National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

[Instructions in this font/colour are from the World Health Organisation Public Assessment Report WHOPAR guidelines.]

1. NAME OF THE MEDICINAL PRODUCT

Metformin Tablets BP 500 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Sr. No.	Ingredients	Spec.	Qty/ Tab (mg)	Ovg.	Function
1	Metformin Hydrochloride	BP	500.00	--	Active
2	Macrogols – 4000	BP	40.00	--	Binder
3	Povidone (K – 30)	BP	10.00	--	Diluent
	Lubrication				
4	Magnesium stearate	BP	5.00	--	Lubricant
5	Colloidal anhydrous silica	BP	2.00	--	Lubricant
		Total	**557.00**		
6	**Film Coating**			--	
7	Purified Talc	BP	2.00	--	Glidant
8	Sheff coat PVA White (5y00079)	IH	9.50	--	Colour
9	* Purified water	BP	24.00	--	Solvent
		Total	**568.50**	--	

BP: British Pharmacopoeia
Average weight of uncoated tablet : 557.00 mg ± 5.0%
Average weight of film coated tablet : 568.50 mg ± 5.0%

* Purified water used as solvents and are not found in the final product.

3. PHARMACEUTICAL FORM

Film coated tablets

White coloured, Circular shaped, biconvex film coated tablet plain on both sides.

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4. Clinical particulars

4.1 Therapeutic indications

Metformin hydrochloride tablets, as monotherapy, are indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. Metformin is indicated in patients 10 years of age and older.
Metformin may be used concomitantly with a sulfonylurea or insulin to improve glycemic control in adults (17 years of age and older).

4.2 Posology and method of administration

Route of administration: Oral

Adult Dosage

- The recommended starting dose of metformin tablets is 500 mg orally twice a day or 850 mg once a day, given with meals.
- Increase the dose in increments of 500 mg weekly or 850 mg every 2 weeks on the basis of glycaemic control and tolerability, up to a maximum dose of 2550 mg per day, given in divided doses.
- Doses above 2000 mg may be better tolerated given 3 times a day with meals.

Paediatric Dosage for Metformin Tablets

- The recommended starting dose of metformin tablets for paediatric patients 10 years of age and older is 500 mg orally twice a day, given with meals.
- Increase dosage in increments of 500 mg weekly on the basis of glycaemic control and tolerability, up to a maximum of 2000 mg per day, given in divided doses twice daily.

Recommendations for Use in Renal Impairment

- Assess renal function prior to initiation of metformin tablets and periodically thereafter.
- Metformin tablets are contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73m2.
- Initiation of metformin tablets in patients with an eGFR between 30 – 45 mL/minute/1.73 m2 is not recommended.
- In patients taking metformin tablets whose eGFR later falls below 45 mL/min/1.73 m2, assess the benefit risk of continuing therapy.
- Discontinue metformin tablets if the patient's eGFR later falls below 30 mL/minute/1.73 m2.

Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue metformin tablets at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra- arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin hydrochloride tablets if renal function is stable.

4.3 Contraindications

Metformin tablets are contraindicated in patients with:

a. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and.
b. Known hypersensitivity to metformin hydrochloride.
c. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Metformin tablets should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

4.3 Special warnings and precautions for use

- Lactic acidosis: Warn against excessive alcohol use. Metformin tablet is not recommended in hepatic impairment or hypoxic states and is contraindicated in renal impairment. Ensure normal renal function before initiating and at least annually thereafter.

- Temporarily discontinue Metformin tablet in patients undergoing radiologic studies with intravascular administration of iodinated contrast materials or any

surgical procedures necessitating restricted intake of food and fluids

- Hypoglycemia: When used with a sulfonylurea (SU), a lower dose of the SU may be required to reduce the risk of hypoglycemia

- Vitamin B12 deficiency: Metformin may lower vitamin B12 levels. Monitor hematologic parameters annually.

- Macrovascular outcomes: No conclusive evidence of macrovascular risk reduction with Metformin tablet or any other antidiabetic drug.

4.5 Interaction with other medicinal products and other forms of interaction

Glyburide—In a single-dose interaction study in type 2 diabetes patients, coadministration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and Cmax were observed but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain,

Furosemide—A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration.

Furosemide increased the metformin plasma and blood Cmax by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the Cmax and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance.

Nifedipine—A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin Cmax and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. ^{T}max and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic drugs—Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma

and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of Other—Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the 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 Metformin, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving 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 the sulfonylureas, which are extensively bound to serum proteins.

