1. NAME OF THE MEDICINAL PRODUCT

METFOSYN TABLETS

2. Generic Name

METFORMIN HYDROCHLORIDE TABLETS BP 500 mg

3. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Tablet Contains:

METFORMIN HYDROCHLORIDE BP.....500 mg

Excipients .....QS

4. PHARMACEUTICAL FORM

Solid Oral Dosage Form.

Clinical particulars

4.1 Therapeutic indications

It is the first-line drug of choice for the treatment of type 2 diabetes, in particular, in overweight and obese people and those with normal kidney function. Its use in gestational diabetes has been limited by safety concerns. It is also used in the treatment of polycystic ovary syndrome, and has been investigated for other diseases where insulin resistance may be an important factor such as non alcoholic fatty liver disease. Metformin works by suppressing glucose production by the liver.

4.2 Posology and method of administration

Posology

Route : Oral

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 improve gastro-intestinal tolerability. If control is incomplete a cautious increase in dosage to a maximum of 3 g daily is justified. Once control has been 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.

4.3 Contraindications

Metformin is contraindicated in people with any condition that could increase the risk of lactic acidosis, including kidney disorders (arbitrarily defined as creatinine levels over 150 µmol/l (1.7 mg/dl), lung disease and liver disease. According to the prescribing information, heart failure (in particular, unstable or acute congestive heart failure) increases the risk of lactic acidosis with metformin. A 2007 systematic review of controlled trials, however, suggested metformin is the only antidiabetic drug not associated with any measurable harm in people with heart failure, and it may reduce mortality in comparison with other antidiabetic agents.

Metformin is recommended to be temporarily discontinued before any radiographic study involving iodinated contrast agents, (such as a contrast-enhanced CT scan orangiogram), as the contrast dye may temporarily impair kidney function, indirectly leading to lactic acidosis by causing retention of metformin in the body. Metformin can be resumed after two days, assuming kidney function is normal.

4.4 Special warnings and precautions for use

WARNINGS

Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with Metformin HCl; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 mcg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin HCl is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking Metformin HCl and by use of the minimum effective dose of Metformin HCl. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin HCl treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible

to developing lactic acidosis. In addition, Metformin HCl should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, Metformin HCl should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking Metformin HCl, since alcohol potentiates the effects of metformin HCl on lactate metabolism. In addition, Metformin HCl should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure. The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Metformin HCl should be withdrawn until the situation is clarified.

PRECAUTIONS:

Before taking this medication, ensure that not allergic to metformin. Before using this medication, check medical history, especially of: severe breathing problems (such as obstructive lung disease, severe asthma), blood problems (such as anemia, vitamin B12 deficiency), kidney disease, liver disease.

Before having surgery or any X-ray/scanning procedure using injectable iodinated contrast material, need to temporarily stop this medication before the time of surgery/procedure. Experience of blurred vision, dizziness, or drowsiness may happen due to extremely low or high blood sugar levels. Limit alcohol while using this medication because it can increase y risk of lactic acidosis and developing low blood sugar. High fever, "water pills" (diuretics such as hydrochlorothiazide), too much sweating, diarrhea, or vomiting may cause loss of too much body water (dehydration) and increase risk of lactic acidosis, prolonged diarrhea or vomiting. Older adults may be at greater risk for side effects such as low blood sugar or lactic acidosis. During pregnancy, this medication should be used only when clearly needed. Metformin can cause changes in the menstrual cycle (promote ovulation) and increase the risk of becoming pregnant. Consult your doctor or pharmacist about the use of reliable birth control while using this medication. Metformin passes into breast milk in small amounts.

4.5 Interaction with other medicinal products and other forms of interaction

Metformin can interact with other diabetes medications, like insulin, sulfonylureas, and meglitinides. It may also interact with medications that can raise blood sugar, like some diuretics and corticosteroids. And it may interact with substances that increase the risk of lactic acidosis.

4.6 Pregnancy and Lactation

Pregnancy

Pregnancy Category B

Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. Because animal reproduction studies are not always predictive of human response, Metformin should not be used during pregnancy unless clearly needed.

There are no adequate and well-controlled studies in pregnant women with Metformin. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to Metformin.

Nursing Mothers

Studies in lactating rats show that Metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If Metformin is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

The safety and effectiveness of Metformin hydrochloride tablets for the treatment of type 2 diabetes have been established in pediatric patients ages 10 to 16 years (studies have not been conducted in pediatric patients below the age of 10 years). Use of Metformin hydrochloride tablets in this age group is supported by evidence from adequate and well-controlled studies of Metformin hydrochloride tablets in adults with additional data from a controlled clinical study in pediatric patients ages 10 to 16 years with type 2 diabetes, which demonstrated a similar response in glycemic control to that seen in adults. In this study, adverse effects were similar to those described in adults. A maximum daily dose of 2000 mg is recommended.

