GLUCOPHAGE®

Metformin hydrochloride

Blood glucose lowering drugs

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Glucophage® 500 mg: film-coated tablet contains 500 mg Metformin hydrochloride corresponding to 390 mg Metformin base.

Glucophage® 850 mg: film-coated tablet contains 850 mg Metformin hydrochloride corresponding to 662.9 mg Metformin base.

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

2. PHARMACEUTICAL FORM

- Glucophage 500 mg: White, round, bevelled edge, biconvex, film-coated tablet, engraved GL 500 on one side and plain on the other side.
- Glucophage 850 mg: White, round, biconvex, film-coated tablet engraved with GL 850 on one side and plain on the other side.

3. CLINICAL PARTICULARS

3.1 Therapeutic Indications

Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

- In adults, Glucophage film-coated tablet may be used as monotherapy or in combination with other oral anti-diabetic agents or with insulin.
- In children from 10 years of age and adolescents, Glucophage film-coated tablet may be used as monotherapy or in combination with insulin.

3.2 Posology and Method of Administration

Posology

It is important that Glucophage tablets should be taken in divided doses with meals.

Glucophage 500 mg: 1 tablet 3 times daily.
Glucophage 850 mg: 1 tablet 2 times daily.

N.B.: In combination therapy with either a Sulfonylureas or insulin, diabetic control should be checked by blood sugar readings, because of the possibility of hypoglycaemia.

Monotherapy and Combination with Other Oral Antidiabetic Agents

- The usual starting dose is Glucophage 500 mg or 850 mg 2 to 3 times a day. The dose should be increased gradually. Glucophage 500 mg 3 or 4 times a day or 1 Glucophage 850 mg 2 times a day is often enough to give good diabetic control.
  This may be achieved within a few days, but it is not unusual for the full effect to be delayed for up to two weeks. If control is incomplete, a cautious increase in dosage by increments of 1 Glucophage 500 mg or 850 mg is justified. The maximum recommended dose of Metformin hydrochloride is 3 g daily, taken as 3 divided doses. Once control has been obtained it may be possible to reduce the dosage.
- When combined with existing Sulfonylureas therapy which is not giving adequate control, 1 to 3 Glucophage 500 mg or 1 to 3 Glucophage 850 mg tablets should be added initially, the dosage of Glucophage being gradually increased until optimal control is obtained. Often the Sulfonylureas may be reduced and in some patients even withdrawn. Glucophage can then be continued as the sole therapy.

Combination with Insulin

DISETUJUI OLEH BPOM: 05/06/2026

ID: EREG10014912600069
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When used with insulin, the following are the guidelines:

a. When the dosage of insulin is less than 60 units a day, 1 to 3 Glucophage 500 mg or 1 to 3 Glucophage 850 mg tablets may be added initially, followed by gradual reduction of the insulin (4 unit every 2 - 4 days). The tablets may be increased at weekly intervals.

b. When the dosage of insulin is more than 60 units a day, the addition of Glucophage may occasionally cause a rapid fall in the blood sugar level. Careful observation of such patients is advised in the first 24 hours after the introduction of Glucophage. After this, the recommendations in (a) above should be followed.

Elderly

Due to the potential for decreased renal function in elderly subjects, the Metformin hydrochloride dosage should be adjusted based on renal function. Regular assessment of renal function is necessary.

Children and Adolescents

Monotherapy and combination with insulin

- Glucophage 1000 mg film-coated tablet can be used in children from 10 years of age and adolescents.
- The usual starting dose is 500 mg or 850 mg Metformin hydrochloride once daily, given during meals or after meals.

After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose of Metformin hydrochloride is 2 g daily, taken as 2 or 3 divided doses.

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.

3.3 Contraindications

- Hypersensitivity to metformin hydrochloride or to any of the excipients listed in section 5.1 List of Excipients.
- Any type of metabolic acid dosis (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.
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: unstable congestive heart failure, respiratory failure, recent myocardial infarction, shock.
- Major surgery.
- 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 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.

Lactic acidosis can accur due to Metformin accumulation. Reported cases of lactic acidosis in patients treated with Metformin have accured primarily in diabetic patients with acute-renal failure or acute

DISETUJUI OLEH BPOM: 05/06/2026

ID: EREG10014912600069
EREG10014912600070

worsening of renal function.

