GLUCOPHAGE® XR

Metformin hydrochloride

Oral blood glucose lowering drugs

1. QUALITATIVE AND QUANTITATIVE 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.

For the full list of excipients, see section 5.1 List of Excipients.

2. PHARMACEUTICAL FORM

Prolonged release tablet.

- Glucophage XR 500 mg: white to off-white, round, biconvex tablet, debossed '500' on one side
- Glucophage XR 750 mg: white to off-white, capsule-shaped, biconvex tablet, debossed with '750' on one face and 'MERCK' on the other face
- Glucophage XR 1000 mg: white to off-white, capsule-shaped, biconvex tablet, debossed with '1000' on one face and 'MERCK' on the other face

3. CLINICAL PARTICULARS

3.1 Therapeutic Indications

- Reduction in the risk or delay of the onset of type 2 diabetes mellitus in adult, overweight patients with IGT* (Prediabetes) 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 mellitus 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.

3.2 Posology and Method of 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 Glucophage XR 500 mg once daily with the evening meal.

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- 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 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.
- Dosage increases should be made in increments of 500 mg every 10-15 days, up to a maximum of 2000 mg 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.
- Glucophage XR 750 mg and 1000 mg is intended for patients who are already treated with Metformin tablets (prolonged or immediate release). The dose of Glucophage XR 750 mg or 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.
- 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 3.4 Special Warnings and Special Precautions for Use*).

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.

Patients with Renal Impairment

Metformin may be used in patients with moderate renal impairment (creatinine clearance or glomerular filtration rate (GFR) between 30 and 59 mL/min) only in the absence of other conditions that may increase the risk of lactic acidosis and with the following dose adjustments:

- Patients with creatinine clearance or a GFR between 45 and 59 mL/min: the starting dose is 500 mg or 750 mg Metformin hydrochloride, once daily. The maximum dose is 1000 mg daily. The renal function should be closely monitored (every 3 - 6 months).
- Patients with creatinine clearance or a GFR between 30 and 44 mL/min: it is not recommended to initiate Metformin hydrochloride, but Metformin can be maintained in patients already treated, provided that the

maximum daily dose is not higher than 1000 mg. The renal function should be closely monitored every 3 months.

If creatinine clearance or GFR fall below 30 mL/min, Metformin must be discontinued immediately.

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

3.3 Contraindications
- Hypersensitivity to Metformin or to any of the excipients listed in section 5.1 List of Excipients.
- Any type of metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).
- Diabetic pre-coma.
- Severe renal failure or renal dysfunction (creatinine clearance or GFR <30 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 3.4 Special Warnings and Special Precautions for Use*).
- Disease (especially acute disease, or worsening of chronic disease) which may cause tissue hypoxia such as unstable congestive heart failure, respiratory failure, recent myocardial infarction or shock.
- Elective major surgery *see section 3.4 Special Warnings and Special Precautions for Use*).
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.

3.4 Special Warnings and Special Precautions for Use
Lactic Acidosis
Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication. Risk factors include poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, severe infection, hepatic insufficiency, and any condition associated with hypoxia (such as decompensated cardiac failure, acute myocardial infarction) or the concomitant use of medications which might cause lactic acidosis (such as NRTIs), (*see also section 3.3 Contraindications*).

Lactic acidosis can occur due to Metformin accumulation. Reported cases of lactic acidosis in patients treated with Metformin have occurred primarily in diabetic patients with acute renal failure or acute worsening of renal function.

Special caution should therefore be paid to situations where renal function may become acutely impaired (*see also section 3.3 Contraindications*), for example in case of dehydration (severe or prolonged diarrhoea or vomiting) or when initiating drugs which can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs).

In the acute conditions listed, Metformin must be immediately and temporarily discontinued.

The following non-specific symptoms could be signs of lactic acidosis: such as muscle cramps, digestive disorders as abdominal pain and severe asthenia.

