1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

1.1 (Invented) Name of the medicinal product

GLIBENCLAMIDE & METFORMIN HYDROCHLORIDE TABLETS

1.2 Strength

Each uncoated tablet contains:

Glibenclamide BP	5mg
Metformin Hydrochloride BP	500 mg
Excipients	q.s

1.3 Pharmaceutical Form

Oral Tablet

2. Qualitative and Quantitative Formula

Batch size: 1,00,000 Tablets

Sr. No.	Name of Ingredients	Label Claim (mg)	Quantity / Tab (mg)	Quantity /Batch (kg)	%	Function
Mixing I						
1	Lactose BP	------	70.000	7.000	9.15%	Diluent
Mixing II						
2	Metformin Hydrochloride BP	500.000	500.000	50.000	65.36%	Antidiabetic Biguanide
3	Lactose BP	------	55.000	5.500	7.19%	Diluent
4	Maize Starch BP	------	32.000	3.200	4.18%	Diluent
5	Microcrystalline Cellulose BP	------	45.000	4.500	5.88%	Diluent
Binding I						
6	Polyethylene Glycol (Laffcol 4000) BP	------	8.000	0.800	1.05%	Surfactant
7	Glibenclamide BP	5.000	5.000	0.500	0.65%	Antidiabetic Sulfonylurea
8	Methylene Dichloride BP*	------	0.03 ml	3.000Lit.	-	Solvent
9	Sodium Lauryl Sulphate BP	------	2.000	0.200	0.26%	Surfactant
Binding II						
10	PVPK-30 BP	------	22.000	2.200	2.88%	Binder
11	Purified Water BP*	------	0.120 ml	12.00Lit.	-	Solvent
Lubrication						
12	Crosscarmellose Sodium BP	------	15.000	1.500	1.96%	Disintegrant
13	Purified Talc BP	------	3.000	0.300	0.39%	Glidant
14	Colloidal Anhydrous Silica BP	------	3.000	0.300	0.39%	Glidant
15	Magnesium Stearate BP	------	5.000	0.500	0.65%	Lubricant
Total Average weight of Uncoated Tablet			**765.000 mg**	**76.500 kg**	**100%**	

* Material will not remain the final product.

BP =British Pharmacopoeia

3. Pharmaceutical form

A white colored, oblong shaped biconvex uncoated tablet break line on one side and plain on other side.

4. Clinical particulars:

4.1 Therapeutic Indication:

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).

[Nationally completed name, 500mg/5mg, film-coated tablets]:
[Nationally completed name, 500mg/5mg, film-coated tablets] should preferably be used in patients who cannot be sufficiently controlled with [Nationally completed name, 500mg/2,5mg, film-coated tablets]

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:

[Nationally completed name, 500mg/2.5mg, film-coated tablets]:

- The maximum daily recommended dose is 6 tablets.

[Nationally completed name, 500mg/5mg, film-coated 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 ([Nationally completed name, 500mg/2.5mg, film-coated tablets]) or for a dosage 3 tablets/day ([Nationally completed name, 500mg/5mg, film-coated tablets]).

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 atleast 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<60 ml/min.

If no adequate strength of [Nationally completed name] is available, individual monocomponents should be used instead of the fixed dose combination.

GFR ml/min	Metformin	Glibenclamide
60-89	Maximum daily dose is 3000 mg Dose reduction may be considered in relation to declining renal function.	No dose reduction is required.
45-59	Maximum daily dose is 2000 mg The starting dose is at most half of the maximum dose.	Maximum daily dose is 10.5 mg.
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 10.5 mg. Initiation of therapy is not recommended due to the risk of hypoglycaemia.
<30	Metformin is contraindicated.	Glibenclamide is contraindicated.

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.
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.

Paediatric patients:
[Nationally completed name] is not recommended for use in children.

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,
- 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.

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.

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.

Factors favouring hypoglycaemia:

- concomitant administration of alcohol, especially combined with fasting,
- refusal or (more particularly in elderly patients) inability of the patient to co-operate,
- malnutrition, irregular meals, missed meals, fasting or changes to diet,
- poor balance between physical exercise and carbohydrate intake,
- renal failure,
- severe liver failure,
- overdose of [Nationally completed name],
- certain endocrine disturbances: thyroid insufficiency, pituitary and adrenal gland insufficiency,
- concomitant administration of certain other drugs.

Renal and hepatic failure:

The pharmacokinetics and/or pharmacodynamics of [Nationally completed name] may be modified in patients with hepatic failure or severe renal failure. If hypoglycaemia occurs in such patients, it may be prolonged, and appropriate treatment must be initiated.

