administration of glibenclamide to diabetics induces an increase in the postprandial insulinstimulating response. The increased postprandial responses in insulin and C-peptide secretion persist after at least 6 months of treatment. Metformin and glibenclamide have different mechanisms and sites of action, but their action is complementary. Glibenclamide stimulates the pancreas to secrete insulin, while metformin reduces cell resistance to insulin by acting on peripheral (skeletal muscle) and hepatic sensitivity to insulin. Results from controlled, double blind clinical trials versus reference products in the treatment of type 2 diabetes inadequately controlled by monotherapy with metformin or glibenclamide combined with diet and exercise, have demonstrated that the combination had an additive effect on glucose regulation. Paediatric patients: In a 26-week, active controlled, double-blind, clinical study performed in 167 paediatric patients aged 9 to 16 years with type 2 diabetes not adequately controlled with diet and exercise, with or without an oral antidiabetic treatment, a fixed combination of metformin hydrochloride 250 mg and glibenclamide 1.25 mg was not shown more effective to either metformin hydrochloride or glibenclamide in reducing HbA1c from baseline. Therefore, [Nationally completed name] should not be used in paediatric patients.

5.2 Pharmacokinetic properties

Related to the combination The bioavailability of metformin and glibenclamide in the combination is similar to that noted when one tablet of metformin and one tablet of glibenclamide are taken simultaneously. The bioavailability of metformin in the combination is unaffected by the ingestion of food. The bioavailability of glibenclamide in the combination is unaffected by the ingestion of food, but the absorption speed of glibenclamide is increased by eating. Related to metformin Absorption: After an oral dose of metformin, Tmax 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 nonabsorbed 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 (Cmax) did not exceed 4 µg/ml, even at maximum doses.

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 volume of distribution Vd ranged from 63 to 276 l. Biotransformation: 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. Related to glibenclamide Absorption: Glibenclamide is very readily absorbed (> 95%) following oral administration. The peak plasma concentration is reached in about 4 hours. Distribution: Glibenclamide is extensively bound to plasma albumin (99%), which may account for certain drug interactions. Biotransformation: Glibenclamide is completely metabolised in the liver to two metabolites. Hepatocellular failure decreases glibenclamide

metabolism and appreciably slows down its excretion. Elimination: Glibenclamide is excreted in the form of metabolites via biliary route (60%) and urine (40%), elimination being complete within 45 to 72 hours. Its terminal elimination half-life is 4 to 11 hours. Biliary excretion of the metabolites increases in cases of renal insufficiency, according to the severity of renal impairment until a creatinine clearance at 30 ml/min. Thus, glibenclamide elimination is unaffected by renal insufficiency as long as the creatinine clearance remains above 30 ml/min. Paediatric patients There were no differences in pharmacokinetics of glibenclamide and metformin between paediatric patients and weight-and gender-matched healthy adults.

5.3 Preclinical safety data

No preclinical studies have been performed on the combination product. Preclinical evaluation of the constituents metformin and glibenclamide revealed no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential. Animal studies on metformin and glibenclamide do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/ foetal development, parturition or postnatal development. (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dextrin, Sodium starch glycolate, film-coated powder

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

PVC/ aluminium blisters.

Packs of 30 tablets

6.6 Special precautions for disposal <and other handling>

No special requirements

7. APPLICANT/MANUFACTURER

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