Patients with Known or Suspected Mitochondrial Diseases
In patients with known mitochondrial diseases such as Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome and Maternal inherited diabetes and deafness (MIDD), metformin is not recommended due to the risk of lactic acidosis exacerbation and neurologic complications which may lead to worsening of the disease.

In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of metformin, treatment with metformin should be withdrawn immediately and prompt diagnostic evaluation should be performed.

Diagnosis

Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH (below 7.35), plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. In case of lactic acidosis, the patient should be immediately hospitalised (*see also section 3.9 Overdose*)**.**

Physicians must alert the patients on the risk and on the symptoms of lactic acidosis.

Patients should be instructed to immediately seek medical attention and to stop taking Metformin.

Metformin must be immediately discontinued, at least temporarily, until the situation is clarified.

Reintroduction of Metformin should then be discussed taking into account the benefit/risk ratio on an individual basis as well as renal function.

Renal Function
As Metformin is excreted by the kidney, it is recommended that creatinine clearance or GFR 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 or GFR at the lower limit of normal or between 45 and 59 mL/min and in elderly subjects.
- at least four times a year in patients with creatinine clearance or GFR between 30 and 44 mL/min. In case creatinine clearance or GFR is <45 mL/min, it is not recommended to initiate Metformin.

GFR should be assessed before treatment initiation and regularly thereafter (see section *3.2 Posology and Method of Administration)*. Metformin is contraindicated in patients with GFR<30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function (see section *3.3 Contraindication)*.

Special caution should be exercised in situations where renal function may become impaired, for example in the elderly, in case of dehydration, or when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID). In these cases, it is also recommended to check renal function before initiating treatment with Metformin.

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 (*see section 3.3 Contraindications*).

Administration of Iodinated Contrast *Agents*
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 reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (*see section 3.5 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 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 anemia 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 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.

3.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Contraindicated Combinations

Iodinated contrast agents

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 reinstituted until 48 hours afterwards (*see section 3.2 Posology and method of administration and 3.4 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.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of Metformin with:

- Substrates/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.
- Substrates/inhibitors of OCT2 (such as Cimetidine, Dolutegravir, Crizotinib, Olaparib, Daclatasvir, Vandetanib) may decrease the renal elimination of Metformin and thus lead to an increase 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

3.6 Fertility, Pregnancy, and Lactation

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 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.

3.7 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).

3.8 Undesirable 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

Common: Vitamin B12 decrease/deficiency (*see section Special Warnings and Precautions for Use*)

Very rare: Lactic acidosis (*see section 3.4 Special Warnings and Precautions for Use*),

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: 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
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to PT Merck Tbk via email ICSR_SEA@merckgroup.com and/or to Pusat Farmakovigilans/MESO Nasional BPOM via subsite https://e-meso.pom.go.id/ADR.

3.9 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.

4. PHARMACOLOGICAL PROPERTIES
4.1 Pharmacodynamic Properties
ORAL ANTI-DIABETICS
(A10BA02 - Gastrointestinal tract and metabolism)

Mechanism of Action
Metformin is a biguanide with antihyperglycaemic effects, on both basal and postprandial hyperglycaemia. It does not stimulate Insulin secretion and therefore does not cause hypoglycaemia. Metformin reduces basal hyperinsulinemia, and in combination with insulin, reduces insulin requirement.

Metformin exerts its antihyperglycaemic effect via multiple mechanisms:
1. Metformin reduces hepatic glucose production.
2. Metformin facilitates peripheral glucose uptake and utilization, in part by increasing insulin action.
3. Metformin alters glucose turnover in the gut: Uptake from circulation is increased and absorption from food is decreased. Additional mechanisms attributed to the gut include an increase in release of glucagon-like peptide 1 (GLP-1) and a decrease of bile acid resorption. Metformin alters the gut microbiome.

Metformin can improve the lipid profile in hyperlipidaemic individuals.

In clinical studies, use of Metformin was associated with either a stable body weight or modest weight loss.

