Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

DIABMET

Metformin Tablets BP 1000 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

- Metformin Hydrochloride BP ….1000 mg
- Titanium Dioxide BP

3. PHARMACEUTICAL FORM

Oral Tablets

White to off white colour, caplet shape, and biconvex film coated tablet plain on both sides

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metformin is indicated for: Type II diabetes mellitus when diet has failed and especially if the patient is overweight. Metformin can be given alone as initial therapy, or can be administered in combination with a sulphonylurea or insulin.

4.2 Route of administration, Posology and method of Administration:

Route of administration

Oral route administration

Mode of administration

Taking Metformin with or just after food may reduce gastrointestinal symptoms associated with metformin

Posology

It is important that Metformin tablets be taken in divided doses with meals.

Adults: Initially, one 500 mg tablet three times a day, with or after food.

After 10 to 15 days the dose should be adjusted, or increased to 850 mg or 1000 mg twice daily. A slow increase in dose may improvegastro-intestinal tolerability. If control is

incomplete a cautious increase in dosage to a maximum of 3 g daily is justified. Once control hasbeen obtained it may be possible to reduce the dosage of Metformin.

Children: Metformin is not recommended for use in Type 1 diabetes mellitus.

Elderly: Metformin is indicated in the elderly, but not when renal function is impaired (see Special precautions).

Combination therapy: See Special precautions.

4.3 Contraindications:

- Hypersensitivity to metformin hydrochloride or any of the excipients.
- Diabetic ketoacidosis, diabetic pre-coma, or the history thereof.
- Renal failure or impaired renal function.
- Pancreatitis.
- Chronic liver disease.
- History of or states associated with lactic acidosis such as shock or pulmonary insufficiency.
- Cardiac failure and recent myocardial infarction.
- Conditions associated with hypoxia.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.
- Safety in pregnancy and lactation has not been established.
- Children, as safety and efficacy have not been established.

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 withsignificant renal failure.

The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlleddiabetics, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

Diagnosis

Lactic acidosis is characterized by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findingsare 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.

Renal function

As Metformin is excreted by 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 renalfunction may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with aNSAID.

The administration of Metformin may be associated with increased cardiovascular mortality as compared to treatment with diet alone ordiet with insulin.

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function.

For patients with acute and unstable heart failure, metformin is contraindicated (see section 4.3).

Elderly:

Due to the limited therapeutic efficacy data in the reduction of risk or delay of type 2 diabetes in patients 75 years and older, metformin initiation is not recommended in these patients.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin with

• Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.

• Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.

• Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.

• Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

Administration of iodinated contrast agent

As the intravascular administration of iodinate d contrast materials in radiological studies can lead to renal failure, Metformin should bediscontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been reevaluatedand found to be normal.

Surgery

Metformin should be discontinued 48 hours before elective surgery with general anesthesia and should usually not be resumed earlierthan 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.
- Although Metformin alone never causes hypoglycaemia, caution is advised when it is used in combination with insulin or sulphonylureas.

4.5 Interaction 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 iodinate d 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 reinstituted until 48 hours afterwards, and only after renalfunction has been re-evaluated and found to be normal.

Glucocorticoids (systemic and local routes), beta-2-agonists and diuretics have intrinsic hyperglycaemic activity. Inform the patientand perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, adjust the dosage of theantidiabetic drug during therapy with the other drug and upon its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the do sage of the antidiabetic drug during therapy with theother drug and upon its discontinuation.

Cimetidine: Reduced renal clearance of Metformin has been reported during cimetidine therapy, so a dose reduction should beconsidered.

Anticoagulants: Metformin has been reported to diminish the activity of warfarin, and so dose adjustments of Metformin should beconsidered.

Sulphonylurea: Concomitant therapy of Metformin with sulphonylurea may cause hypoglycaemia.

Vitamins: Long-term treatment with Metformin may cause vitamin B12 malabsorption in the gastro -intestinal tract, thus a dose reductionof Metformin should be considered.

4.6 Pregnancy and Lactation

Uncontrolled hyperglycaemia in the periconceptional phase and during pregnancy is associated with increased risk of congenital abnormalities, pregnancy loss, pregnancy-induced hypertension, preeclampsia, and perinatal mortality. It is important to maintain blood glucose levels as close to normal as possible throughout pregnancy, to reduce the risk of adverse hyperglycaemia-related outcomes to the mother and her child.

Metformin crosses the placenta with levels that can be as high as maternal concentrations.

A large amount of data on pregnant women (more than 1000 exposed outcomes) from a register-based cohort study and published data (meta-analyses, clinical studies, and registries) indicates no increased risk of congenital abnormalities nor feto/neonatal toxicity after exposure to metformin in the periconceptional phase and/or during pregnancy.