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 (*see section 3.3 Contraindications and 3.5 Interaction with Other Medicinal Products and Other Forms of Interaction*).

Patients and/or care-givers 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. In 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.

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
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.

Lactic acidosis is characterised by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, Metformin hydrochloride should be discontinued and the patient should be hospitalized immediately.

Renal Function
As Metformin hydrochloride 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.

In case creatinine clearance or GFR is <30 mL/min, metformin is contraindicated (*see section 3.3 Contraindications*).

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.

DISETUJUI OLEH BPOM: 05/06/2026

ID: EREG10014912600069
EREG10014912600070

For patients with acute and unstable heart failure, Metformin is contraindicated (*see section 3.3 Contraindications*).

Administration of Iodinated Contrast Agent
Intravascular administration of iodinated contrast materials in radiodiagnostic examinations 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 hydrochloride must be discontinued 48 hours before elective major surgery. Therapy may be restarted no earlier than 48 hours following surgery and only if normal renal function has been established.

Children and Adolescents
The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with Metformin hydrochloride is initiated.

No effect of Metformin hydrochloride on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of Metformin hydrochloride on these parameters in Metformin hydrochloride-treated children, especially pre-pubescent children, is recommended.

Children Aged Between 10 and 12 Years
Only 15 subjects aged between 10 and 12 years were included in the controlled clinical studies conducted in children and adolescents. Although efficacy and safety of metformin hydrochloride in these children did not differ from efficacy and safety in older children and adolescents, particular caution is recommended when prescribing to children aged between 10 and 12 years.

Other Precautions
- It is recommended that all patients continue their diet with a regular distribution of carbohydrate intake during the day and that overweight patients continue their energy-restricted diet.
- It is recommended that the usual laboratory tests for diabetes monitoring 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 never cause hypoglycaemia, although caution is advised when it is used in combination with insulin or sulfonylureas or meglitinides.

3.5 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 or from the time of the intravascular administration of iodinated contrast media (*see section 3.3 Contraindications and Special Warnings and Precautions for Use*).

Combinations to be Used with Caution
Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids and tetracosactides [systemic and local routes], beta-2-agonists, Danazol, and Chlorpromazine at high dosages of 100 mg per day, 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 its

DISETUJUI OLEH BPOM: 05/06/2026
ID: EREG10014912600069
EREG10014912600070

discontinuation.

Diuretics
Especially loop diuretics, may increase the risk of lactic acidosis due to their potential to decrease renal function (further to their intrinsic hyperglycaemic effect, see above).

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.
- Inhibitors of OCT2 (such as Cimetidine, Dolutegravir, Ranolazine, Trimethoprime, Vandetanib, Isavucanazole) 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.

Interaction with Alcohol
The risk of lactic acidosis is increased in acute alcohol intoxication, particularly in case of fasting or malnutrition or hepatic insufficiency. It is recommended that consumption of alcohol and alcohol-containing medicinal product be avoid.

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 milk in lactating rats.

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

DISETUJUI OLEH BPOM: 05/06/2026

ID: EREG10014912600069
EREG10014912600070

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
frequency not known:	cannot be estimated from the available data

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. To prevent them, it is recommended that Metformin hydrochloride be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Skin and Subcutaneous Tissue Disorders

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

Metabolism and Nutrition Disorders

Common: Vitamin B12 decrease/deficiency (*see section 3.4 Special Warnings and Precautions for Use*)

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

Hepatobiliary Disorders

Very rare: Liver function tests abnormalities or hepatitis resolving upon Metformin discontinuation.

Children and Adolescents

In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year, adverse event reporting was similar in nature and severity to that reported in adults.

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.

DISETUJUI OLEH BPOM: 05/06/2026

ID: EREG10014912600069
EREG10014912600070

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)
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).

A similar action has not been demonstrated with the prolonged-release formulation, possibly due to the evening administration, and an increase in triglycerides may occur.

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.

Controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year

DISETUJUI OLEH BPOM: 05/06/2026
ID: EREG10014912600069
EREG10014912600070

demonstrated a similar response in glycaemic control to that seen in adults.

