Glucovance®

Metformin hydrochloride - Glibenclamide

Combinations of oral blood glucose lowering drugs

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Glucovance® 250 mg/1.25 mg: each film-coated tablet contains Metformin hydrochloride 250 mg with Glibenclamide 1.25 mg.

Glucovance® 500 mg/2.5 mg: each film-coated tablet contains Metformin hydrochloride 500 mg with Glibenclamide 2.5 mg.

Glucovance® 500 mg/5 mg: each film-coated tablet contains Metformin hydrochloride 500 mg with Glibenclamide 5 mg.

Glucovance® 1000 mg/5 mg: each film-coated tablet contains Metformin hydrochloride 1000 mg with Glibenclamide 5 mg.

2. PHARMACEUTICAL FORM

Film-coated tablet.

3. CLINICAL PARTICULARS

3.1 Indications

Glucovance® 250 mg/1.25 mg, Glucovance® 500 mg/2.5 mg

Glucovance is indicated as initial therapy, as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes with HbA1c above 8% whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone.

Glucovance® 250 mg/1.25 mg, Glucovance® 500 mg/2.5 mg, Glucovance® 500 mg/5 mg, Glucovance® 1000 mg/5 mg

Glucovance is indicated as second-line therapy when diet, exercise, and initial treatment with a Sulfonylurea or Metformin do not result in adequate glycemic control in patients with type 2 diabetes with HbA1c above 8%.

3.2 Posology and Method of Administration

General Considerations

Dosage of Glucovance must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended daily dose of 2000 mg Metformin/20 mg Glibenclamide. Glucovance should be given with meals and should be initiated at a low dose, with gradual dose escalation as described below, in order to avoid hypoglycemia (largely due to Glibenclamide), to reduce GI side effects (largely due to Metformin), and to permit determination of the minimum effective dose for adequate control of blood glucose for the individual patient.

With initial treatment and during dose titration, appropriate blood glucose monitoring should be used to determine the therapeutic response to Glucovance and to identify the minimum effective dose for the patient. Thereafter, HbA1c should be measured at intervals of approximately 3 months to assess the effectiveness of therapy. The therapeutic goal in all patients with type 2 diabetes is to decrease FPG, PPG, and HbA1c to normal or as near normal as possible. Ideally, the response to therapy should be

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evaluated using HbA1c (glycosylated hemoglobin), which is a better indicator of long-term glycemic control than FPG alone.

No studies have been performed specifically examining the safety and efficacy of switching to Glucovance therapy in patients taking concomitant Glibenclamide (or other Sulfonylurea) plus Metformin. Changes in glycemic control may occur in such patients, with either hyperglycemia or hypoglycemia possible. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring.

Glucovance As Initial Therapy
Recommended starting dose: 250 mg/1.25 mg once or twice daily with meals.

For patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone, the recommended starting dose of Glucovance is 250 mg/1.25 mg once a day with a meal. As initial therapy in patients with baseline HbA1c >9% or an FPG >200 mg/dL, a starting dose of Glucovance 250 mg/1.25 mg twice daily with the morning and evening meals may be used. Dosage increases should be made in increments of 250 mg/1.25 mg per day every twice weeks up to the minimum effective dose necessary to achieve adequate control of blood glucose. In clinical trials of Glucovance as initial therapy, there was no experience with total daily doses greater than 2000 mg/10 mg per day.

Glucovance Use in Previous Treated Patients (Second-Line Therapy)
Recommended starting dose: 500 mg/2.5 mg or 500 mg/5 mg twice daily with meals.

For patients already treated with a combination of Metformin and Glibenclamide, two tablets of Metformin hydrochloride/Glibenclamid 500 mg/2.5 mg can be replaced by one tablet of Glucovance 1000 mg/5 mg.

For patients not adequately controlled on either Glibenclamide (or another Sulfonylurea) or Metformin alone, the recommended starting dose of Glucovance is 500 mg/2.5 mg or 500 mg/5 mg twice daily with the morning and evening meals. In order to avoid hypoglycemia, the starting dose of Glucovance should not exceed the daily doses of Glibenclamide or Metformin already being taken. The daily dose should be titrated in increments of no more than 500 mg/5 mg up to the minimum effective dose to achieve adequate control of blood glucose or to a maximum dose of 2000 mg/20 mg per day.

For patients previously treated with combination therapy of Glibenclamide (or another Sulfonylurea) plus Metformin, if switched to Glucovance, the starting dose should not exceed the daily dose of Glibenclamide (or equivalent dose of another Sulfonylurea) and Metformin already being taken. Patients should be monitored closely for signs and symptoms of hypoglycemia following such a switch and the dose of Glucovance should be titrated as described above to achieve adequate control of blood glucose.

