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

EFFIMET®
EFFIMET®XR

(Metformin HCl)

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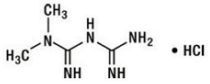
EFFIMET/ EFFIMET XR contain the anti-hyperglycemic agent metformin, which is a biguanide, in the form of monohydrochloride. Its molecular formula is C4H11N5.HCl. The structural formula is as shown below;



QUALITATIVE & QUANTITATIVE COMPOSITION:

EFFIMET & EFFIMET X Rare available for oral administration as:
EFFIMET-500: Each tablet contains Metformin HCl 500 mg.
EFFIMET-850: Each tablet contains Metformin HCl 850 mg.
EFFIMET-500 XR: Each extended release tablet contains Metformin HCl 500 mg.
EFFIMET-850 XR: Each extended release tablet contains Metformin HCl 850 mg.
EFFIMET-1000 XR: Each extended release tablet contains Metformin HCl 1000 mg.

CLINICAL PHARMACOLOGY:

Mechanism of Action:

Metformin is an anti-hyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

Pharmacokinetics:

Absorption: The absolute bioavailability of anEFFIMET 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of Metformin 500 to 1500 mg and 850 to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. At usual clinical doses and dosing schedules of EFFIMET, steady state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 µg/mL. Following a single oral dose of EFFIMET XR, Cmax is achieved with a median value of 7 hours and a range of 4 to 8 hours. Peak plasma levels are approximately 20% lower compared to the same dose of EFFIMET, however, the extent of absorption (as measured by AUC) is comparable to EFFIMET. At steady state, the AUC and Cmax are less than dose proportional for EFFIMET XR within the range of 500 to 2000 mg administered once daily. Peak plasma levels are approximately 0.6, 1.1, 1.4 and 1.8 mcg/mL for 500, 1000, 1500, and 2000 mg once-daily doses, respectively. The extent of metformin absorption (as measured by AUC) from EFFIMET XR at a 2000 mg once-daily dose is similar to the same total daily dose administered as EFFIMET tablets 1000 mg twice daily. After repeated administration of EFFIMET XR, metformin did not accumulate in plasma.

Effect of food: Food decreases the extent of absorption and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (Cmax), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (Tmax) following administration of a single 850 mg tablet of EFFIMET with food, compared to the same tablet strength administered fasting. Although the extent of metformin absorption (as measured by AUC) from the EFFIMET XR tablet increased by approximately 50% when given with food, there was no effect of food on Cmaxand Tmax of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of EFFIMET XR.

Distribution: The apparent volume of distribution (V/F) of metformin following single oral doses of EFFIMET 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time.

Metabolism: Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Elimination: Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

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.

INDICATIONS AND USAGE:

EFFIMET is indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus.
EFFIMET XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

WARNINGS AND PRECAUTIONS:

Lactic Acidosis: There have been postmarketing cases of metformin-associated lactic acidosis, including fatalcases. These cases had a subtle onset and were accompanied by nonspecific symptoms such asmalaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however,hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/L),anion gap acidosis (without evidence of ketonuria orketonemia), and an increased lactate:pyruvate ratio; metformin plasma levels were generally >5 mcg/mL.Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should beinstituted promptly in a hospital setting, along with immediate discontinuation of EFFIMET/EFFIMET XR. In EFFIMET/EFFIMET XR treated patientswith a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended tocorrect the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzablewith a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis hasoften resulted in reversal of symptoms and recovery.

For each of the known and possible risk factors for metformin-associated lactic acidosis,recommendations to reduce the risk of and manage metformin-associated lactic acidosis areprovided below:

Renal impairment—thepostmarketing metformin-associated lactic acidosis cases primarilyoccurred in patients with significant renal impairment.The risk of metformin accumulation and metformin-associated lactic acidosis increases withthe severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include:

- Before initiating EFFIMET/EFFIMET XR, obtain an estimatedglomerular filtration rate (eGFR).
- EFFIMET/EFFIMET XR is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m2.
- Initiation of EFFIMET/EFFIMET XR is not recommended inpatients with eGFR between 30-45 mL/min/1.73 m2.
- Obtain an eGFR at least annually in all patients taking EFFIMET/EFFIMET XR. In patients at risk for the development of renal impairment(e.g., the elderly), renal function should be assessed more frequently.
- In patients taking EFFIMET/EFFIMET XR whose eGFR fallsbelow 45 mL/min/1.73 m2, assess the benefit and risk of continuing therapy.
- Drug interactions — the concomitant use of EFFIMET/EFFIMET XR withspecific drugs may increase the risk of metformin-associated lactic acidosis: those thatimpair renal function, result in significant hemodynamic change, interfere with acid-basebalance, or increase metformin accumulation. Consider more frequent monitoring ofpatients.
- Age 65 or greater — the risk of metformin-associated lactic

acidosis increases with thepatient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.