4.2 Pharmacokinetic Properties

Absorption

After an oral dose of Metformin hydrochloride, T_{max} is reached in 2.5 hours. Absolute bioavailability of a 500 mg or 850 mg Metformin hydrochloride tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, Metformin hydrochloride absorption is saturable and incomplete. It is assumed that the pharmacokinetics of Metformin hydrochloride absorption is non-linear.

At the recommended Metformin hydrochloride doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/mL. In controlled clinical trials, maximum Metformin hydrochloride plasma levels (C_{max}) did not exceed 4 microgram/mL, even at maximum doses.

Food decreases the extent and slightly delays the absorption of Metformin hydrochloride. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these findings is unknown.

Distribution

Plasma protein binding is negligible. Metformin hydrochloride 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 hydrochloride is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination

Renal clearance of metformin hydrochloride is >400 mL/min, indicating that Metformin hydrochloride 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 hydrochloride in plasma.

Children and adolescents

Single dose study

After single doses of Metformin hydrochloride 500 mg paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

Multiple dose study

Data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (C*max*) and systemic exposure (AUC_{0-t}) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

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.

5. PHARMACEUTICAL PARTICULARS

5.1 List of Excipients

Povidone, Magnesium stearate, Hypromellose.

DISETUJUI OLEH BPOM: 05/06/2026

ID: EREG10014912600069
EREG10014912600070

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 and dry place.

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® 500 mg, Box, 10 blisters @ 10 film-coated tablets
Reg. No. DKL9815807217A1

Glucophage® 850 mg, Box, 15 blisters @ 8 film-coated tablets
Reg. No. DKL9815807217B1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Glucophage 500 mg
Date of first authorisation: 3 Nov 1998
Date of last renewal: 10 Sep 2019

Glucophage 850 mg
Date of first authorisation: 9 Aug 2005
Date of last renewal: 13 Mar 2020

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

DISETUJUI OLEH BPOM: 05/06/2026

ID: EREG10014912600069
EREG10014912600070

GLUCOPHAGE®
Metformin hydrochloride
Tablet salut selaput

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 dan apa kegunaannya
2 Apa yang perlu Anda ketahui sebelum Anda minum Glucophage
3 Bagaimana meminum Glucophage
4 Efek samping yang mungkin terjadi
5 Bagaimana menyimpan Glucophage
6 Isi dari kemasan dan informasi lain

1 Apa yang dimaksud dengan Glucophage dan apa kegunaannya
Glucophage mengandung zat aktif metformin yang merupakan turunan dari biguanide, digunakan untuk mengobati diabetes.

Insulin adalah hormon yang dihasilkan oleh pankreas yang membuat tubuh mengubah gula dari dalam darah menjadi energi atau disimpan terlebih dahulu untuk kebutuhan selanjutnya. Pasien dengan diabetes tidak bisa memproduksi cukup insulin dari pankreas atau tubuh mereka yang tidak dapat menggunakan insulin seperti seharusnya. Hal ini menyebabkan kadar gula di dalam darah meningkat. Glucophage membantu menurunkan kadar gula darah menjadi normal.

Glucophage digunakan untuk mengobati diabetes tipe 2 (yang tidak tergantung dengan insulin) ketika dengan diet dan olahraga saja tidak cukup untuk mengontrol kadar gula darah.

Pasien dewasa dapat menggunakan Glucophage saja atau bersamaan dengan obat lain untuk mengobati diabetes (obat yang diminum atau insulin).

Anak-anak usia 10 tahun dan di atasnya dan remaja dapat menggunakan Glucophage saja atau bersamaan dengan insulin.

2 Apa yang perlu Anda ketahui sebelum Anda minum Glucophage
Jangan minum obat ini jika:
- 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.
- Anda mempunyai penurunan fungsi ginjal yang parah.
- Anda menderita diabetes yang tidak terkontrol, diiringi dengan misalnya hiperglikemia (gula darah tinggi), 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 sakit pada perut, napas yang tidak teratur, mengantuk, atau napas memiliki bau khas seperti buah.

