

EFFIMET 1000 XR

Metformin Hydrochloride extended release tablet

BRAND NAME: Effimet XR.

THERAPEUTIC CATEGORY: Anti-Diabetic

PHARMACOLOGIC CLASS: Biguanides

COMPOSITION AND PRESENTATION

Composition

Each extended release tablet contains 1000 mg Metformin Hydrochloride ion extended release dosage form.

Presentation

10 Tablets x 10 Blisters

MOLECULAR INTRODUCTION:

Metformin is an insulin-sensitizing agent with potent antihyperglycemic properties. Efficacy of metformin as antihyperglycemia is similar to that of sulfonylureas, thiazolidinediones, and insulin. The antihyperglycemic properties of metformin are mainly attributed to suppressed hepatic glucose production, especially hepatic gluconeogenesis, and increased peripheral tissue insulin sensitivity. Although the precise mechanism of hypoglycemic action of Metformin remains unclear, it probably interrupts mitochondrial oxidative processes in the liver and corrects abnormalities of intracellular calcium metabolism in insulin-sensitive tissues (liver, skeletal muscle, and adipocytes) and cardiovascular tissue.

MECHANISM OF ACTION:

- Metformin acts by increasing the sensitivity of liver, muscle, fat, and other tissues to the uptake and effects of insulin. These actions lower the level of sugar in the blood. Unlike glucose-lowering drugs of the sulfonylurea class, e.g. glyburide, metformin does not increase the concentration of insulin in the blood and, therefore, does not cause excessively low blood glucose levels (hypoglycemia) when used alone.
- It directly stimulates peripheral anaerobic glycolysis in tissues and increases glucose removal from blood, Reduces hepatic gluconeogenesis, Slows glucose absorption from GIT and Reduces plasma glucagon levels.

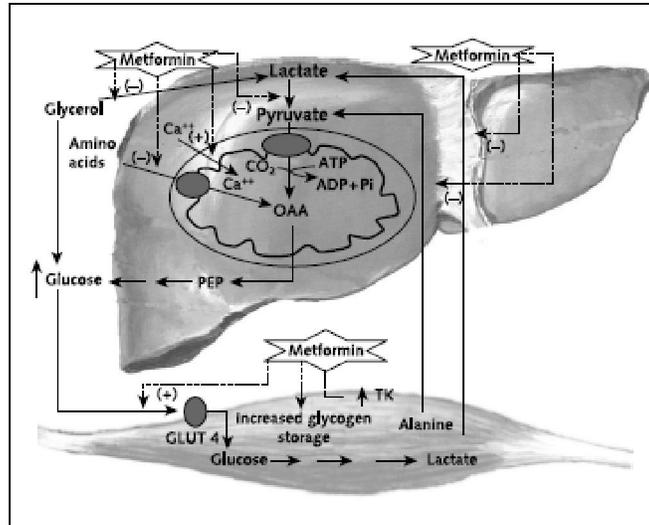


Figure1: Mechanism of Metformin action on hepatic glucose production and muscle glucose consumption.

PHARMACOKINETICS:

Absorption: The active and saturable absorption process is involved. The appearance of Metformin in the plasma after administration of EFFIMET XR is slower and prolonged compared to EFFIMET.

Distribution: Metformin is rapidly distributed following absorption and does not bind to plasma protein.

Metabolism: No metabolites of Metformin have been identified. The absence of liver metabolism clearly differentiates the pharmacokinetics of Metformin from that of other Biguanides.

Elimination: Metformin undergoes renal excretion and has a mean plasma elimination half life after oral administration of between 4.0 to 8.7 hours (*Clin Pharmacokinet*, 1996 May; 30(5):359-71.). This elimination is prolonged in patients with renal impairment and correlates with creatinine clearance.

INDICATION:

1. NIDDM (Non Insulin Dependent Diabetes Mellitus): When diet alone has failed, especially maturity onset NIDDM. EFFIMET XR can be used as an adjunct to diet and exercise to improve the glycemic condition.
2. MODY (Maturity Onset Diabetes of the Young) (Unstable cases): Combination with insulin to give better and smooth blood glucose levels.

DOSAGE AND ADMINISTRATION:

The normal dose of EFFIMET XR is 1tablet per day with evening meal. Daily dose should not exceed 2000 mg /day.

EFFIMET XR should be swallowed whole with water.

