Glimaryl® XR 2/500

Glimepiride / Metformin Hydrochloride XR

FORMS AND PRESENTATION
Glimaryl® XR 2/500: Tablets: Box of 30.
COMPOSITION
Glimaryl® XR 2/500: Each tablet contains Glimepiride 2mg and Metformin Hydrochloride 500mg in extended release form.
Excipients: sodium starch glycolate, povidone, lactose, yellow ferric oxide, titanium dioxide, starch, microcrystalline cellulose, magnesium stearate, hydroxypropyl methylcellulose, carboxy methylcellulose, methacrylic acid copolymer, polyethylene glycol.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Therapeutic class: Drugs used in diabetes.
ATC code: Glimepiride (A10BB12) and Metformin Hydrochloride (A10BA02).
For Glimepiride
Glimepiride is an orally active hypoglycemic substance belonging to the sulfonylurea group. It may be used in non-insulin dependent diabetes mellitus.
Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells.
As with other sulfonylureas this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, Glimepiride seems to have pronounced extrapancreatic effects also postulated for other sulfonylureas.
Sulfonylureas regulate insulin secretion by closing the ATP-sensitive potassium channel in the beta cell membrane. Closing the potassium channel induces depolarisation of the beta cell and results - by opening of calcium channels - in an increased influx of calcium into the cell.
This leads to insulin release through exocytosis.
Glimepiride binds with a high exchange rate to a beta cell membrane protein which is associated with the ATP-sensitive potassium channel but which is different from the usual sulfonylurea binding site.
For Metformin
Metformin is a biguanide with antihyperglycemic effects, lowering both basal and Postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia. Metformin may act via 3 mechanisms:
- Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization
- Delay of intestinal glucose absorption.
Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.
Pharmacokinetic Properties
For Glimepiride
- Absorption: The bioavailability of Glimepiride after oral administration is complete. Food intake has no relevant influence on absorption, only absorption rate is slightly diminished. Maximum serum concentrations (C_{max}) are reached approx. 2.5 hours after oral intake (mean 0.3 µg/ml during multiple dosing of 4 mg daily) and there is a linear relationship between dose and both C_{max} and AUC (area under the time/concentration curve).
- Distribution: Glimepiride has a very low distribution volume (approx. 8.8 liters) which is roughly equal to the albumin distribution space, high protein binding (>99%), and a low clearance (approx. 48 ml/min).
- Biotransformation and elimination: Mean dominant serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is about 5 to 8 hours. After high doses, slightly longer half-lives were noted.
After a single dose of radio-labeled Glimepiride, 58% of the radioactivity was recovered in the urine, and 35% in the feces. No unchanged substance was detected in the urine. Two metabolites - most probably resulting from hepatic metabolism (major enzyme is CYP2C9) - were identified both in urine and feces: the hydroxy derivative and the carboxy derivative. After oral administration of Glimepiride, the terminal half-lives of these metabolites were 3 to 6 and 5 to 6 hours respectively.
For Metformin
- Absorption: After an oral dose of the extended release tablet, Metformin absorption is significantly delayed compared to the immediate-release tablet with a T_{max} at 7 hours (T_{max} for the immediate-release tablet is 2.5 hours).
At steady state, similar to the immediate-release formulation, C_{max} and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000 mg of Metformin extended release tablets is similar to that observed after administration of 1000 mg of Metformin immediate-release tablets b.i.d.
Intrasubject variability of C_{max} and AUC of Metformin prolonged-release is comparable to that observed with Metformin immediate-release tablets. When the extended release tablet is administered in fasting conditions the AUC is decreased by 30% (both C_{max} and T_{max} are unaffected).
Metformin absorption from the extended release formulation is not altered by meal composition. No accumulation is observed after repeated administration of up to 2000 mg of Metformin as extended release tablets.
- 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.
INDICATIONS
For Glimepiride and Metformin: As an adjunct to diet and exercise in type 2 diabetes mellitus patients:
- In case that the monotherapy with Glimepiride or Metformin does not result in adequate glycemic control.
- Replacement of combination therapy of Glimepiride and Metformin.
CONTRAINDICATIONS
For Glimepiride
- In patients hypersensitive to Glimepiride, other sulfonureas, other sulfonamides, or any other excipients of Glimaryl® XR 2/500.
- In pregnant women, in breast-feeding women.
