METFORMIN HYDROCHLORIDE
METFOR XR

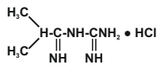
500 mg Extended Release Tablet

ORAL HYPOGLYCEMIC AGENT (BIGUANIDE)

CYDC

FORMULATION
Each Extended Release Tablet contains:
Metformin hydrochloride, USP……500 mg

DESCRIPTION
Metformin Hydrochloride (METFOR XR) Extended-Release Tablets contain an oral antihyperglycemic drug used in the management of type 2 diabetes. Metformin hydrochloride (N,Ndimethylimidodicarbonimidic diamide hydrochloride) is a member of the biguanide class of oral antihyperglycemics and is not chemically or pharmacologically related to any other class of oral antihyperglycemic agents. The empirical formula of metformin hydrochloride is $C_4H_{11}N_5$•HCl and its molecular weight is 165.63. Its structural formula is:



Metformin Hydrochloride (METFOR XR) is a white to off-white crystalline powder that is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. METFOR XR (Metformin Hydrochloride) Extended-Release Tablets are designed for once-a-day oral administration and deliver 500 mg or 1000 mg of metformin hydrochloride.

PHARMACODYNAMIC PROPERTIES
ORAL ANTI-DIABETICS
(A10BA02: Gastrointestinal tract and metabolism)
Metformin is a biguanide with antihyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not cause insulin secretion and therefore does not produce hypoglycemia.
Mechanism of action
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 (GLUT).

Pharmacodynamic effects
In clinical studies, the major non glycemic effect of metformin is either weight stability or modest weight loss.
In humans, independently of its action on glycaemia, immediate release metformin has favorable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: immediate release metformin reduces total cholesterol, LDL cholesterol and triglyceride levels. A similar action has not been demonstrated with the extended release formulation, possibly due to the evening administration, and an increase in triglycerides may occur.

Pharmacokinetic properties
Absorption
After an oral dose of the extended release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a Tmax at 7 hours (Tmax for the immediate release tablet is 2.5 hours).
At steady state, similar to the immediate release formulation, Cmax and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000mg of metformin extended release tablets is similar to that observed after administration of 1000mg of metformin immediate release tablets b.i.d.
Intrasubject variability of Cmax and AUC of metformin extended release is comparable to that observed with metformin immediate release tablets.
During fasting conditions, there is a reduction of 30% in AUC (both in Cmax and Tmax are unaffected) when the extended release tablet is administered.
Meal composition has essentially little effect on metformin absorption from the sustained release formulation. After repeated delivery of up to 2000mg of metformin as extended release tablets, no accumulation is detected.
A mean peak plasma concentration of 1193 ng/ml is attained after a single oral dosage of 1500 mg of Metformin Hydrochloride Extended Release 750 mg, with a median value of 5 hours and a range of 4 to 12 hours.
Metformin Hydrochloride Extended Release 750 mg was proven in healthy fed and fasted volunteers to be bioequivalent to Metformin HCl ER 500 mg at a 1500 mg dose in terms of Cmax and AUC.
A single oral dosage of one tablet of Metformin HCl ER 1000 mg in the fed state results in a mean peak plasma concentration of 1214 ng/ml at a median time of 5 hours (range: 4 to 10 hours). Metformin HCl ER 1000 mg was proven in healthy fed and fasted subjects to be bioequivalent to Metformin HCl ER 500 mg at a 1000 mg dose in terms of Cmax and AUC.
When the 1000 mg extended release tablet is taken in fed settings, the AUC increases by 77% (Cmax increases by 26% and Tmax is somewhat delayed by around 1 hour).
Distribution
Plasma protein binding is insignificant. Metformin partitions into erythrocytes. The plasma peak is higher than the blood peak and appears almost simultaneously. The red blood cells most likely serves as a secondary compartment of distribution. The mean Vd ranged between 63-276 L.
Metabolism
Metformin is excreted unaltered in the urine. No metabolites have been found in humans.
Elimination
Metformin has a renal clearance of more than 400 ml/min, indicating that it is removed via glomerular filtration and tubular secretion. The apparent terminal elimination half-life after an oral dose is approximately 6.5 hours.
When renal function is reduced, renal clearance decreases in proportion to creatinine, causing the elimination half-life to be extended and metformin levels in plasma to rise.
Characteristics in specific group of patients
Renal impairment
There is a scarcity of data in participants with mild renal insufficiency, and no valid assessment of systemic metformin exposure in this subgroup compared to subjects with normal renal function could be performed. As a result, dose adjustments should be based on clinical efficacy/tolerability considerations.

