Martin Dow

Glucophage® XR Tablets
(Metformin Hydrochloride) USP

گلوکوفیج® ایکس آر ٹیبلیٹس

Oral Antidiabetic

1. COMPOSITION
Glucophage®XR Tablet 500mg:
Each extended release tablet contains: Metformin Hydrochloride Ph. Eur ..... 500 mg

Glucophage®XR Tablet 750mg:
Each extended release tablet contains: Metformin Hydrochloride Ph. Eur ..... 750 mg

Glucophage®XR Tablet 1000mg:
Each extended release tablet contains: Metformin Hydrochloride Ph. Eur ..... 1000 mg

2. DESCRIPTION
GLUCOPHAGE XR contain the antihyperglycemic agent metformin, which is a biguanide, in the form of monohydrochloride. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform.

3. THERAPEUTIC INDICATIONS
Glucophage XR 500 mg, 750 mg, 1000 mg Tablet
- Reduction in the risk or delay of the onset of type 2 diabetes mellitus in adult, overweight patients with IGT* and/or IFG*, and/or increased HbA1C who are:
- at high risk for developing overt type 2 diabetes mellitus and
- still progressing towards type 2 diabetes mellius despite implementation of intensive lifestyle change for 3 to 6 months.

Treatment with Glucophage 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.
*IGT: Impaired Glucose Tolerance; IFG: Impaired Fasting Glucose
- 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. Glucophage XR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

4. DOSAGE AND ADMINISTRATION
Posology
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 glycemic control.
- The therapy should be initiated with one tablet Glucophage XR 500 mg once daily with the evening meal.
- After 10 to 15 days dose adjustment based on 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 Glucophage XR 500 mg,4 tablets (2000 mg) once daily with the evening meal OR
- Glucophage XR 750 mg, 2 tablets (1500 mg) once daily with the evening meal OR
- Glucophage XR 1000 mg is 2 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:
Glucophage XR 500mg tablets
- The usual starting dose is one tablet of Glucophage XR 500mg once 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 glycemic control is not achieved on Glucophage XR 2000mg once daily, a twice daily dosing schedule of Glucophage XR 1000mg must be considered, with both doses being given with food but if glycemic 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 Glucophage 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 Glucophage XR is not recommended.
- If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate Glucophage XR at the dose indicated above.
- Glucophage XR 750 mg and Glucophage XR 1000 mg are intended for patients who are already treated with metformin tablets (extended or immediate release).
- The dose of Glucophage XR 750 mg or Glucophage XR 1000 mg should be equivalent to the daily dose of metformin tablets (extended 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 Glucophage XR is one 500 mg tablet once daily, while insulin dosage is adjusted based on blood glucose measurements.
For patients already treated with metformin and insulin in combination therapy, the dose of Glucophage XR 750 mg or Glucophage 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 based on 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.

Pediatric population:
In the absence of available data, Glucophage XR should not be used in children.

5. CONTRAINDICATIONS
- Hypersensitivity to metformin or to any of the excipients.
- Any type of acute 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

6. WARNINGS AND PRECAUTIONS
Lactic acidosis
Lactic acidosis, a very rare, but serious, metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. 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.
Patients and/or caregivers should be informed of the risk of lactic acidosis.
Lactic acidosis is characterised by:
- acidotic dyspnoea
- abdominal pain
- muscle cramps
- asthenia and
- hypothermia followed by coma.

Case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.
Renal function
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.
Cardiac function
Patients with heart failure are more at risk of hypoxia and renal insufficiency. 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.
Elderly
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.
Administration of iodinated contrast agents
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.
Surgery:
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.
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 may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.
- 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).
- Tablet shells may be present in the faeces. Patients should be advised that this is normal.
- This medicine contains less than 1mmol sodium (23mg) per dosage unit, that is to say it is essentially 'sodium free'

7. ADVERSE EFFECTS

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, which resolve spontaneously in most cases.
The following adverse reactions may occur with Glucophage XR.
Frequencies are defined as follows:

- very common: >1/10;
- common >1/100, <1/10;
- uncommon >1/1,000, <1/100;
- rare >1/10,000, <1/1,000;
- very rare <1/10,000.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Metabolism and nutrition disorders
Common:

- Vitamin B12 decrease/deficiency.

Very rare:

- Lactic acidosis.

Nervous system disorders
Common

- Taste disturbance

Gastrointestinal disorders
Very common:

- Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders
Very rare:

- Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders
Very rare:

- Skin reactions such as erythema, pruritus, urticaria

8. DRUG INTERACTIONS

Concomitant use not recommended:

- **Alcohol:** Alcohol 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:

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- 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.
- 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.

9. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.

However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (e.g. sulphonylureas, insulin, or meglinitides).

10. PREGNANCY LACTATION AND FERTILITY

Pregnancy
Uncontrolled hyperglycaemia in the periconceptional phase and during pregnancy is associated with increased risk of congenital abnormalities, pregnancy loss, pregnancy-induced hypertension, preeclampsia, and perinatal mortality. It is important to maintain blood glucose levels as close to normal as possible throughout pregnancy, to reduce the risk of adverse hyperglycaemia-related outcomes to the mother and her child.

Metformin crosses the placenta with levels that can be as high as maternal concentrations.

A large amount of data on pregnant women (more than 1000 exposed outcomes) from a register-based cohort study and published data (meta-analyses, clinical studies, and registries) indicates no increased risk of congenital abnormalities nor feto/neonatal toxicity after exposure to metformin in the periconceptional phase and/or during pregnancy.
There is limited and inconclusive evidence on the metformin effect on the long-term weight outcome of children exposed in utero. Metformin does not appear to affect motor and social development up to 4 years of age in children exposed during pregnancy although data on long term outcomes are limited.
If clinically needed, the use of metformin can be considered during pregnancy and in the periconceptional phase as an addition or an alternative to insulin.
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.

11. CLINICAL PHARMACOLOGY

Pharmacotherapeutic group: Blood glucose lowering drugs. Biguanides.

11.1 Mode/Mechanism of Action

Metformin is a biguanide with antihyperglycaemic effects on both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia. Metformin reduces basal hyperinsulinemia, and in combination with insulin, reduces insulin requirement.
Metformin exerts its antihyperglycaemic effect via 3 mechanisms:
Metformin may act via 3 mechanisms:
1. Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
2. In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
3. And delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.
Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

11.2 Pharmacokinetics

Absorption

- After an oral dose of Glucophage XR 500mg tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a Tmax at 7 hours (Tmax for the immediate release tablet is 2.5 hours).
- Following a single oral administration of 1500 mg of Glucophage XR 750 mg, a mean peak plasma concentration of 1193 ng/ml is achieved with a median value of 5 hours and a range of 4 to 12 hours. Glucophage XR 750 mg was shown to be bioequivalent to Glucophage XR 500 mg at a 1500 mg dose with respect to Cmax and AUC in healthy fed and fasted subjects.
- Following a single oral administration in the fed state of one tablet of Glucophage XR 1000 mg, a mean peak plasma concentration of 1214 ng/ml is achieved with a median time of 5 hours (range of 4 to 10 hours). Glucophage XR 1000 mg was shown to be bioequivalent to Glucophage XR 500 mg at a 1000 mg dose with respect to Cmax and AUC in healthy fed and fasted subjects.
- The bioequivalent product shows the following properties:

o At steady state, like the immediate release formulation, Cmax and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000 mg of metformin prolonged release tablets is similar to that observed after administration of 1000 mg of metformin immediate release tablets b.i.d.

o Intrasubject variability of Cmax and AUC of metformin prolonged release tablets is comparable to that observed with metformin immediate release tablets.
o When the prolonged release tablet is administered in fasting conditions the AUC is decreased by 30% (both Cmax and Tmax are unaffected).
o When the 1000 mg prolonged release tablet is administered in fed conditions the AUC is increased by 77% (Cmax is increased by 26% and Tmax is slightly prolonged by about 1 hour).
o Mean metformin absorption from the prolonged release formulation is almost not altered by meal composition. No accumulation is observed after repeated administration of up to 2000 mg of metformin prolonged 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.
Renal impairment
The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations,

12. OVERDOSAGE

Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin or concomitant risks 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.

HOW SUPPLIED

Presentation

GLUCOPHAGE®XR Tablets 500mg : Available in a pack of 3x10's Tablets
GLUCOPHAGE®XR Tablets 750mg : Available in a pack of 3x10's Tablets
GLUCOPHAGE®XR Tablets 1000mg : Available in a pack of 3x10's Tablets

Special Precautions for Storage

- Store below 30°C.
- Protect from light, heat and moisture.
- Keep all the medications out of the reach of Children.

۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
روشنی، گرمی اور نمی سے محفوظ رکھیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

WARNING: LACTIC ACIDOSIS
Life threatening lactic acidosis can occur due to accumulation of metformin. The main risk factor is renal impairment, other risk factors include old age associated with reduced renal function.

Manufactured by:
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