No experience has been gained concerning the use of Glimepiride in patients with severe impairment of liver function and in dialysis patients. In patients with severe impairment of hepatic function, change-over to insulin is indicated, not least to achieve optimal metabolic control.
For Metformin
- Hypersensitivity to Metformin or any of the excipients.
- Diabetic ketoacidosis, diabetic pre-coma.
- Renal failure or renal disfunction (e.g., serum creatine levels > 135 micromol/L in males and > 110 micromol/L in females).
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, intravascular administration of iodinated contrast agent.
- Acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, shock.
- Hepatic insufficiency.
- Acute alcohol intoxication, alcoholism.
- Lactation.
PRECAUTIONS
For Glimepiride
In exceptional stress situations (e.g. trauma, surgery, febrile infections) blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control.
In the initial weeks or treatment, the risk of hypoglycemia may be increased and necessitates especially careful monitoring.
Factors favoring hypoglycemia include:
- Unwillingness or (more commonly in older patients) incapacity of the patient to cooperate.
- Undernourishment, irregular mealtimes or skipped meals.
- Imbalance between physical exertion and carbohydrate intake.
- Alterations of diet.
- Consumption of alcohol, especially in combination with skipped meals.
- Impaired renal function.
- Severe impairment of liver function.
- Overdosage with Glimepiride.
- Certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter-regulation of hypoglycemia (as for example in certain disorders of thyroid function and in anterior pituitary or corticoadrenal insufficiency).
- Concurrent administration of certain other medicines.
- Treatment with Glimepiride in the absence of any indication.
If such risk factors for hypoglycemia are present, it may be necessary to adjust the dosage of Glimepiride or the entire therapy. This also applies whenever an illness occurs during therapy or the patient's life-style changes. Those symptoms of hypoglycemia which reflect the body's adrenergic counter regulation may be milder or absent where hypoglycemia develops gradually, in the elderly, and where there is autonomic neuropathy or where the patient is receiving concurrent treatment with beta-blockers, clonidine, reserpine, guanethidine or other sympatholytic drugs. Hypoglycemia can almost always be promptly controlled by immediate intake of carbohydrates (glucose or sugar). It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycemia may recur. Patients must, therefore, remain under close observation. Severe hypoglycemia further requires immediate treatment and follow-up by a physician and, in some circumstances, in-patient hospital care.
Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to hemolytic anemia. Since Glimepiride belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.
For Metformin
- Lactic acidosis: Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to Metformin accumulation. Reported cases of lactic acidosis in patients on Metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.
Diagnosis: Lactic acidosis is characterized by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, Metformin should be discontinued and the patient should be hospitalized immediately.
- Renal function: As Metformin is excreted by the kidney, serum creatinine levels should be determined before initiating treatment and regularly thereafter: at least annually in patients with normal renal function; at least two to four times a year in patients with serum creatinine levels at the limit of normal and in elderly subjects.
Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with an NSAID.
- Administration of iodinated contrast agents: As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, Metformin should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.
- Surgery: Metformin Hydrochloride should be discontinued 48 hours before elective surgery with general anesthesia and should not be usually resumed earlier than 48 hours afterwards.
Other precautions
- 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 hypoglycemia, although caution is advised when it is used in combination with insulin or sulfonylureas.
Ability to drive and use machines
For Glimepiride
Alertness and reactions may be impaired due to hypo- or hyperglycemia, especially when beginning or after altering treatment or when Glimepiride is not taken regularly.
This may, for example, affect the ability to drive or to operate machinery.
For Metformin
Metformin monotherapy does not cause hypoglycemia and therefore has no effect on the ability to drive or to use machines. However, patients should be alerted to the risk of hypoglycemia when Metformin is used in combination with other antidiabetic agents (sulfonylureas, insulin, repaglinide).
PREGNANCY AND LACTATION
For Glimepiride
Glimepiride must not be taken during pregnancy. Otherwise there is risk of harm to the child. The patient must change over to insulin during pregnancy.
Patients planning a pregnancy must inform their physician. It is recommended that such patients change over to insulin.