4.7 Effects on ability to drive and use machines

If your blood sugar levels are stable, taking metformin should not affect your ability to drive, cycle or use machinery and tools.

4.8 Undesirable effects

Side effects:

Commonly reported side effects of Metformin include lactic acidosis, nausea and vomiting, diarrhea, nausea, vomiting, and flatulence. Other side effects include diarrhea, nausea, vomiting, decreased vitamin b12 serum concentrate, and weakness.

Adverse Reactions:

The following undesirable effects may occur with Metformin.

Frequencies are as follows:

Very common: ≥1/10

Common: ≥ 1/100 to <1/10

Uncommon: ≥ 1/1000 to <1/100

Rare: ≥1/10,000 to <1/1000

Very rare: <1/10,000

Gastrointestinal Disorders:

Very common: Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite are very common: these occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent these gastrointestinal symptoms, 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.

Nervous system disorders:

Common: Taste disturbance

Metabolism and nutrition disorders:

Very rare: Decrease of vitamin B12 absorption with decrease of serum levels has been observed in patients treated long-term with metformin and appears generally to be without clinical significance. Consideration of such aetiology is recommended if a patient presents with megaloplastic anaemia.

Lactic acidosis is very rare (see 4.4 “Special warnings and precautions for use”).

Skin and subcutaneous tissue disorders:

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

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.

Hepatobiliary disorders:

Isolated reports: Liver function test abnormalities or hepatitis resolving upon metformin discontinuation

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Oral blood glucose lowering drugs, A10B A02

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) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis (2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation (3) 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 (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.

Clinical efficacy:

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in 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 sulphonylurea 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 sulphonylurea 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)

For metformin used as second-line therapy, in combination with a sulphonylurea, benefit regarding clinical outcome has not been shown.

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.

Controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year demonstrated a similar response in glycaemic control to that seen in adults.

5.2 Pharmacokinetic properties

Absorption:

After an oral dose of metformin, Tmax is reached in 2.5 hours. Absolute bioavailability of a 500mg or 850mg 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.

Paediatrics:

Single dose study: After single doses of metformin 500 mg, paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg BID for 7 days in paediatric patients the peak plasma concentration (Cmax) and systemic exposure (AUC0-t) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg BID for 14 days. As the dose is individually titratedbased on glycaemic control, this is of limited clinical relevance.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with Metformin was found in either

male or female mice. Similarly, there was no tumorigenic potential observed with Metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of Metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

S. No.	Ingredients	Specification	Quantity per tablet	Active or Inactive
1.	Metformin Hydrochloride	BP	500.00 mg	Active
2.	Maize Starch	BP	5.00 mg	Inactive
3.	Di-Basic Calcium Phosphate	BP	5.00 mg	Inactive
4.	Gelatin	BP	5.00 mg	Inactive
5.	Sodium Methyl Paraben	BP	0.100 mg	Inactive
6.	Sodium Propyl Paraben	BP	0.010 mg	Inactive
7.	Copovidone (K-30)	BP	4.00 mg	Inactive
8.	Purified Talc	BP	3.00 mg	Inactive
9.	Magnesium Stearate	BP	4.00 mg	Inactive
10.	Sodium Starch Glycolate	BP	20.00 mg	Inactive
11.	Croscarmellose Sodium	BP	5.00 mg	Inactive
12.	Uniqcoat FC White	IH	5.00 mg	Inactive

13.	Isopropyl Alcohol	BP	60.00 mg	Inactive
14.	Dichloromethane	BP	40.00 mg	Inactive

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from the date of manufacturing.

Special precautions for storage.

Store in a cool & dry place below 30°C. Protect from Light.

Keep all medicines out of the reach of children.

6.4 Nature and contents of container

10 x 10 Alu Pvc Strip are packed in a printed carton along with 1 package insert.

6.5 Special precautions for disposal and other handling

Any unused portion should be discarded as per local regulations

7. Applicant

Synermed Nigeria LTD

No 3 Abike jokogbola street, Solebo Estate ,Aga Ikorodu, Lagos

8. MANUFACTURER

ZEST PHARMA
275, Sector 'F' Sanwer
Road,Indore, INDIA

NAFDAC REG NO: B4-6658