DISETUJUI OLEH BPOM: 05/06/2026

ID: EREG10014912600069
EREG10014912600070

- Tubuh Anda kehilangan banyak cairan (dehidrasi) yang diakibatkan oleh diare yang parah atau berkepanjangan, atau jika Anda muntah beberapa kali secara beruntun. 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 banyak mengonsumsi alkohol.

Jika Anda memiliki kondisi seperti di atas, konsultasikan kepada dokter sebelum Anda minum obat ini.

Pastikan untuk meminta saran dokter jika Anda:
- Perlu melakukan pemeriksaan seperti rontgen atau scan yang melibatkan suntikan obat kontras yang mengandung iodine ke dalam aliran darah.
- Perlu menjalani tindakan operasi besar.

Anda harus berhenti meminum Glucophage untuk jangka waktu tertentu sebelum dan sesudah pemeriksaan atau tindakan operasi. Dokter akan menentukan apakah Anda memerlukan pengobatan dalam jangka waktu tersebut. Penting bagi Anda mengikuti petunjuk dokter dengan tepat.

Peringatan dan Pencegahan
Risiko asidosis laktat
Kejadian asidosis laktat jarang terjadi, namun bersifat serius, terutama jika ginjal Anda tidak berfungsi secara normal. Risiko terjadinya asidosis laktat juga meningkat seiring dengan diabetes tak terkontrol, infeksi berat, puasa atau 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 jika Anda dalam kondisi dehidrasi (kehilangan cairan tubuh secara signifikan) 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
- Merasa tidak sehat yang disertai dengan kelelahan berat
- 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*).

DISETUJUI OLEH BPOM: 05/06/2026
ID: EREG10014912600069
EREG10014912600070

- 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.

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

Glucophage sendiri tidak menyebabkan hipoglikemia (kadar gula darah terlalu rendah). Namun, jika Anda menggunakan Glucophage bersamaan dengan obat lain untuk mengobati diabetes yang dapat menyebabkan hipoglikemia (seperti sulphonylurea, insulin, meglitinide), terdapat risiko hipoglikemia. Jika Anda mengalami gejala-gejala hipoglikemia seperti lunglai, pusing, keringat berlebih, detak jantung cepat, gangguan penglihatan atau kesulitan dalam berkonsentrasi, biasanya dapat dibantu dengan makan atau minum sesuatu yang mengandung gula.

Selama Anda menjalani pengobatan dengan Glucophage, 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.

Obat lain dan Glucophage
Jika Anda harus menggunakan suntikan kontras yang mengandung iodine ke dalam aliran darah, misalnya pada rontgen atau *scan*, Anda harus berhenti menggunakan Glucophage sebelum atau pada saat penyuntikkan. Dokter akan menentukan kapan Anda harus berhenti minum dan mulai minum kembali Glucophage.

Konsultasikan ke dokter jika Anda sedang atau akan menggunakan obat lain. Anda mungkin akan membutuhkan pemeriksaan gula darah dan fungsi ginjal lebih sering, atau dokter akan menyesuaikan dosis Glucophage. Hal tersebut penting terutama jika Anda sedang menggunakan:
- Obat yang meningkatkan produksi urin (diuretik)
- Obat yang digunakan untuk meredakan nyeri dan inflamasi (NSAID dan penghambat COX-2, seperti ibuprofen dan celecoxib)
- Obat tertentu untuk pengobatan tekanan darah tinggi (inhibitor ACE dan reseptor antagonis angiotensin II)
- Agonis beta-2 seperti salbutamol atau terbutaline (digunakan untuk mengobati asma)
- Kortikosteroid (digunakan untuk berbagai macam kondisi, seperti inflamasi berat pada kulit atau pada asma)
- Obat yang dapat mengubah jumlah Glucophage dalam darah, terutama jika fungsi ginjal Anda menurun (seperti verapamil, rifampicin, cimetidine, dolutegavir, ranolazine, trimethoprim, vandetanib, isavuconazole, crizotinib, olaparib)
- Obat antidiabetes lain

Glucophage dengan Alkohol
Hindari meminum alkohol berlebih ketika sedang minum Glucophage 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 sendiri tidak menyebabkan gejala hipoglikemia (kadar gula darah yang terlalu rendah) sehingga tidak mempengaruhi kemampuan Anda dalam berkendara atau mengoperasikan mesin.