To prevent possible ingestion with the breast milk and possible harm to the child, Glimepiride must not be taken by breast-feeding women. If necessary the patient must change over to insulin, or must stop breast-feeding.

For Metformin

To date, no relevant epidemiological data are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or fetal development, parturition or postnatal development.

When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with Metformin but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of fetal malformations associated with abnormal glucose levels.

Metformin is excreted in the milk in lactating rats. Similar data is not available in humans and a decision should be made whether to discontinue nursing or to discontinue Metformin, taking into account the importance of the compound to the mother.

DRUG INTERACTIONS

For Glimepiride

Based on experience with Glimepiride and on what is known of other sulfonylureas, the following interactions must be considered:

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). This should be taken into account when Glimepiride is co-administered with inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole) of CYP2C9. Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycemia may occur when one of the following drugs is taken, for example insulin and other oral antidiabetics; ACE inhibitors; anabolic steroids and male sex hormones; chloramphenicol; coumarin derivatives; cyclophosphamide; disopyramide; fenfluramine; fenyramidol; fibrates; fluoxetine; guanethidine; ifosfamide; MAO inhibitors; miconazole; fluconazole; para-aminosalicylic acid; pentoxifylline (high dose parenteral); phenylbutazone; azapropazone; oxyphenbutazone; probenicid; quinolones; salicylates; sulfinpyrazone; calithromycin; sulfonamide antibiotics; tetracyclines; tritoqualine; trofosfamide.

Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following drugs is taken, for example: acetazolamide; barbiturates; corticosteroids; diazoxide; diuretics; epinephrine (adrenaline) and other sympathomimetic agents; glucagon; laxatives (after protracted use); nicotinic acid (in high doses); estrogens and progestogens; phenothiazines; phenytoin; rifampicin; thyroid hormones. H2 receptor antagonists, beta-blockers; clonidine and reserpine may lead to either potentiation or weakening of the blood-glucose-lowering effect.

Under the influence of sympatholytic drugs such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation to hypoglycemia may be reduced or absent. Both acute and chronic alcohol intake may potentiate or weaken the blood glucose-lowering action of Glimepiride in an unpredictable fashion. The effect of coumarin may be potentiated or weakened.

For Metformin

- Inadvisable combinations:

Alcohol increased the risk of lactic acidosis in acute alcohol intoxication, particularly in case of fasting or malnutrition, or hepatic insufficiency.

Iodinated contrast agents: intravascular administration of iodinated contrast agents may lead to renal failure, resulting in Metformin accumulation and a risk of lactic acidosis. Metformin should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

- Associations requiring precautions for use:

Glucocorticoids (systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycemic activity. Inform the patient and perform more frequent blood glucose monitoring, especially at the beginning or the treatment. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug upon its discontinuation. ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon discontinuation.

ADVERSE EFFECTS

For Glimepiride and Metformin

The use of a combination of both compounds, either as a free combination or as a fixed combination, is associated with the same safety characteristics as the use of each compound separately.

For Glimepiride

- Metabolism and nutrition disorders: As a result of the blood-glucose-lowering action of Glimepiride, hypoglycemia may occur, which may also be prolonged.

Possible symptoms of hypoglycemia include headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, impaired alertness and reactions, depression, confusion, speech disorders, aphasia, visual disorders, tremor, pareses, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, somnolence and loss of consciousness up to and including coma, shallow respiration and bradycardia. In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris, and cardiac arrhythmias.

The clinical picture of a severe hypoglycemic attach may resemble that of a stroke.

The symptoms nearly always subside when hypoglycemia is corrected.

- Eye disorders: Especially at the start of the treatment, there may be temporary visual impairment due to the change in blood glucose levels. The cause is a temporary alteration in the turgidity and hence the refractive index of the lens, this being dependant on blood glucose level.

- Gastrointestinal disorders: Occasionally, gastrointestinal symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhea may occur. In isolated cases, there may be hepatitis, elevation of liver enzyme levels and/or cholestasis and jaundice, which may progress to life-threatening liver failure but can regress after withdrawal of Glimepiride.

- Blood and lymphatic system disorders: Changes in the blood picture may occur: rarely, thrombopenia and, in isolated cases, leucopenia, hemolytic anemia, erythropenia, granulocytopenia, agranulocytosis or pancytopenia may develop.

- General disorders: Occasionally, allergic or pseudoallergic reactions may occur, e.g. in the form of itching, urticaria or rashes. Such mild reactions may develop into serious reactions with dyspnea and a fall in blood pressure, sometimes progressing to shock. In the event of urticaria a physician must therefore be notified immediately. In isolated cases, a decrease in serum sodium concentration and allergic vasculitis or hypersensitivity of the skin to light may occur.

For Metformin

- Gastrointestinal symptoms such as nausea, vomiting, diarrhea, abdominal pain and loss of appetite (>10%) are very common: These occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent theses gastrointestinal symptoms, it is recommended that Metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

- Metallic taste (3%) is common.

