METFORMIN HYDROCHLORIDE

METFOR XR

750 mg Extended-Release Tablet

ORAL HYPOGLYCEMIC

FORMULATION
Each Extended-Release Tablet contains:
Metformin hydrochloride..... 750mg

PRODUCT DESCRIPTION
Metformin Hydrochloride (Metfor XR) 750 mg Extended-Release Tablet: White, oblong, biconvex tablet, plain on both sides

PHARMACODYNAMICS
Metformin is a biguanide with antihyperglycemic effects on both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia.
Metformin exerts its antihyperglycemic effect via 3 mechanisms: (1) in the liver, reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis, (2) in muscle, improvement of peripheral glucose uptake by increasing insulin sensitivity and (3) in the intestines, delay of intestinal glucose absorption.
In clinical studies, the major non glycemic effect of metformin is either weight stability or modest weight loss.
Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.
Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

Effects on body weight
In contrast to other commonly used antihyperglycemic agents, such as sulphonylureas or thiazolinediones, treatment with metformin offers a considerable benefit for patients with type 2 diabetes by not causing an increase in body weight. By maintaining or reducing body weight, metformin limits other risk factors associated with increased weight. Over the long term this translates into more stable glycemic control and a decreased risk of diabetes complications.

PHARMACOKINETICS
Absorption
Metformin absorption from the extended release formulation is not altered by meal composition.
No accumulation is observed after repeated administration of up to 2 grams metformin extended release.

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.

Characteristics in specific groups of patients
Renal impairment
The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations.

INDICATIONS
Metformin hydrochloride is used for the management of type 2 diabetes mellitus as monotherapy, and as an adjunct to diet and exercise to improve glycemic control.

DOSAGE AND ADMINISTRATION
Extended-Release Tablet
Adult Dose:
Monotherapy and combination with other oral hypoglycemic agents.
The usual starting dose is 750 mg given with evening meals. Maximum dose of up to 1500 mg given with evening meals. After 10 to 15 days, it is recommended to check if the dose given to the patient is adequate on the basis of blood glucose measurement.

Combination with Insulin:
For patients treated with combination therapy of metformin and insulin, metformin dose 750 mg with evening meals, up to a maximum dose of 1500 mg given with evening meals. Insulin dosage is adjusted on the basis of blood glucose measurement of the patient.

CONTRAINDICATIONS
Metformin MUST NOT BE USED in the following cases:
- Hypersensitivity to metformin or to any of the excipients.
- Any type of metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma
- Severe renal failure (CrCl below 30 mL/min or eGFR below 30 mL/min/1.73 m^2).
- Acute conditions with the potential to alter renal function such as dehydration, severe infection, or shock.
- Disease (especially acute disease or worsening of chronic disease) which may cause tissue hypoxia such as unstable congestive heart failure, respiratory failure, recent myocardial infarction or shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism

Metformin must be discontinued 48 hours prior to elective major surgical interventions and may not be reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further.

SPECIAL WARNINGS AND PRECAUTIONS
Lactic acidosis
Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication. Risk factors include poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, severe infection, hepatic insufficiency, and any condition associated with hypoxia (such as decompensated cardiac failure, acute myocardial infarction) or the concomitant use of medications which might cause lactic acidosis (such as NRTIs). (see also Contraindications).
Lactic acidosis can occur due to metformin accumulation. Reported cases of lactic acidosis in patients treated with metformin have occurred primarily in diabetic patients with acute renal failure or acute worsening of renal function.
Special caution should therefore be paid to situations where renal function may become acutely impaired (see also Contraindications). For example in case of dehydration (severe or prolonged diarrhea or vomiting) or when initiating drugs which can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs).
In the acute conditions listed, metformin must be immediately and temporarily discontinued.
The following non-specific symptoms could be signs of lactic acidosis: such as muscle cramps, digestive disorders as abdominal pain and severe asthenia.
Diagnosis
Lactic acidosis is characterized by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH (below 7.35), plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. In case of lactic acidosis, the patient should be immediately hospitalized (see also Overdose).
Physicians must alert the patients on the risk and on the symptoms of lactic acidosis. Patients should be instructed to immediately seek medical attention and to stop taking metformin. Metformin must be immediately discontinued, at least temporarily, until the situation is clarified. Reintroduction of metformin should then be discussed taking into account the benefit/risk ratio on an individual basis as well as renal function.
Renal function:
As metformin is excreted by the kidney, it is recommended that CrCl (this can be estimated from serum creatinine levels by using the Cockcroft-Gault formula) or eGFR should be determined before initiating treatment and regularly thereafter:
- At least annually in patients with normal renal function
- At least every 3 to 6 months in patients with CrCl between 45 and 59 mL/min or eGFR between 45 and 59 mL/min/1.73 m^2 and in elderly subjects
- At least every 3 months in patients with CrCl between 30 and 44 mL/min or eGFR between 30 and 44 mL/min/1.73m^2

In case CrCl is below 30 mL/min or eGFR is below 30 mL/min/1.73m^2 respectively, metformin is contraindicated (see Contraindications). Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution is needed in situations where renal function may become acutely impaired, for example due to dehydration (severe or prolonged diarrhea or vomiting), or when initiating drugs which can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs). In the acute conditions listed, metformin must be immediately and temporarily discontinued. In these cases, it is also recommended to check renal function before initiating treatment with metformin.

