For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Metformin Hydrochloride Prolonged Release Tablets IP
(Brand Name: K-MET™ 500 mg / 1000 mg Tablets)

2. Qualitative and Quantitative Composition

Each Uncoated Prolonged-release Tablet Contains:
Metformin Hydrochloride IP …… 500 mg / 1000 mg.
Excipients ……. q.s.

3. Dosage Form and Strength

Dosage Form: Prolonged-release Tablets.
Dosage Strength: Metformin hydrochloride 500 mg (in a prolonged-release form) per tablet; Metformin hydrochloride 1000 mg (in a prolonged-release form) per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

K-MET Tablets are indicated for the treatment of type 2 diabetes mellitus in adults when dietary management and exercise alone do not result in adequate glycemic control.
K-MET Tablets may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

4.2Posology and Method of Administration

For oral administration in adults.
The recommended starting dose of prolonged-release metformin is 500 mg (i.e., one tablet of K-MET 500) once daily preferably with the evening meal. If the glycemic control is not achieved in 1 to 2 weeks, dose may be increased to 1000 mg (one tablet of K-MET 1000 or two tablets of K-MET 500) once daily.
Increase the dose in increments of 500 mg weekly on the basis of glycemic control and gastrointestinal (GI) tolerability, up to a maximum of 2000 mg once daily. However, dosage should be individualized. If glycemic control is not achieved with 2000 mg once daily, 1000 mg twice daily should be considered, with both doses being given with food. If effect is still not satisfactory, consider a change to more appropriate treatment.
Swallow the tablet whole and never crush, cut or chew.
Or, as prescribed by the physician.

4.3Contraindications

K-MET Tablets are contraindicated in the following:

- Known hypersensitivity to metformin or to any component of the product.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.
- Severe renal impairment (eGFR below 30 ml/min/1.73 m^2).
- Acute conditions with the potential to alter renal function such as dehydration, severe infection, shock.
- Acute or chronic disease which may cause tissue hypoxia, such as cardiac or respiratory failure, recent myocardial infarction, shock.
- Hepatic insufficiency, alcoholism, acute alcohol intoxication.
- Patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials should temporarily discontinue taking metformin, because use may result in acute alteration of renal function.

4.4Special 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 with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency, and any condition associated with hypoxia. If metformin-associated lactic acidosis is suspected, immediately discontinue metformin therapy and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients.

Excessive Alcohol Intake: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Acute alcohol intoxication is associated with an increased risk of lactic acidosis. Thus, it is advised that patients should strictly avoid consumption of excessive alcohol while on metformin therapy.

Radiologic Studies with Iodinated Contrast Media: Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Metformin hydrochloride must be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Hypoxic States: Cardiovascular collapse (shock) of any kind, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on metformin therapy, the drug should be promptly discontinued.

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.

Renal Function: As metformin is excreted by the kidney, creatinine clearance or eGFR should be determined before initiating treatment and regularly thereafter at least annually in patients with normal renal function and at least 2 to 4 times a year in patients with creatinine clearance levels at the upper limit of normal and in elderly subjects.

Loss of Blood Glucose Control: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold oral antidiabetic agents and temporarily administer insulin. Metformin may be reinstituted after the acute episode is resolved.

Surgery: Metformin should be discontinued 48 hours before elective surgery with general spinal or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or when normal renal function has been established.

Hepatic Impairment: Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of metformin in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} Deficiency: Long-term use of metformin may decrease absorption of vitamin B_{12} with resultant decrease in plasma B_{12} levels. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, may be associated with anemia, but appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. It is recommended to measure hematologic parameters on an annual basis and vitamin B_{12} at 2 to 3 year intervals in patients on metformin therapy.

Other Precautions: While on metformin therapy, disease progression should be closely observed with monitoring of blood glucose levels at regular intervals. Metformin alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetic drugs.

4.5Drug Interactions

Carbonic Anhydrase Inhibitors (e.g., topiramate, zonisamide, acetazolamide or dichlorphenamide): Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce hyperchloremic non-anion gap metabolic acidosis. Concomitant use of these drugs with metformin may increase the risk for lactic acidosis. More frequent monitoring of these patients is recommended.

Drugs that Reduce Metformin Clearance (e.g., ranolazine, vandetanib, dolutegravir, and cimetidine): Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors) could increase systemic exposure to metformin and may increase the risk for lactic acidosis.