INDICATIONS AND CLINICAL USE
•Risk reduction or delayed onset of type 2 diabetes mellitus in adult, overweight patients with IGT* and/or IFG*, and/or increased HbA1C who are:
  –with high risk for developing overt type 2 diabetes mellitus and still improving towards type 2 diabetes mellitus despite exertion of intensive change in lifestyle for 3 to 6 months
Treatment with Metformin Hydrochloride Extended Release Tablets should be based on a risk score with appropriate measures to control glycemic activity which also includes evidence of high cardiovascular risk.
  –Other than medical reason that the patient is unable to do lifestyle modifications, it should be continued when metformin is initiated.
  –*IGT: Impaired Glucose Tolerance; IFG: Impaired Fasting Glucose
•Treatment of type 2 diabetes mellitus in adults, particularly in obese patients, when food and exercise therapy alone do not achieve optimal glycemic control. Metfor XR can be used alone or in combination with other oral diabetes medications or insulin.

POSOLOGY AND METHOD OF ADMINISTRATION
Posology
Adults with normal renal function (GFR ≥ 90 mL/min)
Risk reduction or delayed onset of type 2 diabetes
•Metformin should only be used where thorough lifestyle modifications for 3 to 6 months have not caused sufficient glycemic control.
•The therapy should be introduced with one tablet Metformin Hydrochloride Extended Release Tablets 500 mg once daily with the evening meal
•After 10 to 15 days, dose adjustment based on blood glucose measurements is advised (OGTT and/or FPG and/or HbA1C values to be within the normal range). Improvement in gastrointestinal tolerability may happen with gradual increase of dose. The maximum recommended dose is 4 tablets (2000 mg) once daily with the evening meal.
•It is recommended to monitor regularly (probably every 3-6 months) the glycemic status (such as OGTT and/or FPG and/or HbA1c value) as well as the risk factors to assess if the treatment needs to be continued, modified, or discontinued.
•A conclusion to re-evaluate therapy is also required if the patient consequently applies improvements to diet and/or exercise, or if alterations to the medical condition will allow increased lifestyle interferences to be possible.
Monotherapy in Type 2 diabetes mellitus and combination with other oral antidiabetic agents:
•The usual starting dose is one tablet of Metformin Hydrochloride Extended Release Tablets 500 mg once daily.
•After 10 to 15 days the dose should be adjusted based on blood glucose measurements. Improvement in gastrointestinal tolerability may happen with gradual increase of dose. The maximum recommended dose is 4 tablets daily.
•Increase in dosage should be made in increments of 500 mg every 10-15 days, up to a maximum of 2000 mg once daily with the evening meal. If control in glycemic activity is not achieved on Metformin Hydrochloride Extended Release Tablets 2000 mg once daily, Metformin Hydrochloride Extended Release Tablets 1000 mg twice daily should be contemplated, with both doses given with food. If glycemic control is still not reached, patients may be changed to standard metformin tablets with a maximum dose of 3000 mg daily.
•In patients who started to use metformin tablets, the starting dose of Metformin Hydrochloride Extended Release Tablets should be equivalent to the daily dose of metformin immediate release tablets. In patients who started to use metformin at a dose above 2000 mg daily, switching to Metformin Hydrochloride Extended Release Tablets is not advised.
•If transfer from another oral antidiabetic agent is anticipated: discontinue the other agent and initiate Metformin Hydrochloride Extended Release Tablets at the dose indicated above.
•Metformin Hydrochloride Extended Release Tablets 750 mg and 1000 mg are intended for patients who are already treated with metformin tablets (extended or immediate release).
•The dose of Metformin Hydrochloride Extended Release Tablets 750 mg or 1000 mg should be equivalent to the daily dose of metformin tablets (extended or immediate release), up to a maximum dose of 1500 mg or 2000 mg respectively, given with the evening meal.
Combination with insulin
Metformin and insulin may be used concomitantly to achieve better blood glucose control. The usual starting dose of Metformin Hydrochloride Extended Release is one 500 mg tablet once daily, while insulin dosage is adjusted based on blood glucose measurements.
For patients already treated with metformin and insulin concomitantly, the dose of Metformin Hydrochloride Extended Release Tablets 750 mg or 1000 mg should be equivalent to the daily dose of metformin tablets maximum of 1500 mg or 2000 mg respectively, given with the evening meal, while insulin dosage is adjusted based on blood glucose measurements.
Elderly
Due to the potential for decreased renal function, the metformin dosage should be modified based on renal function. Regular assessment of renal function is required. Benefit in the risk reduction or delayed onset of type 2 diabetes mellitus has not been proven in patients 75 years and older and metformin initiation is therefore not advised in these patients.
Renal impairment
A GFR should be evaluated before initiation of treatment with metformin containing products and at least annually subsequently. In patients with an increased risk of further progression of renal impairment and in the elderly, renal function should be reviewed more often (every 3-6 months).