When Glucovance is co-administered with a bile acid sequestrant, it is recommended that Glucovance should be administered at least 4 hours prior to the bile acid sequestrant in order to minimize the risk of reduced absorption (*see section Drug Interactions*).

Pediatric use
Safety and effectiveness of Glucovance in pediatric patients have not been established.

Geriatric use
Of the 642 patients who received Glucovance in double-blind clinical studies, 23.8% were 65 and older while 2.8% were 75 and older. Of the 1302 patients who received Glucovance in open-label clinical studies, 20.7% were 65 and older while 2.5% were 75 and older. No overall differences in effectiveness

or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Metformin hydrochloride is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, Glucovance should only be used in patients with normal renal function. Because aging is associated with reduced renal function, Glucovance should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of Glucovance.

3.3 Contraindications

Glucovance (Glibenclamide and Metformin hydrochloride tablets) is contraindicated in patients with:

- Hypersensitivity to Metformin hydrochloride or Glibenclamide or other Sulfonylurea(s) and Sulfonamide(s) or to any of the excipients listed in section List of excipients.
- Diabetic pre-coma.
- Any type of metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).
- Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL (males), ≥ 1.4 mg/dL (females), or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicermia.
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as decompensated heart failure, respiratory failure, recent myocardial infarction, shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.
- Porphyria.
- Lactation.
- In association with Miconazole.

3.4 Special Warnings and 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.

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 Contraindication and Drug 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.

The reported incidence of lactic acidosis in patients receiving Metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency,

including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking Metformin and by use of the minimum effective dose of Metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Glucovance treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, Glucovance should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, Glucovance should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking Glucovance, since alcohol potentiates the effects of Metformin hydrochloride on lactate metabolism. In addition, Glucovance should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Glucovance should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood Metformin levels may be useful. Once a patient is stabilized on any dose level of Glucovance, gastrointestinal symptoms, which are common during initiation of therapy with Metformin, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking Glucovance do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking Glucovance, the drug shoud be discontinued immediately and general supportive measures promptly instituted. Because Metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated Metformin. Such management often results in prompt reversal of symptoms and recovery.

Impaired hepatic function
Since impaired hepatic function has been associated with some cases of lactic acidosis, Glucovance should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Change in clinical status of patients with previously controlled type 2 diabetes
A patient with type 2 diabetes previously well controlled on Metformin who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes

and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and Metformin levels. If acidosis of either form occurs, Glucovance must be stopped immediately and other appropriate corrective measures initiated.

Hypoglycemia
Glucovance is capable of producing hypoglycemia or hypoglycemic symptoms, therefore, proper patient selection, dosing, and instructions are important to avoid potential hypoglycemic episodes. The risk of hypoglycemia is increased when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents or ethanol. Renal or hepatic insufficiency may cause elevated drug levels of both Glibenclamide and Metformin hydrochloride and the hepatic insufficiency may also diminish gluconeogenic capacity, both of which increase the risk of hypoglycemic reactions. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Alcohol intake
Alcohol is known to potentiate the effect of Metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute chronic, while receiving Glucovance. Due to its effect on the gluconeogenic capacity of the liver, alcohol may also increase the risk of hypoglycemia.

Elderly patients
Age of 65 years and older has been identified as a risk factor for hypoglycemia in patients treated with Sulfonylureas. Hypoglycemia can be difficult to recognize in the elderly. Starting and maintenance doses of Glibenclamide must be carefully adjusted to reduce the risk of hypoglycaemia (*see Posology and Method of Administration*).

Cardiac Function
Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, Glucovance may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, Glucovance is contraindicated (*see section Contraindication*).

Renal Function
Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive Glucovance. In patients with advanced age, Glucovance should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those ≥ 80 years of age, renal function should be monitored regularly and, generally, Glucovance should not be titrated to the maximum dose. Before initiation of Glucovance therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and Glucovance discontinued if evidence of renal impairment is present.

Use of concomitant medications that may affect renal function or metformin disposition
Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion, should be used with caution.

Administration of Iodinated Contrast Agents

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving Metformin. Therefore, in patients in whom any such study is planned, Glucovance should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been reevaluated and found to be normal.

Surgery
Glucovance therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Vitamin B12 levels
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.

Other Precautions
Treatment of patients with G6PD-deficiency with Sulfonylurea agents can lead to haemolytic anaemia. Since Glibenclamide belongs to the chemical class of Sulfonylurea drugs, caution is recommended when using Glucovance in patients with G6PD-deficiency and a non-Sulfonylurea alternative may be considered.

Glucovance contains Lactose. Therefore its use is not recommended in patients with rare hereditary problems of Galactose-intolerance, the Lapp lactase deficiency or Glucose-Galactose malabsorption.

