Composition

Glucophage XR 500 mg prolonged release tablet contains 500 mg metformin hydrochloride corresponding to 390 mg metformin base.

Glucophage XR 750 mg prolonged release tablet contains 750 mg metformin hydrochloride corresponding to 585 mg metformin base.

Glucophage XR 1000 mg prolonged release tablet contains 1000 mg metformin hydrochloride corresponding to 780 mg metformin base.

Pharmacodynamic properties

Pharmacotherapeutic group: Oral Blood glucose lowering drugs. Biguanides; ATC code: A10BA02

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

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 utilization.
3. 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 (GLUTs) known to date.

In clinical studies, use of metformin was associated with either a stable body weight or modest weight loss. In humans, independently of its action on glycaemia, metformin immediate-release has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical efficacy:

The prospective randomised study (UKPDS) has established the long-term benefit of intensive blood glucose control in adult patients with type 2 diabetes.

Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:
a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1000 patient-years) versus diet alone (43.3 events/1000 patient-years), p = 0.0023, and versus the combined sulfonylurea and insulin monotherapy groups (40.1 events/1000 patient-years), p = 0.0034;
a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/1000 patient-years, p = 0.017;
a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1000 patient-years versus diet alone 20.6 events/1000 patient-years (p = 0.011), and versus the combined sulfonylurea and insulin monotherapy groups 18.9 events/1000 patient-years (p = 0.021);
a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1000 patient-years, diet alone 18 events/1000 patient-years (p = 0.01).

Benefit regarding clinical outcome has not been shown for metformin used as second-line therapy, in combination with a sulfonylurea.

In type 1 diabetes, the combination of metformin and insulin has been used in selected patients, but the clinical benefit of this combination has not been formally established.

Pharmacokinetic

Absorption

After an oral dose of Glucophage XR 500, metformin absorption is significantly delayed compared to the immediate-release tablet [T_{max} at 2.5 hours] with a T_{max} at 7 hours. Following a single oral administration of 1500 mg of Glucophage XR 750, 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 was shown to be bioequivalent to Glucophage XR 500 at a 1500 mg dose with respect to C_{max} and AUC in healthy fed and fasted subjects.

Following a single oral administration in the fed state of one tablet of Glucophage XR 1000, 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 was shown to be bioequivalent to Glucophage XR 500 at a 1000 mg dose with respect to C_{max} and AUC in healthy fed and fasted subjects.

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 metformin prolonged-release is similar to that observed after administration of 1000 mg metformin immediate-release twice daily. Intrasubject variability of C_{max} and AUC of metformin prolonged-release is comparable to that observed with metformin immediate-release.

When 2 tablets of 500 mg metformin prolonged-release is administered in fed conditions the AUC is increased by approximately 70% (both C_{max} and T_{max} are only slightly increased).

When the 1000 mg prolonged release tablet are administered in fed conditions the AUC is increased by 77% (C_{max} is increased by 26 % and T_{max} is slightly prolonged by about 1 hour).

Metformin absorption from the prolonged-release formulation is not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000 mg metformin prolonged release.

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 volume of distribution (V_d) 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.

Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies on safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity reproduction.

Indications
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.

Dosage and administration

Monotherapy of Glucophage XR 500 mg, 750 and 1000 mg:
- The usual starting dose is one tablet of Glucophage 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 2000 mg XR once daily with the evening meal.
- If glycaemic control is not achieved on 2000 mg once daily, Glucophage XR 1000 mg twice daily should be considered, with both doses being given with food. If glycaemic control is still not achieved, patients may be switched to metformin tablets IR 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 IR 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.

Combination with insulin:
Metformin hydrochloride and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose of Glucophage XR is 500 mg once daily with the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements. After titration, switch to Glucophage XR 1000 mg should be considered.

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 (see section special warnings and special precautions for use).

Children: In the absence of available data, Glucophage XR should not be used in children.
Special warnings and precautions for use

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:

The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps with digestive disorders as abdominal pain and severe asthenia.

This can be followed by acidotic dyspnea, hypothermia and 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 must be discontinued and the patient should be hospitalised immediately (see section overdose).

