Summary of Product Characteristics (SPC)

SUMMARY OF PRODUCT CHARACTERISTICS/PACKAGE INSERT

1.	**NAME OF THE FINISHED PHARMACEUTICAL PRODUCT**
	Glimepiride and Metformin Hydrochloride Sustained Release Tablets
2.	**QUALITATIVE AND QUANTITATIVE COMPOSITION**
	Each uncoated bilayered tablet contains: Glimepiride USP … 2 mg Metformin Hydrochloride BP.... 1000 mg (In sustained release form) Excipients: q. s. Colour : Ferric oxide USP-NF (Yellow) **For the full list of excipients, see section 6.1.**
3.	**PHARMACEUTICAL FORM**
	Sustained Release Tablets Oval shaped uncoated biconvex bilayered tablets debossed with "MBN" on one side i.e. white coloured Metformin layer and debossed with "CM-F" on other side i.e. yellow coloured Glimepiride layer and blister packed.
4.	**CLINICAL PARTICULARS**
4.1	**Therapeutic indications**
	Non-insulin dependent (type II) diabetes, whenever blood sugar levels cannot be controlled adequately by diet, physical exercise and weight reduction. Also, for replacement therapy in diabetic patients stabilized on glimepiride (2 mg) with metformin (1000 mg SR). Indicated in patients of 18 years of age and older.
4.2	**Posology and method of administration**
	The mode of administration is oral. **Initial Dose:** 1 Glimepiride 2 mg and Metformin Hydrochloride SR 1000 mg Tablets with breakfast, or as prescribed. **Maintenance Dose:** 1-2 Glimepiride 2 mg and Metformin Hydrochloride SR 1000 mg Tablets with breakfast, or as prescribed. **Maximum Dose:** 3 Glimepiride 2 mg and Metformin Hydrochloride SR 1000 mg Tablets as single morning dose with breakfast, or in 2 divided doses with meals, or as prescribed Dosage must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose. The maximum recommended daily dose of metformin in adults is 2000 mg and glimepiride is 8 mg once daily. Do not crush or chew the tablet; the whole tablet to be taken with water. Start with one tablet per day. The aim should be to decrease both fasting plasma glucose and glycosylated hemoglobin levels to normal by using the lowest effective dose of the drug.

4.3	**Contraindications**
	This combination is not suitable for the treatment of insulin-dependent (type 1) diabetes mellitus (e.g. For the treatment of diabetics with a history of ketoacidosis), or of diabetic precoma or coma. lt must not be used in patients hypersensitive to metformin hydrochloride, glimepiride, sulfonylureas, other sulfonamides, or any of the excipients (risk of hypersensitivity reactions). Impaired renal function

4.4	Special warnings and special precautions for use

Glimepiride

If risk factors for hypoglycemia are present, it may be necessary to adjust the dosage of glimepiride or the entire therapy. This also applies whenever illness occurs during therapy or the patient's life-style changes.

Symptoms of hypoglycemia may be milder or absent in those situations where hypoglycemia develops gradually, in the elderly, and in the patients with autonomic neuropathy or those receiving concurrent treatment with beta-blockers, clonidine, reserpine, guanethidine or other sympatholytic drugs.

Hypoglycemia can almost always be promptly controlled by immediate intake of carbohydrates (glucose or sugar, e.g. in the form of sugar lumps, sugar-sweetened fruit juice or sugar sweetened tea). For this purpose, patients must carry a minimum of 20 grams of glucose with them at all times. They may require assistance of other persons to avoid complication. Artificial sweeteners are ineffective in controlling hypoglycemia.

Continued close observation is necessary. Severe hypoglycemia requires immediate treatment and follow - up by a physician and in some circumstances, hospitalization.

In exceptional stress situations (e.g. trauma, surgery, infections with fever) blood sugar control may deteriorate, and a temporary change to insulin may be necessary.

During treatment with glimepiride, glucose levels in blood and urine must be checked regularly, as should, additionally, the proportion of glycated hemoglobin. Alertness and reactions may be impaired due to hypo-or - hyperglycemia, especially when beginning or after altering treatment, or when glimepiride is not taken regularly. This may affect the ability to operate vehicle or machinery.

Metformin

Lactic Acidosis:

Metformin can provoke lactic acidosis; however, the reported incidence is very low. Conditions like impaired hepatic function, renal dysfunction, hypoxemia, dehydration, sepsis, excessive alcohol intake can increase the risk of lactic acidosis. The risk can be decreased by regular monitoring of renal function and by use of minimum effective dose. In a patient with lactic acidosis, who is on metformin treatment, the drug should be discontinued immediately. Supportive measures & prompt hemodialysis to be started. Impaired renal function: Caution should be exercised with concomitant therapies that may affect renal function or interfere with the disposition of metformin (e.g. cationic drugs).

