Xormet XR®

(Metformin HCl)

Highnoon

COMPOSITION
Xormet XR 500mg Tablet:
Each extended-release tablet contains: Metformin HCl 500mg
Xormet XR 750mg Tablet:
Each extended-release tablet contains: Metformin HCl 750mg
Xormet XR 1000mg Tablet:
Each extended-release tablet contains: Metformin HCl 1000mg

DESCRIPTION
Xormet XR contains the antihyperglycemic agent metformin, which is a biguanide.

MECHANISM OF ACTION
Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, 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
Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability of a single 500mg dose is reported to be about 50 to 60%, although this is reduced somewhat if taken with food. Protein binding in plasma is negligible. Metformin is excreted unchanged in the urine. The plasma elimination half-life is reported to range from about 2 to 6 hour. Metformin crosses the placenta and is distributed into the breast milk in small amounts.

INDICATIONS AND USAGE
- Reduction in the risk or delay of the onset of type 2 diabetes mellitus in adult, overweight patients with Impaired Glucose Tolerance and/or Impaired Fasting Glucose, and/or increased HbA1C who are:
  - o at high risk for developing overt type 2 diabetes mellitus and
  - o still progressing towards type 2 diabetes mellitus despite implementation of intensive lifestyle change for 3 to 6 months

  Treatment with Metformin XR must be based on a risk score incorporating appropriate measures of glycaemic control and including evidence of high cardiovascular risk. Lifestyle modifications should be continued when metformin is initiated, unless the patient is unable to do so because of medical reasons.
- Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. Metformin XR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

DOSAGE AND ADMINISTRATION
Adults with normal renal function (GFR ≥ 90 mL/min)
Reduction in the risk or delay of the onset of type 2 diabetes
- Metformin should only be considered where intensive lifestyle modifications for 3 to 6 months have not resulted in adequate glycaemic control.
- The therapy should be initiated with one tablet Metformin XR 500 mg once daily with the evening meal.
- After 10 to 15 days dose adjustment on the basis of blood glucose measurements is recommended (OGTT and/or FPG and/or HbA1C values to be within the normal range). A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended dose is 4 tablets (2000 mg) once daily with the evening meal.
- It is recommended to regularly monitor (every 3-6 months) the glycaemic status (OGTT and/or FPG and/or HbA1c value) as well as the risk factors to evaluate whether treatment needs to be continued, modified or discontinued.
- A decision to re-evaluate therapy is also required if the patient subsequently implements improvements to diet and/or exercise, or if changes to the medical condition will allow increased lifestyle interventions 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 XR 500 mg once daily.
- After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended dose is 4 tablets daily.
- Dosage increases should be made in increments of 500mg every 10-15 days, up to a maximum of 2000mg once daily with the evening meal. If glycaemic control is not achieved on Metformin XR 2000mg once daily, Metformin XR 1000mg twice daily should be considered, with both doses being given with food. If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.
- In patients already treated with metformin tablets, the starting dose of Metformin XR should be equivalent to the daily dose of metformin immediate release tablets. In patients treated with metformin at a dose above 2000 mg daily, switching to Metformin XR is not recommended.
- If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate Metformin XR at the dose indicated above.
- Metformin XR 750 mg and Metformin XR 1000 mg are intended for patients who are already treated with metformin tablets (prolonged or immediate release).
- The dose of Metformin XR 750 mg or Metformin XR 1000 mg should be equivalent to the daily dose of metformin tablets (prolonged 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 in combination therapy to achieve better blood glucose control. The usual starting dose of Metformin XR is one 500 mg tablet once daily, while insulin dosage is adjusted on the basis of blood glucose measurements. For patients already treated with metformin and insulin in combination therapy, the dose of Metformin XR 750 mg or Metformin XR 1000 mg should be equivalent to the daily dose of metformin tablets up to a maximum of 1500 mg or 2000 mg respectively, given with the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements.

Elderly
Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary. Benefit in the reduction of risk or delay of the onset of type 2 diabetes mellitus has not been established in patients 75 years and older and metformin initiation is therefore not recommended in these patients.

Renal impairment
A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. 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. The starting dose is at most half of the maximum dose.
30-44	1000 mg	
<30	-	Metformin is contraindicated.

CONTRAINDICATIONS
Hypersensitivity to metformin or to any of the constituents.
- Any type of acute or chronic metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma
- Severe renal failure (GFR < 30 mL/min)
- Acute conditions with the potential to alter renal function such as:
  - o dehydration
  - o severe infection
  - o shock
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as:
  - o decompensated heart failure
  - o respiratory failure
  - o recent myocardial infarction
  - o shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism

ADVERSE REACTIONS
The reported adverse event are; lactic acidosis, decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin, hypoglycaemia, taste disturbance, nausea, vomiting, diarrhoea, abdominal pain, loss of appetite, liver function tests abnormalities or hepatitis resolving upon metformin discontinuation, skin reactions such as erythema, pruritus and urticaria.

DRUG INTERACTIONS
- Concomitant use not recommended
- Alcohol: Its intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition or hepatic impairment.
- Iodinated contrast agents: Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.
- Combinations requiring precautions for use: Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.
- Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics): More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the other drug and upon its discontinuation.
- Organic cation transporters (OCT): Metformin is a substrate of both transporters OCT1 and OCT2.
- Co-administration of metformin with
  - o Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
  - o Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
  - o Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
  - o Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.
- Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.
- Carbonic Anhydrase Inhibitors frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis.

WARNINGS AND PRECAUTIONS
- Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.
- In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.
- Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention.
- GFR should be assessed before treatment initiation and regularly thereafter. Metformin is contraindicated in patients with GFR<30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function.
- Patients with heart failure are more at risk of hypoxia and renal insufficiency. Metformin-associated lactic acidosis have been seen 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.
- 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.
- Due to the limited therapeutic efficacy data in the reduction of risk or delay of type 2 diabetes in patients 75 years and older, metformin initiation is not recommended in these patients.
- Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.
- Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.
- All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.
- The usual laboratory tests for diabetes monitoring should be performed regularly.
- Metformin alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulphonylureas or meglitinides).

USE IN SPECIFIC POPULATIONS
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 foetal development, parturition or postnatal development.
When the patient plans to become pregnant and during pregnancy, it is recommended that impaired glycaemic 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 foetus.

Breast-feeding
Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breastfeeding is not recommended during metformin treatment. A decision on whether to discontinue breast-feeding should be made, taking into account the benefit of breast-feeding and the potential risk to adverse effect on the child.

Fertility
Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

OVERDOSAGE
Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

DOSAGE AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION
Xormet XR 500mg Tablets:
Alu.PVC. Blister Pack of 5 x 10's.
Xormet XR 750mg Tablets:
Alu.PVC. Blister Pack Blister Pack of 3 x 10's.
Xormet XR 1000mg Tablets:
Alu.PVC. Blister Pack of 5 x 10's.

زورمیٹ ایکس آر®

(میٹ فارمن ہائیڈروکلورائیڈ)

خوراک و ہدایات:
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

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