- Radiologic studies with contrast — Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop EFFIMET/EFFIMET XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m2; in patients with a history of hepatic impairment, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart EFFIMET/EFFIMET XR if renal function is stable.
- Surgery and other procedures — withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension, and renal impairment. EFFIMET/EFFIMET XR should be temporarily discontinued while patients have restricted food and fluid intake.
- Hypoxic states — several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may cause prerenal azotemia. When such an event occurs, discontinue EFFIMET/EFFIMET XR.
- Excessive alcohol intake — Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving EFFIMET/EFFIMET XR.
- Hepatic impairment — Patients with hepatic impairment have developed cases ofmetformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of EFFIMRT/EFFIMET XR in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B12 Deficiency: In Metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of EFFIMET or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Measure hematologic parameters on an annual basis and vitamin B12 at 2 to 3 year intervals in patients on EFFIMET/EFFIMETXR and manage any abnormalities.

Hypoglycemia with Concomitant Use with Insulin and Insulin ***Secretagogues:*** Insulin and insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. EFFIMET/EFFIMET XR may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with EFFIMET/EFFIMET XR.

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with EFFIMET/EFFIMET XR.

DOSAGE AND ADMINISTRATION:

Adult Dosage: EFFIMET: The recommended starting dose of EFFIMET is 500 mg orally twice a day or 850 mg once a day, given with meals. Increase the dose in increments of 500 mg weekly or 850 mg every 2 weeks on the basis of glycemic control and tolerability, up to a maximum dose of 2550 mg per day, given in divided doses. Doses above 2000 mg may be better tolerated given 3 times a day with meals.

EFFIMET XR: Swallow EFFIMET XR tablets whole and never crush, cut or chew. The recommended starting dose of EFFIMET XR is 500 mg orally once daily with the evening meal. Increase the dose in increments of 500 mg weekly on the basis of glycemic control and tolerability, up to a maximum of 2000 mg once daily with the evening meal. If glycemic control is not achieved with EFFIMET XR 2000 mg once daily, consider a trial of EFFIMET XR 1000 mg twice daily. If higher doses are required, switch to EFFIMET at total daily doses up to 2550 mg administered in divided daily doses, as described above. Patients receiving EFFIMET may be switched to EFFIMET XR once daily at the same total daily dose, up to 2000 mg once daily.

Pediatric Dosage for EFFIMET: The recommended starting dose of EFFIMET for pediatric patients 10 years of age and older is 500 mg orally twice a day, given with meals. Increase dosage in increments of 500 mg weekly on the basis of glycemic control andtolerability, up to a maximum of 2000 mg per day, given in divided doses twice daily.

Recommendations for Use in Renal Impairment: Assess renal function prior to initiation of EFFIMET/EFFIMET XR and periodically thereafter. EFFIMET/EFFIMET XR is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m2. Initiation of EFFIMET/EFFIMET XR in patients with an eGFR between 30 – 45 mL/minute/1.73 m2 is not recommended. In patients taking EFFIMET/EFFIMET XR whose eGFR later falls below 45 mL/min/1.73 m2, assess the benefit risk of continuing therapy. Discontinue EFFIMET/EFFIMET XR if the patient's eGFR later falls below 30 mL/minute/1.73 m2.

Discontinuation for Iodinated Contrast Imaging Procedures: Discontinue EFFIMET/EFFIMET XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart EFFIMET/EFFIMET XR if renal function is stable.

ADVERSE REACTIONS:

The most serious side effect is 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. The most common side effect of metformin is gastrointestinal upset. This includes diarrhea, cramps, nausea and vomiting, anorexia, abdominal discomfort. Others include dizziness, confusion, sweating, rash, weakness, and Vitamin B12 malabsorption. Therefore, it is recommended to take with meals.

CONTRAINDICATIOIN:

EFFIMET and EFFIMET XR are contraindicated in patients with: Severe renal impairment (eGFR below 30 mL/min/1.73 m2); Hypersensitivity to metformin; Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

OVERDOSAGE:

Overdose of metformin hydrochloride has occurred, including 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. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

PRODUCT PRESENTATION:

EFFIMET is available as:

- 500 mg Tablets
  Packaging: 20 Tablets x 10 Blisters
- 850 mg Tablets
  Packaging: 10 Tablets x 10 Blisters
- 500 XR Tablets
  Packaging: 10 Tablets x 10 Blisters
- 850 XR Tablets
  Packaging: 10 Tablets x 10 Blisters
- 1000 XR Tablets
  Packaging: 10 Tablets x 10 Blisters

ID: 01 pi EFT 20

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