SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Product Name: BELLBAG METFORMIN BP 500 MG TABLET
(Metformin Tablets BP 500 Mg)

Strength: 500mg
Pharmaceutical Form: Oral Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Metformin Hydrochloride BP…….500 mg
Excipients……q.s
Colour: Titanium Dioxide BP

3. PHARMACEUTICAL FORM

Film-Coated Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

− Non-insulin-dependent diabetes (NIDDM, type II) and, in particular, in obese patients, when adequate dietary treatment has failed.

− Metformin 500 mg Tablets can be given alone as initial therapy, or can be administered in combination with sulphonylureas after careful assessment of the contra-indications.

4.2 Posology and method of administration

Posology

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

Dosage

Usual dosage:

The required daily dose ranges from 500mg to 3 g. Therapy should be initiated with a low dose of 500mg or 850mg daily. Depending on the metabolic state the dose can be increased step wise at intervals of a few days up to two weeks until the therapeutically required dose has been reached. In order to minimise the gastro-intestinal side-effects the daily dose should be divided and taken with or after meals. Generally, daily doses of 1000mg to 1700mg are sufficient. If diabetic control is incomplete a cautious increase in dosage to a maximum of 2 to 3g daily is justified. No additional benefit can usually be achieved by use of doses exceeding 3g daily. Once control has been achieved it may be possible to reduce the daily dose.'

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.

GFR mL/min)	Total maximum daily dose (to be divided into 2-3 daily doses)	Additional considerations
60-89	3000 mg	Dose reduction may be considered in relation to declining renal function
45-59	2000 mg	Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose.
30-44	1000 mg	
< 30	-	Metformin is contraindicated

In cases of metabolic decompensation:

The metformin dosage may be reduced in cases of metabolic decompensation. If only small daily doses are administered an omission of one metformin dose should be tried. This is of importance in elderly patients to reduce the risk of lactic acidosis.

Children and juveniles:

Metformin 500 mg Tablets are not recommended for use in children

Elderly patients:

Metformin 500 mg Tablets are indicated for use in the elderly.

Further dosage information

Combination with sulphonylureas:

Metformin 500 mg Tablets may be used in combination with sulphonylureas if monotherapy with metformin does not lead to a satisfactory response. However, it should be noted that metformin and sulphonylureas have a different mode of action and therefore an additive or potentiating effect of these drugs might cause hypoglycaemic shock.

Substitution for sulphonylureas:

Metformin 500 mg Tablets may be used instead of sulphonylureas in patients who formerly have been treated with sulphonylureas.

Method of administration

Metformin 500 mg Tablets should be taken whole with a glass of water during or after meals. They should not be chewed.

Monitoring advice

See special warnings and special precautions for use.

4.3 Contraindications

− Hypersensitivity to metformin or to any of the excipients listed in ahead.
- 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.
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.

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.

Renal function:

GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2. Metformin is contraindicated in patients with GFR<30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function.

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.

Administration of iodinated contrast media:

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. 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.

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.

The usual laboratory tests for diabetes monitoring should be performed regularly.

Metformin alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulphonylureas or meglitinides).

4.5 Interaction with other medicinal products and other forms of interaction
Concomitant use not recommended:

Alcohol: Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case 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, see sections 4.2 and 4.4.

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.

Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes), sympathomimetics:

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT 2.

Co-administration of metformin with

• Inhibitors of OCT 1 (such as verapamil) may reduce efficacy of metformin.

• Inducers of OCT 1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.

• Inhibitors of OCT 2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.

• Inhibitors of both OCT 1 and OCT 2 (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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of cefuroxime in pregnant women. Studies in animals have shown no harmful effects on pregnancy, embryonal or foetal development, parturition or postnatal development. Cefuroxime axetil should be prescribed to pregnant women only if the benefit outweighs the risk.

Breastfeeding

Cefuroxime is excreted in human milk in small quantities. Adverse effects at therapeutic doses are not expected, although a risk of diarrhoea and fungus infection of the mucous membranes cannot be excluded. Breastfeeding might have to be discontinued due to these effects. The possibility of sensitisation should be taken into account. Cefuroxime should only be used during breastfeeding after benefit/risk assessment by the physician in charge.

Fertility

There are no data on the effects of cefuroxime axetil on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, as this medicine may cause dizziness, patients should be warned to be cautious when driving or operating machinery.

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 metformin in 2 or 3 daily doses and to increase slowly the doses.

List of adverse reactions

The following adverse reactions may occur under treatment with metformin. Frequencies are defined as follows: very common ≥1/10; common ≥1/100, <1/10; uncommon ≥1/1,000, <1/100; rare ≥1/10,000, <1/1,000; very rare <1/10,000, not known (cannot be estimated from available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders:	
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.
Nervous system disorders:	
Common:	Taste disturbance.
Gastrointestinal disorders:	
Very common:	Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, 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.
Hepatobiliary disorders:	
Very Rare:	Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.
Skin and subcutaneous tissue disorders:	

Very rare:	Skin reactions such as erythema, pruritus, urticaria.

4.9 Overdose
Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85g, although lactic acidosis has occurred in such circumstances. High overdose of metformin or concomitant risks 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
Pharmacotherapeutic group: Blood glucose lowering drugs. Biguanides; ATC code: A10BA02

Mechanism of action

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:

• reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.

• in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization.

• 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 (GLUTs) known to date.

Pharmacodynamic effects

In clinical studies, use of metformin was associated with either a stable body weight or modest weight loss.

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 study (UKPDS) has established the long-term benefit of intensive blood glucose control in adult patients with 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 sulfonylurea 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 sulfonylurea 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).

Benefit regarding clinical outcome has not been shown for metformin used as second-line therapy, in combination with a sulfonylurea.

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 hydrochloride tablet, maximum plasma concentration (C_{max}) is reached in approximately 2.5 hours (t_{max}). Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride 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 recommended metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 5 microgram/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following oral administration of a 850 mg tablet, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these findings 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 volume of distribution (Vd) ranged between 63-276 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 is prolonged, leading to increased levels of metformin in plasma.

Characteristics in specific groups of patients
Renal impairment
The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations.

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

NAME OF EXCIPIENT	REFERENCE
Maize Starch	BP
Microcrystalline cellouse	BP
Povidone	BP
Polyethylene glycol 6000	USP
Purified Water	BP
Sodium Lauryl Sulphate	BP
Magnesium stearate	BP
Hydroxy propyl methyl cellulose	BP
Purified Talc	BP
Titanium dioxide	BP
Iso propyl alcohol	BP

6.2 Incompatibilities
Not Applicable.

6.3 Shelf life
36 Months

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store at a temperature not exceeding 30°C.

Keep out of reach and sight of children.

6.5 NATURE AND CONTENTS OF CONTAINER
Packing: 10 X 10 Alu -Pvc Blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

7.0 APPLICANT/MANUFACTURER

Marketing Authorisation Holder:
Bell Bag Pharmaceuticals
Lias Estate, No.39
Section-C, Sahara Dabo Estate
Life Camp, Abuja, Nigeria.

Manufacturer By:
Centurion Laboratories Private Limited.
Plot No. P-2, Savli Bio-tech Park at Manjusar.
Tal. Savli, Dist. Vadodara, India.

8.0 MARKETING AUTHORISATION NUMBER

Not Available

9.0 DATE OF FIRST AUTHORISATION /RENEWAL OF THE AUTHORISATION

Not Available

10.0 DATE OF REVISION OF THE TEXT