Drugs Affecting Glycemic Control (e.g., thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid,

sympathomimetics, calcium channel blockers, and isoniazid): These drugs tend to produce hyperglycemia and may lead to loss of glycemic control. When these drugs are administered to a patient receiving metformin, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving metformin, observe the patient closely for hypoglycemia.

Insulin Secretagogues or Insulin: Co-administration of metformin with an insulin secretagogue (e.g., sulfonylurea) or insulin may increase the risk of hypoglycemia. Patients receiving an insulin secretagogue or insulin may require lower doses of the insulin secretagogue or insulin.

Interactions with Other Drugs:

1. Some drugs may adversely affect renal function which may increase the risk of lactic acidosis, e.g., NSAIDs, including selective cyclooxygenase (COX)-2 inhibitors, angiotensin converting enzyme (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.
2. Glucocorticoids (systemic and local routes), β_2-agonists, and diuretics have intrinsic hyperglycemic activity. More frequent blood glucose monitoring, especially at the beginning of treatment is required. If necessary, adjust the metformin dosage during therapy with these drugs and upon its discontinuation.
3. ACE inhibitors may decrease the blood glucose levels. If necessary, adjust the metformin dosage during therapy with these drugs and upon its discontinuation.

4.6Use in Special Populations

Pregnant Women

Pregnancy Category B. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or fetal development, parturition or postnatal development. No adverse developmental effects were observed when metformin was administered to pregnant rats and rabbits.

Also, a limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk. However, these studies cannot definitely establish the absence of any metformin-associated risk to fetus or pregnant women. Thus, due to lack of safety data and as a precautionary measure, use of metformin should be best avoided during pregnancy.

Uncontrolled or poorly controlled diabetes during pregnancy (gestational or permanent) increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. It also increases the fetal risk for major birth defects, still birth, and macrosomia-related morbidity. Thus, when the patient plans to become pregnant and during pregnancy, it is recommended that insulin be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of fetal malformations associated with abnormal blood glucose levels.

Lactating Women

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. Accordingly, a decision should be made whether to discontinue nursing or to discontinue metformin, taking into account the importance of the compound to the mother.

Paediatric Patients
The safety and effectiveness of metformin prolonged release tablets in paediatric patients have not been established. Thus, K-MET Tablets are not recommended for use in children.

Geriatric Patients
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Assess renal function more frequently in elderly patients.

Renal Impairment Patients
In patients with decreased renal function the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased. Metformin is known to be substantially excreted by the kidney and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. K-MET Tablets are contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 ml/minute/1.73 m^2. Initiation of metformin in patients with an eGFR between 30 to 45 ml/minute/1.73 m^2 is not recommended. Metformin therapy should be discontinued immediately if evidence of renal impairment is present i.e., if eGFR falls below 30 ml/minute/1.73 m^2.
Before initiation of metformin therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients at risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Hepatic Impairment Patients
Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Thus, K-MET Tablets are not recommended in patients with hepatic impairment.

4.7Effect 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).

4.8Undesirable Effects

The most common adverse reactions reported with metformin are nausea, vomiting, diarrhoea, indigestion, abdominal pain, abdominal discomfort, constipation, dyspepsia/heartburn, flatulence, dizziness, taste disturbance, headache, upper respiratory infection, asthenia, and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. Very rarely metformin may cause skin reactions such as erythema, pruritus, urticaria; abnormal liver function test or hepatitis; and lactic acidosis which generally resolve upon metformin discontinuation. Cholestatic, hepatocellular, and mixed hepatocellular liver injury have been reported with post-marketing use of metformin.

4.9Overdose

Overdose of metformin hydrochloride has been reported with ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Lactic acidosis is a medical emergency and must be treated in the hospital. Metformin is dialyzable, with a clearance of up to 170 ml/min under good hemodynamic conditions. Therefore, in case of overdose, hemodialysis may be useful for the removal of metformin.

5. Pharmacological Properties

5.1 Mechanism of Action

Metformin is a biguanide class of oral antidiabetic drugs. Metformin produces its antihyperglycemic effect via following 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) Delay of intestinal glucose absorption.

5.2Pharmacodynamic Properties

Metformin is a biguanide with antihyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT). In clinical studies, the major non-glycemic effect of metformin is either weight neutral or modest weight loss.