GFR (mL/min)	Total maximum daily dose	Additional considerations
60 - 89	2000 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 should be reviewed before considering initiation of metformin
30 - 44	1000 mg	The starting dose is at most half of the maximum dose.
<30	-	Metformin is contraindicated.

Pediatric population
In the absence of sufficient data, Metformin Hydrochloride Extended Release Tablets should not be used in children.

CONTRAINDICATIONS
•Known hypersensitivity to metformin or to any of the excipients.
•Any type of acute metabolic acidosis (including lactic acidosis, diabetic ketoacidosis)
•Severe renal failure (GFR < 30 mL/min).
•Diabetic pre-coma
•Acute conditions that might 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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Lactic acidosis:
Lactic acidosis, an uncommon but significant metabolic consequence, most commonly arises during an acute worsening of renal function, cardiorespiratory disease, or sepsis. Metformin accumulation develops with acute renal function deterioration and increases the risk of lactic acidosis.
Metformin should be temporarily discontinued in the event of dehydration (severe diarrhea or vomiting, fever, or decreased fluid intake), and consultation with a health care provider is advised. Antihypertensives, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) should be used with caution in metformin-treated individuals. Excessive alcohol consumption, hepatic insufficiency, poorly controlled diabetes, ketosis, prolonged fasting, and any conditions linked with hypoxia, as well as concurrent use of medical medications that may cause lactic acidosis, are all risk factors for lactic acidosis.
Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is distinguished by acidotic dyspnea, stomach pain, muscle cramps, asthenia, hypothermia, and\ coma. If symptoms are suspected, the patient should discontinue metformin and seek emergency medical assistance. Reduced blood pH (7.35), elevated plasma lactate levels (>5 mmol/L), and an increased anion gap and lactate/pyruvate ratio are all diagnostic laboratory findings.

Renal function:
GFR should be measured before starting treatment and then on a frequent basis. Metformin is contraindicated in patients with GFR less than 30 mL/min and should be discontinued temporarily in the presence of diseases that impair renal function.
Cardiac function:
Hypoxia and renal insufficiency are more common in patients with heart failure. Metformin may be administered in patients with stable chronic heart failure with regular monitoring of cardiac and renal function. Metformin is not recommended for persons with acute or unstable heart failure.
Elderly:
Due to the insufficient data on therapeutic efficacy in the risk reduction or delayed onset of type 2 diabetes in patients 75 years and older, introduction of metformin is not advisable in these patients.
Administration of iodinated contrast agents:
Intravenous injection of iodinated contrast agents may result in contrast induced nephropathy, which can lead to metformin buildup and an increased risk of lactic acidosis. Metformin should be stopped before to or during the imaging process and not resumed for at least 48 hours, assuming renal function has been re-evaluated and determined to be stable.
Surgery:
Metformin must be stopped before undergoing surgery under general, spinal, or epidural anesthesia. Therapy should be continued no sooner than 48 hours after surgery or the commencement of oral nourishment, and only after renal function has been re-evaluated and proven to be stable.
Other precautions:
All patients should follow their diet with a regular carbohydrate distribution throughout the day. Patients who are overweight should maintain their energy-restricted diet. The standard laboratory tests for diabetes monitoring should be done on a regular basis. Metformin may lower serum vitamin B12 levels. Low vitamin B12 levels become more likely with increased metformin dose, therapy duration, and/or in patients with risk factors for vitamin B12 insufficiency. Vitamin B12 serum levels should be examined if there is a suspicion of vitamin B12 insufficiency (such as anemia or neuropathy).
Patients with risk factors for vitamin B12 insufficiency may require periodic vitamin B12 monitoring. Metformin therapy should be continued for as long as it is tolerated and not contraindicated, and appropriate vitamin B12 deficiency treatment should be offered in accordance with current clinical standards.
Metformin alone does not cause hypoglycemia; however it should be used with caution when combined with insulin or other oral antidiabetics (e.g., sulphonylureas or meglitinides).
Tablet shells may be found in the feces. Patients should be informed that this is common.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Concomitant use not recommended
Alcohol
Alcohol consumption increases the risk of lactic acidosis, especially when combined with fasting, malnutrition, or hepatic impairment.
Iodinated contrast agents
Metformin must be stopped prior to or during the imaging process and not reintroduced for at least 48 hours, assuming renal function has been re-evaluated and determined to be stable.
Combinations requiring precautions for use
Some medications can impair renal function and hence raise the risk of lactic acidosis, for example, NSAIDs, such as selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists, and diuretics, particularly loop diuretics. Close monitoring of renal function is required while starting or using such drugs in conjunction with metformin.
Medicinal products with intrinsic hyperglycemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics).
More frequent blood glucose testing may be necessary, particularly at the start of treatment. Adjust the metformin dosage as needed during the therapy of other drugs and after its discontinuation.
Organic cation transporters (OCT)
Metformin is a substrate of both transporters OCT1 and OCT2. Co-administration of metformin with:
•Inhibitors of OCT1 (such as verapamil) may lessen metformin efficacy.
•Inducers of OCT1 (such as rifampicin) may enhance gastrointestinal absorption and efficacy of metformin.
•Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may reduce the renal elimination of metformin and therefore lead to an enhanced metformin plasma concentration.
•Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may change efficacy and renal elimination of metformin.
Therefore, caution is advised, especially in patients with renal impairment, when these drugs are administered together with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may change the efficacy of metformin.