Use of iodinated contrast media: The drug should be stopped at least two days before X-ray examination with iodinated contrast material and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic states:

Metformin therapy should be promptly discontinued when such events occur in patients.

Surgical procedures:

The drug should be temporarily discontinued and restarted only when the patient resumes

	oral intake and has normal renal function. **Alcohol intake:** Patients to be warned against excessive alcohol intake, acute or chronic, while receiving metformin. **Impaired hepatic function:** The drug should be generally avoided in patients with hepatic disease. **Hypoglycemia:** Does not normally occur when the drug is given alone but has been observed when given in combination with sulfonylureas and I or alcohol. Deficiencies of folic acid, iron and Vitamin B12: Serum Vitamin B12 concentrations should be measured annually during long-term treatment. **Laboratory Tests:** Monitoring of response to therapy to be done periodically through measurement of fasting blood glucose and glycosylated hemoglobin levels. During initial dose titration, fasting glucose can be used to determine the response. Subsequently, both glucose and glycosylated hemoglobin must be monitored, which may be useful in evaluating long-term control.
4.5	**Interaction with other medicinal products and other forms of interaction**
	Cimetidine: Metformin interacts with cimetidine. Therefore, the dose of metformin should be reduced if cimetidine is co-prescribed. **Hyperglycemic agents:** Drugs with hyperglycemic potential (e.g. thiazides, corticosteroids, and others) may partly offset the anti-hyperglycemic action of metformin, and in such cases the glycemic control should be closely monitored. **Alcohol:** Alcohol potentiates the action of metformin on lactate metabolism as well as the anti-hyperglycemic effect. Hence, patients treated with metformin should preferably avoid alcohol, and alcoholism is a definite contraindication. Studies with furosemide and nifedipine suggest a possible interaction by increasing plasma metformin levels. However no such changes were found with propranolol and ibuprofen. The absorption of metformin may be reduced by acarbose and guar gum. Hypoglycemia due to interaction with glimepiride may occur when one of the following medicines is taken, for example : insulin and other oral antidiabetics, ACE inhibitors, allopurinol, anabolic steroids and male sex hormones, chloramphenicol, coumarin derivatives, cyclophosphamide, disopyramide, fenfluramine, fenyramidol, fibrates, fluoxetine, guanethidine, ifsofamide, MAO inhibitors, miconazole, para-aminosalicylic acid, pentoxifylline (high dose parenteral), phenylbutazone, azapropazone, oxyphenbutazone, probenecid, quinolones, salicylates, sulfinpyrazone, sulfonamides, tetracyclines, tritoqualine, trofosfamide. Hyperglycemica due to interaction with glimepiride may occur when one of the following medicines is taken, for example: acetazolamide, barbiturates, corticosteroids, diazoxide, diuretics, epinephrine (adrenaline) and other sympathomimetic agents, glucagons, laxatives (after protracted use), nicotinic acid (in high doses), oestrogens and progestogens, phenothiazines, phenytoin, rifampicin, thyroid hormones. H2 receptor antagonists, clonidine and reserpine may lead to either potentiation or weakening of the blood sugar lowering effect. Beta-blockers may increase the tendency to hypoglycemia. The effect of coumarin derivatives may be potentiated or weakened.
4.6	**Pregnancy and lactation**
	Pregnancy is generally regarded as a contra-indication and insulin should be used in all pregnant diabetic women. The ingredients in the combination may enter breast milk and is

	best avoided in nursing mothers. **Elderly patients:** Caution is advised in elderly patients. Frequent monitoring of serum creatinine and dose reduction is recommended in this age group.
4.7	**Effects on ability to drive and use machines**
	For Glimepiride: Alertness and reactions may be impaired due to hypo- or hyperglycemia, especially when beginning or after altering treatment or when glimepiride is not taken regularly. This may, for example, affect the ability to drive or to operate machinery. For **Metformin:** 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 (sulfonylureas, insulin, repaglinide).
4.8	**Undesirable effects**
	Hypoglycemia: As a result of the blood-sugar lowering action of glimepiride, hypoglycemia may occur and may also be prolonged. Eyes: Especially at the start of treatment, temporary visual impairment may occur due to the change in blood sugar levels. Digestive tract: occasionally nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhoea may occur in isolated cases, liver enzyme levels may increase, and impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis may develop, possible resulting in liver failure. Blood: Rarely thrombocytopenia and in isolated cases, leucopenia, hemolytic anaemia, erythrocytopenia, granulocytopenia, agranulocytosis, and pancytopenia (e.g. due to myelosuppression) may develop. Other adverse reactions: Allergic or psuedoallergic reactions like itching, urticaria or rashes may occur. Such reactions are mild, but may become more serious and be accompanied by dyspnoea, and a fall in blood pressure, sometimes progressing to shock. If urticaria occurs, a physician must be notified immediately. In isolated cases allergic vasculitis, hypersensitivity of the skin to light, and a decrease in serum sodium may occur.

