

5.2 Summary of Product Characteristics:

1. Name of the Medicinal Product

1.1 Product Name: AMATRIX PLUS

1.2 Strength: Each Uncoated tablet contains Glibenclamide 5 mg and Metformin Hydrochloride 500 mg

1.3 Pharmaceutical Dosage Form: Uncoated tablets

2. Qualitative and Quantitative Composition:

Qualitative Declaration: Glibenclamide BP and Metformin Hydrochloride BP

Quantitative Declaration:

Each uncoated tablet contains:

Glibenclamide	BP	5 mg
Metformin Hydrochloride	BP	500 mg
Excipients		Q.S

3. Pharmaceutical Form: White coloured caplet shape uncoated tablet having breakline on one side and plain on other side

4. Clinical Particulars:

4.1 Therapeutic indications

- It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- Treatment of type 2 diabetes in adults as replacement for previous combination therapy with Metformin and Glibenclamide in patients whose glycemia is stable and well controlled.

4.2 Posology and method of administration

Patients inadequately controlled on diet and exercise:

Initial: 1.25 mg/250 mg 1-2 times/day; adjust daily dose in increments of 1.25 mg/250 mg at intervals of not less than 2 week.

Max: Glibenclamide 10 mg and Metformin 2,000 mg/day.

Patients inadequately controlled on sulfonylurea and/or Metformin:

Initial: 2.5 mg/500 mg or 5 mg/500 mg bid; adjust daily dose in increments not more than 5 mg/500 mg.

Max: Glibenclamide 20 mg and Metformin 2,000 mg/day.

Method of administration: - Oral with food

4.3 Contraindications

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GLIBENCLAMIDE AND METFORMIN TABLETS
Part – I: Administrative

Glibenclamide and Metformin Hydrochloride Tablets are contraindicated in patients with:

Renal disease or renal dysfunction

Known hypersensitivity to Metformin hydrochloride or Glibenclamide.

Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Hypersensitivity to the active substances, to other sulphonylurea(s) and sulphonamide(s) or to any of the excipients used.

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.

4.4 Special warnings and precautions for use

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with Glibenclamide and metformin; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.

4.5 Interaction with other medicinal products and other forms of Interactions

Certain drugs tend to produce hyperglycemia and may lead to loss of blood glucose control. These drugs include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving Glibenclamide and metformin, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving Glibenclamide and metformin, the patient should be observed closely for hypoglycemia. Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid as compared to sulfonylureas, which are extensively bound to serum proteins.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women with Glibenclamide and metformin or its individual components

Breast Feeding

Metformin is excreted in human breast. 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 00 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 Adverse effects

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with Glibenclamide and metformin; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.

4.9 Overdose

Symptoms: Mild to severe hypoglycaemia which may lead to hypoglycaemic coma (Glibenclamide); lactic acidosis (metformin).

Management: Mild hypoglycaemia, loss of consciousness may be treated with oral glucose. Severe hypoglycaemic reactions, coma, seizure or other neurological impairment require immediate hospitalisation. Admin rapid IV injection of glucose 50% solution in case of hypoglycaemic coma. Haemodialysis may be useful for removal of accumulated drugs in metformin overdose.

5 Pharmacological Properties:

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Metformin and sulfonamides.

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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 insulin-stimulating 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

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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, 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.

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 V_d 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.

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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

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

6.0 Pharmaceutical Particulars

6.1 List of excipients

- Maize Starch
- Lactose Monohydrate
- Microcrystalline Cellulose Powder
- Povidone
- Purified water
- Purified talc
- Magnesium Stearate
- Sodium Starch Glycolate
- Croscarmellose Sodium
- Colloidal Anhydrous Silica

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C temperature in tightly closed container, protected from light.

6.5 Nature and contents of container

Alu-Alu Blister Pack of 3 x10 Tablets

7.0 Marketing Authorization Holder

AMATRIX PLUS
GLIBENCLAMIDE AND METFORMIN TABLETS
Part – I: Administrative

BEKRA PHARMA UK LTD.
13/091, Lavington Road,
Beddington,
LONDON.
UNITED KINGDOM

8.0 Marketing Authorization Number

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9.0 Date of first authorization/renewal of the authorization

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10.0 Date of revision of the text