FERTILITY, PREGNANCY AND LACTATION
Pregnancy
Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality.
A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or fetal development, parturition, or postnatal development. When the patient plans to become pregnant and during pregnancy, it is recommended that impaired glycemic control or diabetes are not treated with metformin. For diabetes it is recommended that insulin should be used to maintain blood glucose levels as close to normal as possible to reduce the risk of malformations of the fetus.
Breastfeeding
Metformin is found excreted in human breast milk. No adverse effects were seen in breastfed newborns/infants. However, due to limited data available, breastfeeding is not recommended during metformin treatment. A decision on whether to terminate breast-feeding should be made, considering the benefit of breast-feeding and the potential risk to adverse effect on the child.
Fertility
Metformin had no effect on male or female rat fertility when administered at dosages as high as 600 mg/kg/day, which is around three times the maximum recommended human daily dose based on body surface area comparisons.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Since metformin monotherapy does not result in hypoglycemia, it has no impact on the capacity to operate machinery or operate a vehicle.
However, when metformin is combined with other anti-diabetic medications (such as sulphonylureas, insulin, or meglinitides), patients should be informed of the possibility of hypoglycemia.

UNDESIRABLE EFFECTS
In post marketing data and in controlled clinical studies, Metformin Hydrochloride Extended Release Tablets and Metformin Hydrochloride immediate release were similar in nature and severity in adverse event reporting in patients.
During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhea, abdominal pain and loss of appetite, which are resolved spontaneously in most cases.
The following adverse reactions may occur with Metformin Hydrochloride Extended Release Tablets.
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 according to decreasing seriousness.

Metabolism and nutrition disorders
Common:
•Decrease or deficiency in Vitamin B12 levels
Very rare:
•Lactic acidosis
Nervous system disorders
Common:
•Taste disturbance
Gastrointestinal disorders
Very common:
•Gastrointestinal disorders (such as nausea, vomiting, diarrhea, abdominal pain and loss of appetite)
These undesirable effects occur most frequently during the start of the therapy and mostly resolved spontaneously. A gradual increase of the dose may also enhance gastrointestinal tolerability.
Hepatobiliary disorders
Very rare:
•Isolated reports of liver function tests abnormalities or hepatitis that usually resolves upon metformin discontinuation.
Skin and subcutaneous tissue disorders
Very rare:
•Skin reactions (such as erythema, pruritus, urticaria)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 national reporting system.

OVERDOSE
Metformin dosages up to 85 g have not been associated with hypoglycemia, but lactic acidosis has been noted under these conditions. Lactic acidosis can result from a high overdose of metformin or its concurrent risks. Lactic acidosis must be treated in a hospital as a medical emergency.

Hemodialysis is the most efficient way to get rid of lactate and metformin.

Shelf life
3 years.

Special precautions for storage
This medicinal product does not require any special storage conditions.

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.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING STATEMENT
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Seek medical attention right away if any of the adverse reaction occurs.

STORAGE
Store at temperatures not exceeding 30°C.

PACKAGING AND AVAILABILITY
Alu/PVC/PVDC Blister Pack x 10's (Box of 30's)

Reg. No.:
DRP-10478-01

Date of First Authorization / Renewal of Authorization: 06/2024
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