

SUMMARY OF PRODUCT CHARACTERISTICS GLUCOMET
1000 XR TABLETS (METFORMIN EXTENDED RELEASE
TABLETS 1000MG)

1. Name of the Medicinal Product

1.1 Proprietary Name

Glucomet 1000 XR Tablet

1.2 Strength

Each tablet contains 1000mg of Metformin Hydrochloride USP

2. Qualitative and Quantitative Composition

2.1 Qualitative composition

Name of active ingredient: Metformin Hydrochloride

2.2 Quantitative composition

Each extended-release tablet contains:

Metformin Hydrochloride... 1000mg

For full list of excipients, see section 6.1

3. Pharmaceutical

al Form

Extended

Release Tablet

Product

description

Yellow, circular, biconvex film coated tablets embossed 'c' on one side and a breakline on the other side

‘The break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses’

4. Clinical Particulars

4.1 Therapeutic Indications

-Reduction in the risk or delay of the onset of type 2 diabetes mellitus in adult, overweight patients with IGT (Impaired Glucose Tolerance) and/or IFG (Impaired Fasting Glucose), and/or increased HbA1C who are at high risk for

developing overt type 2 diabetes mellitus (see section 5.1) and still progressing towards type 2 diabetes mellitus despite implementation of intensive lifestyle change for 3 to 6 months

Treatment with Glucophage SR must be based on a risk score incorporating appropriate measures of glycaemic control and including evidence of high cardiovascular risk (see section 5.1). 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. Glucophage SR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

-Polycystic ovary syndrome (PCOS)

Ovulation stimulation to support conception in women with PCOS. Glucophage SR can be used as monotherapy or in combination with other treatment options.

4.2 Posology and Method of administration Posology

Monotherapy and combination with other oral antidiabetic agents:

-Glucomet XR 1000 mg are intended for patients who are already treated with metformin tablets (prolonged or immediate release). The dose of Glucomet 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.

Combination with insulin:

For patients already treated with metformin and insulin in combination therapy, the dose of Glucomet XR 1000mg 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.

Ovulation stimulation to support conception in women with PCOS:

The usual dose is 1,500-2000 mg once daily. A slow increase of dose may improve gastrointestinal tolerability.

The maximum recommended dose is 2000 mg once daily with the evening meal.

Glucophage SR should be considered for at least 6 months. The decision to maintain therapy after conception and during pregnancy should be made clinically on a case-by-case basis, taking into consideration the patient needs and an evaluation of the potential risks and benefits.

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.

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.

Children

In the absence of available data, Glucomet XR should not be used in children.

Method of administration

The tablet should be swallowed whole with sufficient amount of water and should not be crushed or chewed.

Due to the hypoglycemic effect, Glucomet XR tablets should be taken after meals, usually after the heaviest meal of the day.

4.3 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,

- Acute or chronic disease which may cause tissue hypoxia such as:

- cardiac or respiratory failure,
- recent myocardial infarction,
- shock

4.4 Hepatic insufficiency, acute alcohol intoxication, alcoholism

4.5 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.

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, abdominal pain, hypothermia and coma.

Renal function:

As metformin is excreted by the kidney, creatinine clearance (this can be estimated from serum creatinine levels using the Cockcroft-Gault formula) 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 creatinine clearance levels at the limit of normal and in elderly subjects.

Administration of iodinated contrast media:

The intravascular administration of iodinated contrast media in radiological studies can lead to renal failure. This may lead to metformin accumulation and risk of lactic acidosis. Metformin must 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 should be discontinued 48 hours before elective surgery with general spinal or peridural anaesthesia. Therapy may be restarted no earlier than 48

hours following surgery or resumption of oral nutrition provided normal renal function has been established.

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 hypoglycaemia, although caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulphonylureas or meglitinides).

The tablet shells may be present in the faeces. Patients should be advised that this is normal.

4.6 Interaction with other medicinal products and other forms of interaction
Concomitant use not recommended Alcohol

Acute alcohol intoxication is associated with an increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:

- fasting or malnutrition,
- hepatic insufficiency.

Avoid consumption of alcohol and alcohol-containing medications. Iodinated contrast media

Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis.

Metformin hydrochloride must 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.

Combinations requiring precautions for use

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.

- Diuretics, especially loop diuretics

4.7 They may increase the risk of lactic acidosis
due to their potential to decrease renal function
Fertility, 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.

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 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.

4.8 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).

4.9 Undesirable Effects

In post marketing data and in controlled clinical studies, adverse event reporting in patients treated with Metformin Extended Release was similar in nature and severity to that reported in patients treated with Metformin immediate release. 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 Glucomet 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 very rare: Lactic acidosis.

Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such an 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 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

Isolated reports: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders

very rare: Skin reactions such as erythema, pruritus, urticaria

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

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.

5 Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic class: Oral

Antihyperglycemic agent ATC code: A10BA02

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

(except in special circumstances) and does not cause hyperinsulinemia.

With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

5.2 Pharmacokinetic Properties

Absorption

After an oral dose of the prolonged 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 2000mg of metformin prolonged release tablets is similar to that observed after administration of 1000mg 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 prolonged release tablet is administered in fasting conditions the AUC is decreased by 30% (both C_{max} and T_{max} are unaffected).

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 2000mg of metformin as

prolonged release tablets.

Following a single oral administration in the fed state of one tablet of Metformin Extended Release 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). Metformin Extended

Release 1000 mg was shown to be bioequivalent to Metformin Extended Release 500 mg at a 1000 mg dose with respect to C_{max} and AUC in healthy fed and fasted subjects.

When the 1000 mg prolonged release tablet is 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).

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 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.

5.3 Preclinical safety data

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

6 Pharmaceutical Particulars

6.1 List of

Excipients

Instamodell

Blend I,

Instamodell

Blend II,

Purified Water

BP

Colloidal Anhydrous Silica

BP Magnesium Stearate BP

6.2 Incompatibilities

None

6.3 Shelf life

3Years

Special precautions
for storage

Store in a dry place below 30°C.

6.4 Nature and contents of container

Glucomet XR 1000mg is available in PVDC coated

PVC/ALU blister packing, in pack sizes of 3 x 10
Tablets

6.5 Instructions for use, handling and disposal

No special requirements.

7 Market Authorization Holder

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8 Marketing Authorization Number

CTD 2531

9 Date of First Authorization

14.10.2015

10 Date of Renewal of Authorization

Aug 26

11 Date of Revision of Text

July 2031