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 (see Contraindications).
Other precautions

- It is recommended that all patients continue their diet with a regular distribution of carbohydrate intake during the day and that overweight patients continue their energy-restricted diet.
- It is recommended that the usual laboratory tests for diabetes monitoring be performed regularly.
- Metformin alone never causes hypoglycemia, although caution is advised when it is used in combination with insulin, sulphonylureas or meglitinides.
- The tablet shells may be present in the feces. It is recommended that patients be advised that this is normal and this is not linked with a decrease in therapeutic activity.

Effects on the Ability to Drive and Use Machines
Metformin monotherapy does not cause hypoglycemia and therefore has no effect on the ability to drive or to use machines. However, it is recommended that patients be alerted to the risk of hypoglycemia when metformin is used in combination with other antidiabetic agents such as sulphonylureas, insulin or meglitinides.

PREGNANCY AND LACTATION
Pregnancy
Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased 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.
However, when the patient plans to become pregnant and during pregnancy, it is recommended that prediabetes and diabetes are not treated with metformin. In diabetes, insulin should be used to maintain blood glucose levels as close to normal as possible.
Lactation
Metformin is excreted into human breast milk in very small amounts. No adverse effects were observed in breastfed newborn/infants. However, as only limited data are available, breastfeeding is not recommended during metformin treatment. A decision on whether to discontinue breastfeeding or to discontinue metformin needs to take into account the benefit of breastfeeding, the importance of the medicinal product to the mother, and the potential risk of adverse effects in the infant.

INTERACTIONS
Contraindicated combinations
In patients with CrCL below 45 mL/min or eGFR below 45 mL/min/1.73 m^2 for intravenous administration or in patients with CrCL below 45 mL/min or eGFR below 60 mL/min/1.73 m^2 for intra-arterial administration of iodinated contrast materials, metformin must be discontinued 48 hours before the test (see Contraindications).
Combinations to be used with caution
Medicinal products with intrinsic hyperglycemic activity (e.g. glucocorticoids and tetracosactides [systemic and local routes], beta-2-agonists, danazol, and chlorpromazine at high dosages of 100 mg per day, diuretics): More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation. Diuretics, especially loop diuretics, may increase the risk of lactic acidosis due to their potential to decrease renal function (further to their intrinsic hyperglycemic effect).
Organic cation transporters (OTC): Metformin is a substrate of both transporters OCTI and OCT2. Co-administration of metformin with:

- Substrates/inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy
- Substrates/inhibitors of OCT2 (such as cimetidine, dolutegravir, crizotinib, olaparib, daclatasvir, vandetanib) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.

Other interactions

- Nifedipine appears to enhance the absorption of metformin.
- Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) could potentially interact with metformin by competing for common renal tubular transport systems.
- Cimetidine increases peak plasma concentration of metformin and whole blood concentrations
- Certain drugs such as thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid, tend to produce hyperglycemia and may lead to loss of glycemic control. Monitor closely for loss of blood glucose control in patients taking these drugs. When such drugs are withdrawn from a patient receiving metformin, the patient should be closely observed for hypoglycaemia.

ADVERSE EFFECTS
Diarrhea, abnormal stools, hypoglycemia, myalgia, light-headed, dyspnea, nail disorder, rash, sweating increased, taste disorder, chest discomfort, chills, flu syndrome, flushing, and palpitations.

OVERDOSAGE
Hypoglycemia has not been seen with metformin 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 a hospital. The most effective method to remove lactate and metformin is hemodialysis.

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 advice from a healthcare professional at the first sign of any adverse reaction.

STORAGE CONDITION
Store at temperatures not exceeding 30°C.

Keep all medicines out of reach of children.

AVAILABILITY
Metformin hydrochloride (Metfor XR) 750 mg Extended-Release Tablet: Strip Foil x 6's (Box of 30's).

Marketing Authorization Holder
THE CATHAY YSS DISTRIBUTORS CO., INC.
2/F Vernida I Condominium, 120 Amorsolo St., Legaspi Village, Makati City

Manufacturer
EL LABORATORIES, INC.
109 North Main Ave., Laguna Technopark, Biñan, Laguna

Registration Number: DR-XY44791
Date of First Authorization: 11 September 2015
Date of revision: 05 March 2020