DISETUJUI OLEH BPOM: 05/06/2026
ID: EREG10014912600069
EREG10014912600070

Anda harus waspada apabila minum bersama dengan antidiabetes lain yang dapat menyebabkan hipoglikemia (seperti sulfonilurea, insulin, meglitinid). Gejala-gejala hipoglikemia termasuk kelemahan, pusing, keringat berlebih, detak jantung cepat, gangguan penglihatan atau kesulitan dalam berkonsentrasi. Jangan berkendara maupun mengoperasikan mesin jika Anda mengalami gejala-gejala ini.

3 Bagaimana meminum Glucophage

Selalu minum obat ini sesuai dengan anjuran dokter. Anda harus cek ke dokter maupun apoteker apabila Anda belum yakin.

Glucophage tidak dapat menggantikan gaya hidup yang sehat. Anda tetap melanjutkan anjuran diet yang diberikan dokter Anda dan rutin melakukan olahraga.

Rekomendasi Dosis

Anak-anak usia 10 tahun dan di atasnya dan remaja biasanya dimulai dengan dosis Glucophage 500 mg atau 850 mg sehari. Setelah minum selama 10 hingga 15 hari, dokter akan mengukur kadar gula darah Anda dan dosis akan disesuaikan. Dosis maksimum Glucophage per hari adalah 2000 mg yang dibagi menjadi 2 atau 3 dosis. Pengobatan anak-anak usia 10 sampai 12 tahun hanya dianjurkan atas saran khusus dari dokter.

Dewasa biasanya dimulai dengan dosis Glucophage 500 mg atau 850 mg 2 atau 3 kali sehari. Dosis maksimum Glucophage per hari adalah 3000 mg yang dibagi menjadi 3 dosis.

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

Jika Anda juga menggunakan insulin, dokter Anda akan memberi tahu cara memulai Glucophage.

Pemantauan

- Dokter akan melakukan tes gula darah secara rutin dan menyesuaikan dosis Glucophage dengan kadar gula darah Anda. Pastikan Anda berkonsultasi dengan dokter secara rutin. Hal tersebut penting untuk anak-anak dan remaja atau jika Anda merupakan pasien lanjut usia.
- Dokter juga akan memeriksa kinerja ginjal Anda minimal 1 kali dalam setahun. Anda mungkin memerlukan pemeriksaan lebih sering jika Anda pasien lanjut usia atau ginjal Anda tidak berfungsi secara normal.

Penggunaan Obat

Minum Glucophage dengan makanan atau setelah makan, hal tersebut dapat mengurangi efek samping yang mempengaruhi pencernaan Anda.

Jangan menggerus atau mengunyah tablet. Telan tiap tablet utuh dengan segelas air.

- Jika Anda diresepkan sekali sehari, minum di pagi hari (saat sarapan)
- Jika Anda diresepkan dua kali sehari, minum di pagi hari (saat sarapan) dan malam (saat makan malam)
- Jika Anda diresepkan tiga kali sehari, minum di pagi hari (saat sarapan), siang (saat makan siang), dan malam (saat makan malam)

Jika dalam sekian waktu Anda merasa efek dari Glucophage terlalu kuat atau rendah tidak berefek, konsultasikan dengan dokter atau apoteker.

Jika Anda Minum Glucophage Berlebih dari Seharusnya

Jika Anda minum tablet Glucophage berlebih, Anda kemungkinan akan mengalami asidosis laktat. Gejala asidosis laktat tidak spesifik, seperti muntah, sakit perut dengan kram otot, merasa tidak sehat yang disertai dengan kelelahan berat, 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 dan hubungi dokter atau rumah sakit terdekat.**

DISETUJUI OLEH BPOM: 05/06/2026

ID: EREG10014912600069
EREG10014912600070

Jika Anda Lupa Minum Glucophage
Jangan minum dosis sebanyak 2 kali lipat untuk mengganti dosis yang terlupakan. Minum dosis selanjutnya di waktu biasa Anda meminum Glucophage.

Jika Anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini, tanyakan kepada dokter atau apoteker.