4.6 Pregnancy and Lactation

Pregnancy

Risk Summary

Limited data with metformin in pregnant women are not sufficient to determine a drug associated risk for major birth defects or miscarriage. Published studies with metformin use during

pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk. There are risks to the mother and fetus associated with poorly controlled diabetes mellitus in pregnancy.

No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during the period of organogenesis at doses up to 2- and 5 times, respectively, a 2550 mg clinical dose, based on body surface area.
The estimated background risk of major birth defects is 6–10% in women with pre-gestational diabetes mellitus with an HbA1C >7 and has been reported to be as high as 20–25% in women with a HbA1C >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk
Poorly controlled diabetes mellitus in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth, and delivery complications. Poorly controlled diabetes mellitus increases

the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human Data

Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Metformin hydrochloride did not adversely affect development outcomes when administered to pregnant rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 5 times a 2550 mg clinical dose based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Lactation

Risk Summary

Limited published studies report that metformin is present in human milk [see Data]. However, there is insufficient information to determine the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for metformin hydrochloride and any potential adverse effects on the breastfed child from metformin hydrochloride or from the underlying maternal condition.

Data

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

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., sulfonylureas, insulin or meglitinides).

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.

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.

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

Metabolism and nutrition disorders

Very rare

- Lactic acidosis.

- 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

Paediatric population

In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1-year, adverse event reporting was similar in nature and severity to that reported in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.

4.9 Overdose

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, 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 Pharmacodynamics properties

Pharmacotherapeutic group: Blood glucose lowering drugs. Biguanides.

ATC code: A10BA02

Mechanism of action:
There are no appropriate dose-response studies in man. Initial daily doses of 0.5 – 1 gm are used. No further effect on blood glucose seems to occur following doses above 3 gm daily. However, high doses (3.5 gm daily) have been used successfully

in hyperlipidemic non-diabetic subjects.

In patients with diabetes metformin reduces the elevated fasting blood glucose concentration and improves both intravenous and oral glucose tolerance. Metformin increases in vitro glucose uptake in human skeletal muscle. Studies with clamp technique indicate a similar action in vivo. There is also evidence of improved insulin action by metformin from other studies. The presence of small amount of circulating insulin seems necessary for the effect of metformin on blood glucose.

Metformin increases binding of insulin to its receptors in vitro and in vivo. Other studies indicate a post-receptor effect, and this may be independent of the effect at the receptor level. The increase in insulin binding is attributed mainly to an augmentation of low-affinity, high-capacity receptor sites.

An increase of hepatic insulin sensitivity with reduced hepatic glucose output and without an increased glucose uptake in periphery has been suggested. Metformin seems to increase gluconeogenesis from lactate (pyruvate) as well as from alanine. Normally serum lactate concentrations are not elevated during metformin therapy and metformin decreases lactate elimination to a lesser degree than phenformin at the same antihyperglycemic level.

Results of the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that intensive blood glucose control with metformin reduces the risk of diabetic complications and death in overweight patients with type 2 diabetes.

5.2 Pharmacokinetic properties

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 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 are 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.

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25%

decrease in AUC (area under the curve) and a 35 minute prolongation of time to peak plasma concentration 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 at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean 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.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

S.No.	Excipients	Specifications
1	Macrogols – 4000	As per BP
2	Povidone (K – 30)	As per BP
3	Magnesium stearate	As per BP
4	Colloidal anhydrous silica	As per BP

5	Purified Talc	As per BP
6	Sheff coat PVA White (5y00079)	As per IH
7	* Purified water	As per BP

BP: British Pharmacopoeia
IH: IN- House Specification

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months (3 years)

6.4 Special precautions for storage

Do not store above 30°C. Protect from light and moisture.

6.5 Nature and contents of container <and special equipment for use, administration, or implantation>

Sr. No.	**Container closure system / Blister pack of 14 tablets Blister pack of 10 tablets**
Primary Packing	
1.	Printed aluminium foil
2.	Non-toxic, clear transparent PVC film
Secondary Packing	
3.	Printed carton
4.	Leaflet
5.	7 ply corrugated shipper

6.6 Special precautions for disposal <and other handling>

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/MANUFACTURER

Name and Address of Manufacturer

Manufactured by:
Fredun Pharmaceuticals Ltd.
14,15,16, Zorabian Industrial Complex,
Veoor, Palghar (E) - 401 404. INDIA

Name and Address of Applicant

Manufactured for:
PREFERRED DRUGS NIGERIA LTD.
20 Erhuvwa Club Street,
Asaba Delta State, Nigeria &
Preferred Groups LLC, Maryland U.S.A.
www.preferred-drugs.com