Elderly patients:

Age 65 years and older has been identified as a risk factor for hypoglycemia in patients treated with sulfonylureas. Hypoglycemia can be difficult to recognize in the elderly. Starting and maintenance doses of glibenclamide must be carefully adjusted to reduce the risk of hypoglycaemia.

Patient information:

The risks of hypoglycaemia, its symptoms and its treatment, as well as its predisposing conditions, must be explained to the patient and his or her family. Similarly, the risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps accompanied by digestive disorders, abdominal pain and severe asthenia, dyspnoea attributed to acidose, hypothermia and coma.
In particular, the patient should be informed of the importance of adhering to a diet, following a programme of regular physical exercise and making regular checks on glycaemia.

Blood sugar imbalance

In case of surgery or any other cause of diabetic decompensation, temporary insulin therapy should be envisaged instead of this treatment.

The symptoms of hyperglycaemia are: increased urinating, raging thirst and a dry skin.

Administration of iodinated contrast agents

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Renal function

GFR should be assessed before treatment initiation and regularly thereafter.
Metformin is contraindicated in patients with GFR<30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function.

Concomitant use of glibenclamide with other medicinal products

The concomitant use of glibenclamide with alcohol, phenylbutazone or danazol is not recommended.

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.

[Nationally completed name] contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Related to glibenclamide
Miconazole (systemic route, oromucosal gel):
Increase in the hypoglycaemic effect with possible onset of hypoglycaemic manifestations, or even coma.
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.
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.

Iodinated contrast agents
Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Combinations requiring precautions for use
Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Related to all antidiabetic agents
Chlorpromazine:
At high dosages (100 mg per day of chlorpromazine), elevation in blood glucose (reduction in release of insulin).
Precaution for use: warn the patient and step up self-monitoring of blood glucose. Possibly adjust the dosage of the antidiabetic treatment during treatment with the neuroleptic and after its withdrawal.

Corticosteroids (glucocorticoids) and tetracosactides (systemic and local routes):
Elevation in blood glucose, sometimes accompanied by ketosis (decreased carbohydrate tolerance with corticosteroids). Precaution for use: warn the patient and step up self-monitoring of blood glucose. Possibly adjust the dosage of the antidiabetic during treatment with corticosteroids and after their withdrawal.

β2-agonists:
Elevation in blood glucose due to the β2-agonists.
Precaution for use: warn the patient, step up blood glucose monitoring and possibly transfer to insulin
therapy.

Angiotensin converting enzyme inhibitors (e.g. captopril, enalapril):
ACE inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of [Nationally completed name] during therapy with an ACE inhibitor and upon its discontinuation.

Related to metformin
Diuretics:
Lactic acidosis due to metformin triggered by any functional renal insufficiency, related to diuretics and more particularly to loop diuretics.

Related to glibenclamide
Beta-blockers:
All beta-blockers mask some of the symptoms of hypoglycaemia: palpitations and tachycardia; Most non-cardioselective beta-blockers increase the incidence and severity of hypoglycaemia. Warn the patient and step up blood glucose self-monitoring, especially at the start of treatment.

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 Fertility, 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
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.

Risk related to glibenclamide
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.

4.9 Overdose:

Overdose may precipitate hypoglycaemia due to the presence of the sulphonylurea.

High overdose or the existence of concomitant risk factors may lead to lactic acidosis due to the
presence of metformin. 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

5.1Pharmacotherapeutic Group

Pharmacotherapeutic group: Metformin and sulfonamides.
ATC code: A10BD02

5.2 Pharmacodynamic properties

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.

5.3 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.

5.4 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.

6. Pharmaceutical particulars

6.1 List of Excipients

Name of Excipients	Specification
Lactose	BP
Lactose	BP
Maize Starch	BP
Microcrystalline Cellulose	BP
Polyethylene Glycol (Laffcol 4000)	BP
Methylene Dichloride	BP
Sodium Lauryl Sulphate	BP
PVPK-30	BP
Purified Water	BP
Crosscarmellose Sodium	BP
Purified Talc	BP
Colloidal Anhydrous Silica	BP
Magnesium Stearate	BP

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 months from the date of manufacturing.

6.4 Special precautions for storage

Do not store above 25°C.

Keep in the original carton to protect from light.

6.5 Nature and contents of container

GLIBENCLAMIDE & METFORMIN HYDROCHLORIDE TABLETS packed as 3 X10 Alu-Alu Blister pack.

6.6 Special precautions for disposal

No special requirements.

7. REGISTRANT/MANUFACTURER

CENTURION LABORATORIES PVT LTD

Plot No. P-2. Savali Bio-Tech Park.

At. - Manjusar. Tal.- Savali. Dist.- Vadodara