4 Efek samping yang mungkin terjadi

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

Glucophage dapat menyebabkan efek samping yang sangat jarang terjadi, namun sangat serius yaitu asidosis laktat (lihat bagian 'Peringatan dan Perhatian'). Jika hal tersebut terjadi, Anda harus **segera hentikan penggunaan Glucophage dan hubungi dokter atau rumah sakit terdekat,** karena asidosis laktat dapat berujung koma.

Sangat Umum Terjadi (dapat terjadi pada >1/10 pasien)
- Gangguan pada saluran pencernaan, seperti mual, muntah, diare, nyeri pada perut, dan hilang nafsu makan. Efek samping ini sering terjadi saat awal pengobatan menggunakan Glucophage. Membagi dosis penggunaan per hari dan menggunakan Glucophage saat atau setelah makan dapat membantu mengurangi efek samping. Apabila gejala berlanjut, **hentikan penggunaan Glucophage dan hubungi dokter Anda.**

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. Ini adalah komplikasi serius yang sangat jarang terjadi terutama saat ginjal Anda tidak berfungsi dengan baik.
  Gejala asidosis laktat tidak spesifik (lihat 'Peringatan dan Pencegahan')
- Abnormalitas saat pengukuran fungsi hati atau hepatitis (inflamasi pada hati; yang dapat menyebabkan kelelahan, kehilangan nafsu makan, penurunan berat badan, dengan atau tanpa penguningan kulit atau bagian putih pada mata). Jika hal ini terjadi pada Anda, **hentikan penggunaan Glucophage dan hubungi dokter**.
- Reaksi pada kulit seperti eritema, gatal, atau ruam.

Anak-anak dan remaja
Data yang terbatas pada anak-anak dan remaja menunjukkan bahwa kejadian yang tidak diinginkan memiliki kesamaan dengan yang terjadi pada pasien dewasa.

Pelaporan Efek Samping
Jika Anda mengalami efek samping apapun, bicarakan dengan dokter atau apoteker Anda. Juga termasuk kemungkinan efek samping yang tidak tercantum dalam petunjuk ini, 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

Simpan obat Glucophage jauh dari jangkauan anak-anak. Jika anak-anak mendapatkan pengobatan Glucophage, orang tua dan pengasuh dianjurkan untuk mengawasi bagaimana obat ini digunakan.

Simpan di tempat kering pada suhu di bawah 30 ^{o}C.

DISETUJUI OLEH BPOM: 05/06/2026

ID: EREG10014912600069
EREG10014912600070

Jangan minum obat setelah tanggal kedaluwarsa berakhir, yang tertera pada kemasan setelah tulisan 'EXP'. Tanggal kedaluwarsa mengacu pada hari terakhir bulan tersebut.

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

Apa Kandungan Glucophage
Zat aktif obat adalah metformin hydrochloride.

Glucophage 500 mg
- Satu tablet salut selaput mengandung 500 mg metformin hydrochloride setara dengan 390 mg metformin base.
- Bahan lainnya adalah povidone K30, magnesium stearate, hypromellose.

Glucophage 850 mg
- Satu tablet salut selaput mengandung 850 mg metformin hydrochloride setara dengan 662.9 mg metformin base.
- Bahan lainnya adalah povidone K30, magnesium stearate, hypromellose.

Seperti Apa Glucophage dan Isi Kemasannya
Tablet salut selaput Glucophage 500 mg berbentuk bulat berwarna putih, cembung, tercetak *GL 500* di salah satu sisi tablet.

Tablet salut selaput Glucophage 850 mg berbentuk bulat berwarna putih, cembung, tercetak *GL 850* di salah satu sisi tablet.

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® 500 mg, Dus, 10 blister @ 10 tablet salut selaput
Reg. No. DKL9815807217A1

Glucophage® 850 mg, Dus, 15 blister @ 8 tablet salut selaput
Reg. No. DKL9815807217B1

HARUS DENGAN RESEP DOKTER

Tanggal Perubahan Informasi
Informasi Untuk Pasien ini selaras dengan *SmPC based on CCDS version 12.0 (14-Feb-2025)*
Persetujuan BPOM terhadap pembaruan terakhir: DD Month YYYY

DISETUJUI OLEH BPOM: 05/06/2026

ID: EREG10014912600069
EREG10014912600070