Renal function:

As metformin is excreted by the kidney, it is recommended that creatinine clearance and/or serum creatinine levels 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 creatinine clearance at the lower 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 a non-steroidal anti-inflammatory drug (NSAID).

Administration of iodinated contrast materials:

The intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure. This may induce metformin accumulation and may expose to lactic acidosis. Therefore, depending on the renal function, metformin must be discontinued 48 hours before the test or from the time of the test and may not be reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section interaction with other medicinal products and other forms of interaction).

Surgery:

Metformin must be discontinued 48 hours before elective major surgery. Therapy may be restarted no earlier than 48 hours following surgery and only after renal function has been re-evaluated and found to be normal

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 does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulfonylureas or meglitinides).
- The tablet shells may be present in the feces. It is recommended that patients be advised that this is normal.

Pregnancy and lactation

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 fetal development, parturition or postnatal development (see section preclinical safety data). However, 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 blood glucose levels.

Lactation

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 should be made whether to discontinue breast-feeding or to discontinue metformin, taking into account the benefit of breast-feeding and the potential risk to adverse effect in the infant.

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. sulfonylureas, insulin, or meglitinides).

Contraindications

- Hypersensitivity to metformin or to any of the excipients.
- Diabetic ketoacidosis, diabetic pre-coma.
- Renal failure or renal dysfunction (creatinine clearance < 60 ml/min).
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, intravascular administration of iodinated contrast agents (see section special warnings and precautions for use).
- Acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, shock.
- Elective major surgery (see section special warnings and precautions for use)
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.

Interaction with other medicinal products and other forms of interaction
Contraindicated combinations

Iodinated contrast materials:
Depending on the renal function, metformin must be discontinued 48 hours before the test or from the time of the test and may not be reinstated until 48 hours afterwards (see section contraindications and special warnings and precautions for use).

Concomitant use not recommended:

Alcohol:
The risk of lactic acidosis is increased in acute alcohol intoxication, particularly in case of fasting or malnutrition, hepatic insufficiency.
Avoid consumption of alcohol and alcohol-containing medicinal product.

Combinations requiring precautions for use:

Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids and tetracosactides (systemic and local routes), beta-2-agonists, danazol, chlorpromazin at high dosages of 100 mg per day and diuretics.

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon discontinuation.

Diuretics especially loop diuretics,
They may increase the risk of lactic acidosis due to their potential to decrease renal function

Angiotensin converting enzyme inhibitors (ACE-inhibitors)
ACE inhibitors may decrease the blood glucose levels. Therefore, dose adjustment of metformin may be necessary during and after addition or discontinuation of such medicinal products.

Adverse effects

The following adverse effects may occur under treatment with metformin. 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,

Metabolism and nutrition disorders:
Very rare: Lactic acidosis (see section Special warnings and precautions for use).
Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin.
Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

Nervous system disorders:
Common: Taste disturbance

Gastrointestinal disorders:
Very common: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and los 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: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders:
Very rare: Skin reactions such as erythema, pruritus, urticaria

Overdose

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

Presentation

Glucophage XR 500 mg: Box of 15 blisters @ 8 tablets
Glucophage XR 750 mg: Box of 8 blisters @ 15 tablets
Glucophage XR 1000 mg: Box of 12 blisters @ 10 tablets

Storage

Glucophage XR 500 mg: Store below 25°C, avoid from moisture
Glucophage XR 750 mg: Store below 30°C
Glucophage XR 1000 mg: Store below 30°C

Shelf Life:

Glucophage XR 500 mg: 3 years
Glucophage XR 750 mg: 3 years
Glucophage XR 1000 mg: 3 years

HARUS DENGAN RESEP DOKTER
On medical prescription only

Manufactured by
Merck Sante s.a.s, France
Imported by
PT. Merck Tbk., Jakarta

Reg. No.:

Glucophage XR 500 mg: DKL0915808414\11
Glucophage XR 750 mg: DKI140160021481
Glucophage XR 1000 mg: DKI1501600214C1