4.9	**Overdose**
	Hypoglycemia has not been seen even with ingestion of up to 85 grams of Metformin, although lactic acidosis has occurred in such circumstances Metformin is dialyzable with a clearance of up to 170 ml/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom Metformin over dosage is suspected. Overdosage of sulphonylureas, including glimepiride, can produce hypoglycaemia. Mild hypoglycaemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger.

5	**PHARMACOLOGICAL PROPERTIES**
5.1	**Pharmacodynamic properties**
	Glimepiride reduces blood glucose levels by correcting both defective insulin secretion and peripheral insulin resistance. It interacts with specific receptors at the plasma membrane of the insulin releasing pancreatic beta- cells where it inhibits ATP- sensitive K+ channels resulting in depolarization of the cell membrane, opening of voltage sensitive Ca2+ channels, increase in intracellular calcium levels and subsequent insulin release. Metformin acts as an antihyperglycemic agent by improving hepatic and peripheral tissue sensitivity to insulin. It also appears to have beneficial effect on serum lipid levels and so on fibrinolytic activity. Metformin therapy is not associated with increase in body weight. Metformin decreases glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.
5.2	**Pharmacokinetic properties**
	Glimepiride is rapidly and completely absorbed after oral administration. The oral bioavailability is approximately 100%. Following oral administration of 1 mg single dose to healthy volunteers, peak serum concentration ((C_{max}) of 103+ 34 ng/ml occurred within 2-3 hours. More than 99% of the drug is bound to plasma proteins. Glimepiride is completely biotransformed by hepatic oxidative metabolism into cyclohexyl-hydroxymethyl derivative (M1) which is further metabolized to form a carboxyl derivative (M2) by cytosolic enzymes. After a single dose, the elimination half life (t1/2) of glimepiride is 5 hours. The urinary excretion of metabolites accounts for 60% of dose, the remainder is found as metabolites in faeces. Metformin has absolute oral bioavailability of 50-60%. GIT absorption is complete within 6 hrs of ingestion within Metformin is rapidly distributed in body after absorption. The renal elimination of Metformin is biphasic. 95% of the absorbed Metformin is eliminated during primary elimination phase having half-life of 6 hours. Rest of the 5% is eliminated during slow terminal elimination phase with mean half-life of 20 hours. Metformin is not bound to plasma proteins; 40-60% of the dose is recovered as unchanged drug in urine with a further 30% recovered as unchanged drug in faeces.
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, toxicity reproduction.
6.	**PHARMACEUTICAL PARTICULARS**
6.1	**List of excipients:**

	Glimepiride Layer	
1	Lactose monohydrate	BP/Ph Eur
2	Sodium Starch Glycolate	BP/Ph Eur
3	Ferric Oxide (Yellow) PH/IN-929	USP-NF
4	Titanium Dioxide	BP/Ph Eur
5	Microcrystalline Cellulose (pH 101)	BP/Ph Eur
6	Pregelatinized Starch	BP/Ph Eur

	7	Povidone K-30	BP/Ph.Eur.	
	8	Magnesium Stearate	BP/Ph.Eur.	
	9	Purified Water	USP/Ph Eur	
		Metformin Hydrochloride Layer		
	1	Hypromellose (K100M)	BP/Ph Eur	
	2	Carboxymethylcellulose Sodium (KDA 8 M 30)	USP	
	3	Methacrylic acid and Ethyl Acrylate Copolymer Dispersion Drug L 30D	USP	
	4	Macrogol (PEG - 6000)	BP/Ph Eur	
	5	Povidone K 90	BP/ Ph Eur	
	6	Magnesium stearate	BP/Ph Eur	
	7	Purified Water	USP/Ph Eur	

6.2	**Incompatibilities :** None
6.3	**Shelf life : 24 months**
6.4	**Special precautions for storage**
	Do not store above 30°C. Protect from light and moisture.
6.5	**Nature and contents of container**
	Alu-PVC/PVDC foil Blister Pack. Blister of 10 Tablets. Box containing 30 tablets.
6.6	**Special precautions for disposal <and other handling>** No special requirements.
7	**MANUFACTURING SITE ADDRESSES** **MANUFACTURING SITE ADDRESSES** **Inventia Healthcare Limited** F1-F1/1-F75/1, Additional Ambernath M.I.D.C., Ambernath (East) - 421 506, Dist. Thane, INDIA.
8	**MARKETING AUTHORIZATION NUMBER** **----**
9	**DATE OF FIRST <REGISTRATION> / RENEWAL OF THE <REGISTRATION** ----
10	**DATE OF REVISION OF THE TEXT** June 2021