Metformin is an adenosine monophosphate-protein-kinase (AMPK) activator and increases the transport capacity of all types of membrane glucose transporters (GLUTs).

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).

For Metformin used as second-line therapy, in combination with a Sulfonylurea, benefit regarding clinical outcome has not been shown.

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.

4.2 Pharmacokinetic Properties

Absorption

After an oral dose of Glucophage XR 500, 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, a mean peak plasma concentration of 1193 mg/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 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, 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 Cmax and AUC in healthy fed and fasted subjects.

At steady state, similar to 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 twice daily.

Intrasubject variability of Cmax and AUC of Metformin prolonged-release is comparable to that observed with Metformin immediate-release tablets.

When 2 tablets of 500 mg Metformin prolonged-release is administered in fed conditions the AUC is increased by approximately 70% (both Cmax and Tmax are only slightly increased).

When the 1000 mg prolonged release tablet are administered in fed conditions the AUC is increased by 77% (Cmax is increased by 26% and Tmax 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 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 volume of distribution (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.

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

5. PHARMACEUTICAL PARTICULARS
5.1 List of Excipients
Magnesium stearate, Hypromellose, Sodium carmellose

5.2 Incompatibilities
None.

5.3 Shelf-life
The expiry date is indicated on the packaging.

5.4 Special Precautions for Storage
Store below 30°C.

6. MANUFACTURER(S)
Manufactured by PT Merck Tbk, Jakarta, Indonesia
Under license from Merck Sante S.A.S, Lyon, France

7. MARKETING AUTHORISATION HOLDER
Registered by PT Merck Tbk, Jakarta, Indonesia

8. PACKAGE QUANTITIES AND MARKETING AUTHORISATION NUMBER(S)
Glucophage® XR 500 mg, Box, 8 blisters @ 15 prolonged-release tablets
Reg. No. DKL1915809314A1

Glucophage® XR 750 mg, Box, 8 blisters @ 15 prolonged-release tablets
Reg. No. DKL1915809314B1

Glucophage® XR 1000 mg, Box, 12 blisters @ 10 prolonged-release tablets
Reg. No. DKL2215809314C1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Glucophage XR 500 mg
Date of first authorisation: 26 Apr 2005
Date of latest renewal: 21 Apr 2021

Glucophage XR 750 mg
Date of first authorisation: 3 Oct 2011
Date of latest renewal: 26 May 2021

Glucophage XR 1000 mg
Date of first authorisation: 9 Aug 2016
Date of latest renewal: 7 Sep 2022

10. CLASSIFICATION OF MEDICINE
Medicinal product subject to medical prescription. Obat Keras

HARUS DENGAN RESEP DOKTER

11. DATE OF REVISION OF THE TEXT
SmPC based on CCDS version 12.0 (14-Feb-2025)
Date of BPOM approval for the update: DD Month YYYY

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GLUCOPHAGE® XR
Metformin hydrochloride

Obat ini diperuntukkan bagi orang dewasa saja.

Baca petunjuk ini dengan hati-hati sebelum mulai minum obat ini.
- Simpan lembar petunjuk ini, Anda mungkin akan memerlukannya kembali.
- Jika Anda mempunyai pertanyaan, harap menghubungi dokter atau apoteker.
- Obat ini diresepkan untuk Anda, jangan diberikan kepada orang lain karena dapat membahayakan orang tersebut meskipun terdapat gejala yang sama pada orang tersebut.
- Jika ada efek samping yang serius atau Anda menemukan efek samping yang tidak terdapat pada petunjuk ini, harap hubungi dokter atau apoteker.

Petunjuk ini terdiri dari informasi sebagai berikut:

1 Apa yang dimaksud dengan Glucophage XR dan apa kegunaannya
Glucophage XR tablet lepas lambat mengandung zat aktif Metformin hydrochloride yang merupakan turunan dari Biguanide, digunakan untuk mengobati diabetes.

