Met® XR

Metformin Hydrochloride

Description: Metformin Hydrochloride USP (extended-release tablets) is an oral antihyperglycemic drug used in the management of Type 2 diabetes. After administration, fluid from the gastrointestinal (GI) tract enters into the tablet, causing the polymers to hydrate and swell & the drug is released slowly from the dosage form by a process of diffusion.

Mode of action: Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with Type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike Sulfonylureas, Metformin does not produce hypoglycemia in either patients with Type 2 diabetes or normal subjects and does not cause hyperinsulinemia.

Pharmacokinetics: *Absorption & Bioavailability:* Following a single oral dose of Metformin Hydrochloride XR, C_{max} 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 Metformin Hydrochloride. At steady state, the AUC and C_{max} are less than dose proportional for Metformin Hydrochloride 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 microgm/ml for 500, 1000, 1500, and 2000 mg once-daily doses, respectively. Although the extent of Metformin absorption from the Metformin Hydrochloride XR tablet increased by approximately 50% 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 Hydrochloride XR.
Distribution: Metformin is negligibly bound to plasma proteins, in contrast to Sulfonylureas, which are more than 90% protein bound. At usual clinical doses and dosing schedule of Metformin Hydrochloride, steady state plasma concentrations of Metformin are reached within 24 to 48 hours and are generally <1 microgm/ml.
Metabolism and Elimination: Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. 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.

Composition: Met® XR 500 mg Tablet: Each extended release tablet contains Metformin Hydrochloride USP 500 mg.
Met® XR 750 mg Tablet: Each extended release tablet contains Metformin Hydrochloride USP 750 mg.
Met® XR 1 gm Tablet: Each extended release tablet contains Metformin Hydrochloride USP 1 gm.

Indications: Non insulin dependent (Type – 2) diabetes mellitus (NIDDM).

Dosage & administration: There is no fixed dosage regimen for the management of hyperglycemia in patients with Type 2 diabetes with Metformin XR. Dosage of Metformin XR must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily doses.
The therapeutic goal should be to decrease both fasting plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of Metformin XR, either when used as monotherapy or in combination with sulfonylurea or insulin.
Recommended Dosing Schedule
Adults — In general, clinically significant responses are not seen at doses below 1500 mg per day. However, a lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms.
The usual starting dose of Metformin Hydrochloride Extended-Release Tablets is 500 mg once daily with the evening meal. Dosage increases should be made in increments of 500 mg weekly, up to a maximum of 2000 mg once daily with the evening meal. If glycemic control is not achieved with Metformin Hydrochloride XR 2000 mg once daily, a trial of Metformin XR 1000 mg twice daily should be considered.
Pediatrics — Safety & effectiveness of Metformin extended release tablet in pediatric patients have not been established. Metformin XR is not recommended in pediatric patients below the age of 17 years.
Transfer from other antidiabetic therapy — When transferring patients from standard oral hypoglycemic agents other than chlorpropamide to Metformin XR, no transition period generally is necessary.
Combination treatment with sulfonylurea in adult patients — If patients have not responded to 4 weeks of the maximum dose of Metformin XR monotherapy, consideration should be given to gradual addition of an oral sulfonylurea while continuing Metformin XR at the maximum dose, even if prior primary or secondary failure to a sulfonylurea has occurred. Clinical and pharmacokinetic drug-drug interaction datas are currently available only for Metformin plus glyburide (glibenclamide). With concomitant Metformin XR and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug.
Combination treatment with insulin in adult patients — The current insulin dose should be continued upon initiation of Metformin XR therapy. Metformin XR therapy should be initiated at 500 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of Metformin XR should be increased by 500 mg after approximately 1 week and by 500 mg every week thereafter until adequate glycemic control is achieved.

Contraindications: Metformin extended release tablets are contraindicated in patients with –
- Renal diseases or renal dysfunction (e.g. as suggested by serum creatinine levels > 1.5 mg/dL in males & > 1.4 mg/dL in females or abnormal creatinine clearance)
- Congestive heart failure requiring pharmacological treatment
- Known hypersensitivity to Metformin Hydrochloride
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

It also should be temporarily discontinued in patients undergoing radiologic studies involving IV administration of iodinated contrast materials because such products may result acute alteration of renal function.

Side effects: GI disturbance, diarrhoea, nausea, vomiting, flatulence, asthenia, headache, indigestion etc.

Use in pregnancy & lactation: USFDA Pregnancy Category B. Most experts recommend that insulin may be used during pregnancy to maintain blood glucose levels as close to normal as possible. It should not be used during pregnancy unless clearly needed.
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 Metformin XR is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.
Use in children: Safety & effectiveness of Metformin extended release tablet in pediatric patients have not been established.
Geriatric use: Metformin XR should only be used in patients with normal renal function. Because aging is associated with reduced renal function, it 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 Metformin XR.

Precautions: Monitor blood glucose level and use with caution in hypoglycemia, severe impaired renal function, disorder of thyroid function.

Drug interactions: In case of Metformin Hydrochloride, certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs and isoniazid.

Over dosage: 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 Hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of Metformin overdose cases.

Storage: Store in a cool & dry place, protected from light.

Packaging: Met® XR 500 mg Tablet: Each carton contains 10X5 tablets in blister pack.
Met® XR 750 mg Tablet: Each carton contains 10X3 tablets in blister pack.
Met® XR 1 gm Tablet: Each carton contains 6X5 tablets in Alu-Alu strip pack.

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Opsonin Pharma
Ideas for healthcare

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