5.3Pharmacokinetic Properties

Absorption: After an oral dose of the prolonged release tablet, metformin absorption is significantly delayed compared to the immediate release tablet. The AUC after a single oral administration of 2000 mg of metformin prolonged release tablets is similar to that observed

after administration of 1000 mg of metformin immediate release tablets twice daily. The extent of absorption (as measured by AUC) of metformin (in prolonged release form) increases when given with food. There was no effect of food on C_{max} and T_{max} of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of metformin in prolonged release form.

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 ranged between 63 to 276 liters.

Metabolism: Metformin is excreted unchanged in the urine. No metabolites have been detected in humans.

Excretion: 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 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.

6. Nonclinical Properties

6.1 Animal Toxicology

Carcinogenesis: 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 3 times the maximum recommended human daily dose of 2550 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.

Mutagenesis: 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.

Impairment of 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 2 times the maximum recommended human daily dose of 2550 mg based on body surface area comparisons.

Teratogenicity: 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.

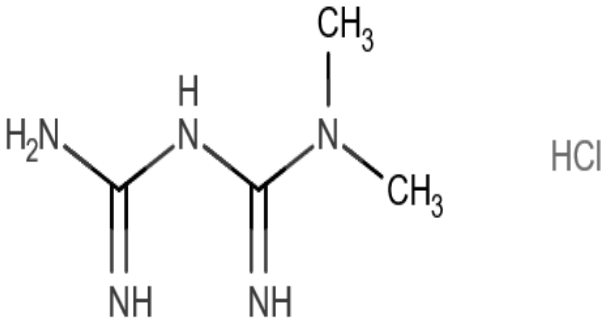
7. Description

K-MET 500 Tablets are White to off-white, elongated, biconvex, plain on both sides & uncoated prolonged release tablets.

K-MET 1000 Tablets are White to off-white, capsule shaped, biconvex, one side scored & uncoated prolonged release tablets.

Each tablet of K-MET 500 contains 500 mg of metformin hydrochloride (in a prolonged release form) for oral administration in adults.
Each tablet of K-MET 1000 contains 1000 mg of metformin hydrochloride (in a prolonged release form) for oral administration in adults.

Metformin hydrochloride is the hydrochloride salt of the biguanide metformin with antihyperglycemic effect.
Metformin hydrochloride is white powder which is freely soluble in water and slightly soluble in alcohol.
Molecular Weight: 165.62 g/mol.
Molecular Formula: C4H12ClN5.
Chemical Name: 3-(diaminomethylidene)-1,1-dimethylguanidine;hydrochloride.
Structural Formula:



Inactive ingredients (excipients) of K-MET 500 & 1000 Tablet contain : Hydroxy Propyl Methyl Cellulose K 100 M, Ethyl Cellulose, Propylene Glycol, Methylene Chloride, Isopropyl Alcohol, Magnesium Stearate, Ethyl Cellulose & Colloidal Silicon Dioxide

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 Months

8.3Packaging Information

Blister of 15 tablets.

8.4Storage and Handling Instructions

Store protected from light and moisture.
Keep out of reach of children.

9. Patient Counseling Information

Instructions to Patients

- Instruct patients to take this medicine exactly as prescribed by your doctor. Do not change the dose or stop therapy without consulting your doctor.
- Pregnant women should consult their doctor before use of this medicine.
- Breastfeeding mothers should avoid use of this medicine.
- Instruct patients not to take this medicine if they have liver and/or kidney dysfunction.
- Advice patients not to take this medicine if they have a severe infection or if they are seriously dehydrated.
- Patients are advised not to take this medicine for the treatment of diabetic ketoacidosis.
- This medicine is not advisable for use in children.
- Instruct patients not to take this medicine if they are going to have a contrast x-ray.
- Advise patients not to drink alcohol excessively while on this drug therapy.

10. Details of Manufacturer

Pure & Cure Healthcare Pvt. Ltd.
(A Subsidary of Akums Drugs & Pharmaceuticals Ltd.) Plot No. 26A-30, Sector-8A, I.I.E., SIDCUL,, Ranipur, Haridwar – 249403, Uttarakhand, India.

11. Details of Permission or License Number with Date

K-MET 500 mg Tablet : Mfg. Lic. No. 31/UA/2013, Date of FDA Product Permission: 03/11/2014
K-MET 1000 mg Tablet : Mfg. Lic. No. 31/UA/2013, Date of FDA Product Permission: 03/11/2014

12. Date of Revision

May 2021.

Marketed by:
EXCEL BLUE CROSS || EXCEL
Division of
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.