Glucophage XR digunakan bersamaan dengan diet dan olahraga untuk menurunkan risiko berkembangnya prediabetes menjadi diabetes tipe 2 pada pasien dewasa dengan berat badan di atas normal (*overweight*), ketika dengan diet dan oleh raga saja selama 3 hingga 6 bulan tidak cukup untuk mengontrol kadar gula darah. Diet dan olahraga harus tetap dilakukan ketika menggunakan Glucophage XR, kecuali terdapat kondisi medis yang tidak memungkinkan untuk melakukannya. Anda dalam risiko terkena diabetes tipe 2 jika Anda memiliki kondisi tambahan seperti tekanan darah tinggi, usia di atas 40 tahun, jumlah lemak dalam darah tidak normal, atau riwayat diabetes selama kehamilan.

Glucophage XR digunakan untuk mengobati diabetes tipe 2 (yang tidak tergantung dengan insulin) ketika dengan diet dan olahraga saja tidak cukup untuk mengontrol kadar gula darah. Insulin adalah hormon yang membuat tubuh mengubah gula dari dalam darah menjadi energi atau disimpan terlebih dahulu untuk kebutuhan selanjutnya. Pasien dengan diabetes tipe 2 tidak bisa memproduksi cukup insulin dari pankreas atau tubuh mereka yang tidak dapat merespon terhadap insulin seperti seharusnya. Hal ini menyebabkan kadar gula di dalam darah meningkat yang memicu beberapa masalah serius jangka panjang dan penting bagi Anda untuk minum obat meskipun gejala-gejala belum tampak jelas terjadi.

Glucophage XR membuat kerja insulin lebih sensitif dan membantu mengembalikan kadar gula darah menjadi normal.

Glucophage XR tablet lepas lambat dibuat khusus untuk dapat melepaskan zat aktif secara perlahan-lahan ke dalam tubuh Anda yang membuat obat ini berbeda dengan sediaan jenis lain yang mengandung Metformin.

2 Apa yang perlu Anda ketahui sebelum Anda minum Glucophage XR
Jangan minum obat ini jika:

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- Anda alergi terhadap Metformin atau salah satu dari bahan-bahan yang terdapat dalam formula obat ini (lihat bagian *6 Isi dari kemasan dan informasi lain*).
- Anda mempunyai kelainan pada hati dan gangguan fungsi ginjal berat dalam waktu yang lama.
- Anda menderita diabetes yang tidak terkontrol, diiringi dengan misalnya mual, muntah, diare, berat badan turun dengan cepat, asidosis laktat (lihat 'Risiko asidosis laktat' di bawah) atau ketoasidosis. Ketoasidosis merupakan kondisi dimana senyawa 'keton tubuh' menumpuk dalam darah, ditandai dengan napas yang tidak teratur, napas memiliki bau khas seperti aseton.
- Tubuh Anda kehilangan banyak cairan (dehidrasi). Dehidrasi dapat menyebabkan gangguan ginjal, yang dapat berisiko terjadi asidosis laktat (lihat 'Peringatan dan Pencegahan').
- Anda mempunyai infeksi berat seperti infeksi yang mempengaruhi sistem pernapasan atau ginjal maupun baru saja mengalami luka/cedera berat. Infeksi berat dapat menyebabkan gangguan ginjal, yang dapat berisiko terjadi asidosis laktat (lihat 'Peringatan dan Pencegahan').
- Anda dalam pengobatan gangguan jantung akut atau baru saja mengalami serangan jantung atau memiliki masalah sirkulasi pernapasan yang berat maupun kesulitan bernapas. Hal ini dapat menyebabkan kekurangan pasokan oksigen ke jaringan yang dapat berisiko terjadi asidosis laktat (lihat 'Peringatan dan Pencegahan').
- Anda memerlukan pemeriksaan rontgen dengan pemberian suntikan kontras kedalam aliran darah.
- Anda banyak mengonsumsi alkohol.
- Anda berusia di bawah 18 tahun.