CONTRAINDICATION:

EFFIMET XR is contraindicated in the patient with:

1. Renal disease or renal dysfunction (e.g. as suggested by serum creatinine levels ≥ 1.5 mg/dl in males and ≥ 1.4 mg/dl in females).
2. Known hypersensitivity to Metformine hydrochloride
3. Acute or chronic acidosis, including diabetic ketoacidosis with or without coma.

SPECIAL PRECAUTION:

1. Monitoring of renal function: Metformin is known to be substantially excreted by the kidney, the risk of Metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. So the serum ceratine level should be regularly monitored in the patient receiving Metformin and the dose should be triturated accordingly.
2. Surgical procedures: EFFIMET XR therapy should be primarily suspended for the patient undergoing the surgical procedure that involves restriction in the intake of food and should not be restarted until the patient's oral food intake has been resumed and the renal function has been evaluated.
3. Alcohol Intake: Alcohol is known to potentiate the effect of Metformin on lactate metabolism. Patient therefore should be warned against excessive alcohol intake, acute or chronic while takine EFFIMET XR.
4. Impaired Hepatic Function: Since impaired hepatic function has been associated with some cases of lactic acidosis, EFFIMET XR should generally be avoided in patient with clinical or laboratory evidence of hepatic disease.
5. Vitamin B₁₂ level: Metformin interfere the absorption of Vitamin B₁₂ from vitamin B₁₂ intrinsic factor complex. So routine Vitamin B₁₂ at 2-3 year interval may be useful.
6. Change in the clinical status of the patient with previously controlled type 2 Diabetes: Type 2 diabetes previously well controlled on GLUCOPHAGE or GLUCOPHAGE XR who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, GLUCOPHAGE or GLUCOPHAGE XR must be stopped immediately and other appropriate corrective measures initiated.
7. Hypoglycemia: Hypoglycemia does not occur in patients receiving EFFIMET XR alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol.
8. Loss of control of blood glucose: 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 EFFIMET XR and temporarily administer insulin. EFFIMET XR may be reinstated after the acute

episode is resolved. The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with EFFIMET XR monotherapy or combine therapy, it may be necessary to consider therapeutic alternatives.

SPECIAL POPULATION:

Pregnancy: EFFIMET XR is Pregnancy category B drug. Should not be used in the pregnancy unless clearly needed.

Nursing Mother: 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 EFFIMET XR is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric use: Safety of Metformin in the pediatric patient under the age of 10 has not been evaluated so the use is contraindicated in the patient age below 10.

Geriatric Use: Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, EFFIMET XR should only be used in patients with normal renal function. Because aging is associated with reduced renal function EFFIMET XR should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of EFFIMET XR

ADVERSE EFFECT:

Commonly seen side effects:

Diarrhea, Nausea and Vomiting

Vitamin B12 deficiency: due to interference with absorption, especially with high doses.

Rarely side effects:

Lactic acidosis is the most serious complication. Alcohol ingestion can precipitate severe lactic acidosis. The symptoms of lactic acidosis are weakness, trouble breathing, abnormal heartbeats, unusual muscle pain, stomach discomfort, light-headedness and feeling cold. Patients at risk for lactic acidosis include those with reduced function of the kidneys or liver, congestive heart failure, severe acute illnesses, and dehydration.

Drug Interactions:

- Cimetidine, by decreasing the elimination of metformin from the body, can increase the amount of metformin in the blood by 40 %. This may increase the frequency of side effects from metformin.
- The other drugs are corticosteroids and oestrogens.
- The diuretics reduce the Metformin effects.
- The monoamine oxidase inhibitors and beta blockers increase the effects of Metformin.

Advantages:

- Since, it is an insulin sparing agent; it does not increase weight or provoke hypoglycemia.
- Has an advantage over insulin and sulfonylureas in treating hyperglycemia.
- Can be used in combination with sulfonylureas in Type2 diabetes in which sulfonylureas therapy alone is inadequate.
- Metformin is the only anti-diabetic drug that has been proven to reduce the complications of diabetes, as evidenced in a large study of overweight patients with diabetes (UKPDS 1998).
- These drugs lower blood sugar primarily by causing more of the body's own insulin to be released. It lowers the amount of sugar in your blood by helping your body respond better to its own insulin. It does not cause your body to produce more insulin. Therefore, it rarely causes hypoglycemia (low blood sugar) and it doesn't usually cause weight gain.

For further information, please contact:

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