- Mild erythema has been reported in some hypersensitive individuals. The incidence of such effects is regarded as very rare (<0.01%).

- A decrease of vitamin B12 absorption with decrease of serum levels has been observed in patients treated long-term with Metformin and appears generally to be without clinical significance (<0.01%).

- Lactic acidosis (0.03 cases/1000 patient-years) is very rare.

DOSAGE AND ADMINISTRATION

Dosage

In principal, the dosage of Glimaryl® XR 2/500 is governed by the desired blood glucose level. The dosage of Glimaryl® XR 2/500 must be the lowest which is sufficient to achieve the desired metabolic control.

During treatment with Glimaryl® XR 2/500 glucose levels in blood and urine must be measured regularly. In addition, it is recommended that regular determinations of the proportion of glycated hemoglobin be carried out.

Mistakes, e.g. forgetting to take a dose, must never be corrected by subsequently taking a larger dose.

Measures for dealing with such mistakes (in particular forgetting a dose or skipping a meal) or situations where a dose cannot be taken at the prescribed time must be discussed and agreed between physician and patient beforehand.

As an improvement in control of diabetes is, in itself, associated with higher insulin sensitivity, Glimepiride requirements may fall as treatment proceeds. To avoid hypoglycemia timely dose reduction or cessation of Glimaryl® XR 2/500 therapy must be therefore considered.

The highest recommended dose per day should be 8mg of Glimepiride and 2000mg of Metformin. Daily doses of Glimepiride of more than 6mg are more effective only in a minority of patients. In order to avoid hypoglycemia the starting dose of Glimaryl® XR 2/500 should not exceed the daily doses of Glimepiride or Metformin already being taken. When switching from combination therapy of Glimepiride plus Metformin as separate tablets, Glimaryl® XR 2/500 should be administered on the basis of dosage currently being taken.

Administration

Glimaryl® XR 2/500 should be administered once per day during breakfast or the first main meal. Due to the extended release formulation, Glimaryl® XR 2/500 must be swallowed whole and not crushed or chewed.

Titration

The daily dose should be titrated in increments of 1 tablet only, corresponding to the lowest strength (in case various strengths are available).

Duration of treatment: Treatment with Glimaryl® XR 2/500 is normally a long-term therapy.

Special populations

- Children: Data are insufficient to recommend pediatric use of Glimaryl® XR 2/500.

OVERDOSAGE

For Glimepiride

- Signs and symptoms: Acute overdosage as well as long-term treatment with too high a dose of Glimepiride may lead to severe life-threatening hypoglycemia.

- Management: As soon as an overdose of Glimepiride has been discovered, a physician must be notified without delay. The patient must immediately take sugar, if possible in the form of glucose, unless a physician has already undertaken the responsibility for treating the overdose. Careful monitoring is essential until the physician is confident that the patient is out of danger. It must be remembered that hypoglycemia may recur after initial recovery. Admission to hospital may sometimes be necessary – even as a precautionary measure. In particular, significant overdoses and severe reactions with signs such as loss of consciousness or other serious neurological disorders are medical emergencies and require immediate treatment and admission to hospital.

If for example, the patient is unconscious, an intravenous injection of concentrated glucose solution is indicated (for adults starting 40ml of 20% solution, for example). Alternatively in adults, administration of glucagon, e.g. in doses of 0.5 to 1mg i.v., s.c. or i.m., may be considered.

In particular when treating hypoglycemia due to accidental intake of Glimepiride in infants and young children, the dose of glucose given must be very carefully adjusted in view of the possibility of producing dangerous hyperglycemia, and must be controlled by close monitoring of blood glucose.

Patients who have ingested life-threatening amounts of Glimepiride require detoxification (e.g. by gastric lavage and medicinal charcoal).

After acute glucose replacement has been completed it is usually necessary to give an intravenous glucose infusion in lower concentration so as to ensure that the hypoglycemia does not recur. The patient's blood glucose level should be carefully monitored for at least 24 hours. In severe cases with a protracted course, hypoglycemia, or the danger of slipping back into hypoglycemia, may persist for several days.

For Metformin

Hypoglycemia has not been seen with Metformin doses up to 85g, 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 hemodialysis.

STORAGE CONDITIONS

Store below 25°C.

Keep in original pack in intact conditions.

Date of Revision: April 2013.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Medicament: keep out of reach of children.

Council of Arab Health Ministers
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