Peringatan dan Pencegahan
Risiko asidosis laktat
Kejadian asidosis laktat jarang terjadi, namun bersifat serius, terutama jika ginjal Anda tidak bekerja normal. Risiko terjadinya asidosis laktat juga meningkat seiring dengan diabetes tak terkontrol, infeksi berat, konsumsi alkohol jangka panjang, dehidrasi (lihat informasi lebih lanjut di bawah), kelainan ginjal dan segala kondisi medis di mana bagian tubuh kekurangan pasokan oksigen (seperti penyakit jantung akut yang parah).

Jika Anda memiliki gejala di atas, bicarakan dengan dokter untuk petunjuk lebih lanjut.

Hentikan sementara penggunaan Glucophage XR jika Anda dalam kondisi dehidrasi seperti muntah berat, diare, demam, terpapar panas dalam waktu lama atau jika Anda kurang mengonsumsi cairan. Bicarakan dengan dokter untuk petunjuk lebih lanjut.

Hentikan penggunaan obat dan hubungi dokter atau rumah sakit terdekat segera mungkin jika Anda mengalami beberapa gejala asidosis laktat, di mana kondisi tersebut dapat menyebabkan koma.

Gejala asidosis laktat meliputi:
- Muntah
- Sakit perut (nyeri pada perut)
- Kram otot
- Kesulitan bernapas
- Suhu tubuh menurun dan detak jantung berkurang

Asidosis laktat merupakan kondisi gawat darurat dan harus dirawat di rumah sakit.

Segera hubungi dokter untuk petunjuk lebih lanjut jika Anda:
- diketahui menderita penyakit bawaan genetik yang memengaruhi mitokondria (komponen penghasil energi dalam sel) seperti sindrom MELAS (*Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes*/ensefalomiopati mitokondria, asidosis laktat, dan episode mirip stroke) atau diabetes dan tuli yang diturunkan dari ibu (MIDD/*Maternal Inherited Diabetes and Deafness*).
- mengalami salah satu gejala berikut setelah mulai minum metformin: kejang, penurunan kemampuan kognitif, kesulitan menggerakkan tubuh, gejala yang mengindikasikan kerusakan saraf (misalnya nyeri atau mati rasa), migrain, dan tuli

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Jika Anda akan menjalani tindakan operasi besar, Anda harus menghentikan Glucophage XR selama operasi dan beberapa saat setelah operasi. Dokter Anda akan menentukan kapan Anda harus berhenti dan kapan harus memulai kembali menggunakan Glucophage XR.

Selama Anda menjalani pengobatan dengan Glucophage XR, dokter Anda akan memeriksa fungsi ginjal Anda minimal satu kali setahun atau lebih sering jika Anda adalah pasien lansia dan/atau jika Anda memiliki fungsi ginjal yang memburuk.

Anda mungkin akan menjumpai sisa tablet dalam feses. Jangan khawatir, hal ini normal untuk jenis tablet lepas lambat.

Anda harus tetap mengikuti anjuran diet yang telah diberikan oleh dokter dan Anda harus pastikan bahwa Anda mengonsumsi karbohidrat secara teratur setiap hari.

Jangan menghentikan penggunaan obat ini tanpa konsultasi terlebih dahulu ke dokter Anda.

Obat lain dan Glucophage XR
Jika Anda harus menjalani pemeriksaan rontgen yang menggunakan suntikan kontras ke dalam aliran darah Anda, informasikan ke dokter bahwa Anda sedang minum Glucopahge XR. Dokter akan memutuskan kapan Anda harus berhenti minum dan mulai minum kembali Glucophage XR.