There is limited and inconclusive evidence on the metformin effect on the long-term weight outcome of children exposed in utero. Metformin does not appear to affect motor and social development up to 4 years of age in children exposed during pregnancy although data on long term outcomes are limited.

If clinically needed, the use of metformin can be considered during pregnancy and in the periconceptional phase as an addition or an alternative to insulin.

Breast-feeding

Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breastfeeding is not recommended during metformin treatment. A decision on whether to discontinue breast-feeding should be made, taking into account the benefit of breast-feeding and the potential risk to adverse effect on the child.

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 comparisons.

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 (e.g. sulphonylureas, insulin, or meglinitides).

4.8 Undesirable Effects

Side-effects:

Blood and the lymphatic system disorders

Less frequent: Megaloblastic anaemia.

Nervous system disorders

Frequent: Metallic taste.

Gastro-intestinal disorders

Frequent: Anorexia, nausea, vomiting, constipation and diarrhoea.

Renal and urinary disorders

Less frequent: Ketoacidosis and ketonuria.

Hepato-biliary disorders

Less frequent: Severe cholestatic hepatitis.

General disorders

Less frequent: Hypersensitivity, hypoglycaemia.

Special Precautions:

Lactic acidosis associated with the use of Metformin. In patients with a metabolic acidosis and not having evidence ofketoacidosis (ketonuria and ketonaemia), lactic acidosis should be

suspected and Metformin therapy stopped. Lactic acidosis isa medical emergency, which must be treated in hospital.

Metformin is excreted by the kidney and regular monitoring of renal function is advised in all diabetics.

Metformin therapy should be stopped 2 to 3 days before surgery and before clinical investigations such a s intravenousurography and intravenous angiography, and reinstated only after control of renal function has been regained.

The use of Metformin is not advised in conditions which may cause dehydration, or in patients suffering from serious infections,trauma or on low calorie intake.

Patients on long-term treatment with Metformin should have an annual estimation of Vitamin B12levels, since Metformin maycause malabsorption of Vitamin B12, which may result in megaloblastic anaemia.

During concomitant treatment with a sulphonylurea, blood glucose should be monitored because combined therapy may causehypoglycaemia. Stabilisation of diabetic patients with Metformin and insulin should be carried out in hospital because of thepossibility of hypoglycaemia until the ratio of the two drugs has been obtained. Contra-indications should be carefully observed.

4.9 Overdosage:

Hypoglycaemia can occur when Metformin is given concomitantly with a sulphonylurea, insulin or alcohol. In excessive dosage, andparticularly if there is a possibility of accumulation, lactic acidosis may develop. Intense symptomatic and supportive therapy isrecommended which should be particularly directed at correcting fluid loss and correcting blood glucose levels.

Treatment of overdosage: There is no specific antidote for overdose with Metformin. Treatment is supportive and symptomatic andshould be directed at correcting fluid loss and metabolic disturbances.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics:

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. Delay of intestinal glucose absorption.

Metformin hydrochloride stimulates intrcellular 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 fovourable 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.

5.2 Pharmacokinetics:

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 isapproximately 50 to 60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20 to 30%.

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

At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generallyless than 1 microgram/mL. In controlled clinical trials, maximum metformin plasma levels (Cmax) did not exceed 4 micrograms/mL, evenat maximum doses.

Food decreases the extent and slightly delays the absorption of metformin; following administration of a dose of 850 mg, a 40% lowerplasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of time to peak plasmaconcentration 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 atapproximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Volume of Distribution ranged between 63 to 276 L.

Metabolism

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 isprolonged, leading to increased levels of metformin in plasma.

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

Dicalcium Phosphate
PVP K-30
Isopropyl Alcohol
Magnesium Stearate
Crospovidone
Purified Talc
Aerosil
Hydroxy Propyl Methyl Cellulose 15 cps
Titanium Dioxide
Polyethylene Glycol 4000
Diethyl Phthalate
Methylene Dichloride

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months from the date of manufacture

6.4 Special precautions for storage

Store at temperature below 30°C.

Keep out of reach of children.

Store in the original package to protect from light and moisture.

Store the blisters in the outer carton until required for use.

6.5 Nature and contents of container

3 x 10 ALU-PVCBlister Pack with insert.

6.6 Special precautions for disposal and other handling:

No Special Requirements

7. NAME AND ADDRESS OF APPLICANT

BDA HEALTHCARE PVT. LTD.,

Plot No.: B-1, 2, 3, Near Gov. ITI MIDC, Parseoni – 441105,

Taluka: Parseoni, District: Nagpur, M.S., India.

8. MARKETING AUTHORISATION NUMBER(S):

05915/08297/NMR/2020

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07.05.2021

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