Konsultasikan ke dokter atau apoteker jika Anda sedang atau akan menggunakan obat lain termasuk obat tanpa resep dokter. Anda mungkin akan membutuhkan pemeriksaan gula darah dan fungsi ginjal lebih sering, atau dokter akan menyesuaikan dosis Glucophage XR. Hal tersebut penting terutama jika Anda sedang menggunakan:
- Obat yang meningkatkan produksi urin (tablet diuretik seperti Furosemide)
- Obat yang digunakan untuk meredakan nyeri dan inflamasi
- Obat tertentu untuk pengobatan tekanan darah tinggi (inhibitor ACE seperti Lisinopril, Captopril)
- Steroid seperti Prednisolon, Mometasone, Beclometasone
- Obat yang dapat mengubah jumlah Glucophage XR dalam darah, terutama jika fungsi ginjal Anda menurun (seperti Verapamil, Rifampicin, Cimetidine, Dolutegavir, Ranolazine, Trimethoprim, Vandetanib, Crizotinib, Olaparib)

Glucophage XR dengan Alkohol
Hindari meminum alkohol berlebih ketika sedang minum Glucophage XR karena dapat meningkatkan risiko asidosis laktat (lihat bagian ‘Peringatan dan Pencegahan’).

Kehamilan dan Menyusui
Jika Anda sedang, merasa, atau berencana untuk hamil, mintalah nasihat dokter untuk mengetahui perlu tidaknya perubahan pengobatan atau pemantauan kadar gula darah Anda.

Obat ini tidak direkomendasikan jika Anda sedang atau berencana untuk menyusui bayi Anda.

Mengendarai Kendaraan atau Mengoperasikan Mesin
Glucophage XR tidak menyebabkan gejala hipoglikemia seperti pingsan, bingung, berkeringat yang berlebihan sehingga tidak mempengaruhi kemampuan Anda dalam berkendara atau mengoperasikan mesin.

Anda harus waspada apabila minum bersama dengan antidiabetes lain yang dapat menyebabkan gejala hipoglikemia di mana dalam keadaan ini Anda harus lebih berhati-hati dalam berkendara maupun mengoperasikan mesin.

3 Bagaimana meminum Glucophage XR

Dokter Anda mungkin meresepkan Glucophage XR untuk Anda dalam obat tunggal, maupun kombinasi dengan obat oral anti diabetes lain atau insulin.

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Selalu minum obat ini sesuai dengan anjuran dokter.

Anda harus cek ke dokter maupun apoteker apabila Anda belum yakin.

Telan tablet dengan air minum dan jangan dikunyah.

Rekomendasi dosis
Biasanya pengobatan dimulai dengan dosis Glucophage XR 500 mg sehari. Setelah minum selama 2 minggu, dokter akan mengukur kadar gula darah Anda dan dosis akan disesuaikan. Dosis maksimum Glucophage XR per hari adalah 2000 mg.

Jika fungsi ginjal Anda menurun, dokter akan meresepkan dosis yang lebih rendah.

Secara normal, Anda minum obat 1 kali sehari setelah makan malam.

Pada beberapa kasus, dokter dapat merekomendasikan untuk minum tablet 2 kali sehari, segera setelah makan.

Jika Anda Minum Glucophage XR Berlebih dari Seharusnya
Jika Anda minum tablet Glucophage XR berlebih secara tidak sengaja, jangan khawatir, akan tetapi apabila terjadi gejala yang tidak biasa, harap hubungi dokter. Jika over dosis dalam jumlah besar, asidosis laktat pada umumnya akan terjadi. Gejala asidosis laktat tidak spesifik, seperti muntah, sakit perut dengan kram otot, dan kesulitan bernapas. Gejala lebih lanjut adalah menurunnya suhu tubuh dan detak jantung. Jika Anda mengalami gejala tersebut, Anda harus segera mencari pertolongan medis karena asidosis laktat dapat berujung koma. Segera hentikan penggunaan Glucophage XR dan hubungi dokter atau rumah sakit terdekat.

Jika Anda Lupa Minum Glucophage XR
Minum sesegera mungkin pada saat Anda ingat (segera setelah makan). Jangan minum dosis sebanyak 2 kali lipat untuk mengganti dosis yang terlupakan.

4 Efek samping yang mungkin terjadi

Seperti halnya obat lain, Glucophage XR dapat menyebabkan efek samping, meskipun tidak semua pasien mengalaminya. Kemungkinan efek samping yang terjadi berdasarkan frekuensinya adalah sebagai berikut:

Sangat Umum Terjadi (dapat terjadi pada >1/10 pasien)
- Gangguan pada saluran pencernaan seperti mual, muntah, diare, nyeri pada perut, dan hilang nafsu makan.

Umum Terjadi (dapat terjadi pada 1/10 pasien)
- Gangguan rasa
- Penurunan atau kadar vitamin B12 rendah dalam darah (gejala termasuk kelelahan ekstrim, lidah sakit dan merah (glositis), parestesia atau kulit pucat atau kuning). Dokter mungkin melakukan tes untuk mencari tahu penyebab gejala Anda karena beberapa gejala ini kemungkinan disebabkan oleh diabetes atau masalah kesehatan lainnya yang tidak berkaitan.

Sangat Jarang Terjadi (dapat terjadi pada <1/10.000 pasien)
- Asidosis laktat (lihat ‘Peringatan dan Pencegahan’)
- Abnormalitas saat pengukuran fungsi hati atau hepatitis yang akan teratasi dengan penghentian pemberian Metformin
- Reaksi pada kulit seperti eritema, pruritus, dan urtikaria

Pelaporan Efek Samping
Jika efek samping menjadi serius atau timbul efek samping yang tidak terdapat pada petunjuk ini, harap hubungi dokter atau apoteker. Anda juga dapat melaporkan keluhan efek samping tersebut ke PT Merck

Tbk melalui email ICSR_SEA@merckgroup.com. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5 Bagaimana menyimpan Glucophage XR

Simpan obat Glucophage XR jauh dari jangkauan anak-anak.

Jangan gunakan obat ini setelah masa kedaluwarsa yang tertera pada kemasan berakhir.

Obat ini tidak memerlukan kondisi khusus pada penyimpanannya.

Jangan membuang obat ini melalui saluran pembuangan air atau limbah rumah tangga. Tanyakan kepada apoteker bagaimana membuang obat-obatan yang tidak diperlukan. Hal ini untuk menjaga lingkungan.

6 Isi dari kemasan dan informasi lain

Isi dari Kemasan

Setiap tablet Glucophage XR mengandung 500 mg, 750 mg, atau 1000 mg zat aktif Metformin hydrochloride. Bahan-bahan lainnya adalah Magnesium stearate, Carmellose sodium, Hypromellose.

Bentuk tablet Glucophage XR

Glucophage XR 500 mg: tablet berwarna putih, bulat, tablet cembung, terdapat gravur “500” pada salah satu sisi.

Glucophage XR 750 mg: tablet berwarna putih, bentuk kapsul, tablet cembung, terdapat gravur “750” pada salah satu sisi dan “MERCK” pada sisi yang lain.

Glucophage XR 1000 mg: tablet berwarna putih, bentuk kapsul, tablet cembung, terdapat gravur “1000” pada salah satu sisi “MERCK” pada sisi yang lain.

Produsen

Diproduksi oleh PT Merck Tbk, Jakarta, Indonesia
Atas lisensi dari Merck Sante S.A.S, Lyon, Prancis

Pemilik Izin Edar

Didaftarkan oleh PT Merck Tbk, Jakarta, Indonesia

Kemasan dan Nomor Izin Edar

Glucophage® XR 500 mg, Dus, 8 blister @ 15 tablet lepas lambat
Reg. No. DKL1915809314A1

Glucophage® XR 750 mg, Dus, 8 blister @ 15 tablet lepas lambat
Reg. No. DKL1915809314B1

Glucophage® XR 1000 mg, Dus, 12 blister @ 10 tablet lepas lambat
Reg. No. DKL2215809314C1

HARUS DENGAN RESEP DOKTER

Tanggal Perubahan Informasi

Informasi Untuk Pasien ini selaras dengan *SmPC based on CCDS version 12.0 (14-Feb-2025)*
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