3.5 Interaction with Other Medicinal Products and Other Forms of Interaction
Contraindicated Combination
Related to Glibenclamide
Miconazole
Increase in the hypoglycaemic effect with possible onset of hypoglycaemic manifestations (*see section Contraindication*).

Combination Not Recommended
Related to Sulfonylurea(s)
Alcohol
Increase of the hypoglycaemic reaction (inhibition of compensation reactions), which may facilitate the onset of a hypoglycaemic coma manifestations (*see section Contraindication*).

Avoid consumption of alcohol and alcohol-containing medications.

Related to All Antidiabetic Agents
Danazol
If the combination cannot avoided, warn the patient and step up self-monitoring of blood glucose. Possibly adjust the dosage of the antidiabetic treatment during treatment with Danazol and after its withdrawal.

Related to Metformin
Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

Iodinated contrast agents
Glucovance must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections Special Warnings and Precautions for Use.

Combinations Requiring Precautions
Related to All Antidiabetic Agents
Chlorpromazine
At high dosages (100 mg per day of Chlorpromazine), elevation in blood glucose (reduction in release of Insulin).

Precaution for use: warn the patient and step up self-monitoring of blood glucose. Possibly adjust the dosage of the antidiabetic treatment with the nueroleptic and after its withdrawal.

Corticosteroids (glucocorticoids) and tetracosactides (sytemic and local routes)
Elevation in blood glucose, sometimes accompanied by ketosis (decreased carbohydrate tolerance with corticosteroids).

Precaution for use: warn the patient and step up self-monitoring of blood glucose. Possibly adjust the dosage of the antidiabetic treatment with the nueroleptic and after its withdrawal.

Beta$_2$-agonists
Elevation in blood glucose due to the beta$_2$-agonists.

Precaution for use: warn the patient, step up blood glucose monitoring and possibly transfer to Insulin therapy.

Drugs reducing glycemic control
Certain drugs tend to produce hyperglycemia and may lead to loss of blood glucose control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isonazid. When such drugs are administrated to a patient receiving Glucovance, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving glucovance, the patient should be observed closely for hypoglycemia.

Drugs that potentiate the hypoglycemic action of Glucovance
The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, beta-adrenergic blocking agents, and potentially with ciprofloxacin. When such drugs are administered to a patient receiving Glucovance, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving Glucovance, the patient should be observed closely for loss of blood glucose control.

Related to Metformin
Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with Metformin, close monitoring of renal function is necessary.

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, Declastasvir, 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.

Related to Glibenclamide
Beta-blockers
All beta-blockers mask some of the symptoms of hypoglycaemia: palpitations and tachycardia; Most non-cardioselective beta-blockers increase the incidence and severity of hypoglycaemia. Warn the patient and step up blood glucose self-monitoring, especially at the start of treatment.

Angiotensin converting enzyme inhibitors (e.g. Captopril, Enalapril)
ACE inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of Glucovance during therapy with an ACE inhibitor and upon its discontinuation.

Fluconazole
Increase in the half-life of sulfonylurea with possible onset of hypoglycaemic manifestations.

Warn the patient and step up blood glucose self monitoring, and possibly adjust the dosage of the antidiabetic treatment during treatment with Fluconazole and after its withdrawal.

Bosentan
Risk of decreased hypoglycaemic affect of Glibenclamide because Bosentan reduces plasma concentration of Glibenclamide. An increased risk of liver enzyme elevations was reported in patients receiving Glibenclamide concomitantly with Bosentan.

Warn the patient, set-up monitoring of glycaemia and liver enzymes and adjust the dosage of the antidiabetic treatment if necessary.

Bile acid sequestrants
When co-administered simultaneously the plasma concentration of Glibenclamide is reduced which may lead to a reduced hypoglycaemic effect. This effect was not observed if Glibenclamide is given in a certain period of time before taking the other medicine. It is recommended that Glucovance should be administered at least 4 hours prior a bile acid sequestrant.

3.6 Fertility, Pregnancy and Lactation
Pregnancy
Teratogenic Effects: Pregnancy Category B

Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that Insulin be used during pregnancy to maintain blood glucose as close to normal as possible. Because animal reproduction studies are not always predictive of human response, Glucovance should not be used during pregnancy unless clearly needed.

There are no adequate and well-controlled studies in pregnant women with Glucovance or its individual components. No animal studies have been conducted with the combined products in Glucovance. The following data are based on findings in studies performed with the individual products.

Glibenclamide
Reproduction studies were performed in rats and rabbits at doses up to 500 times the maximum recommended human daily dose of 20 mg of the Glibenclamide component of Glucovance based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to Glibenclamide.

Metformin hydrochloride
Metformin alone was not teratogenic in rats or rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times the maximum recommended human daily dose of 2000 mg of the Metformin component of Glucovance based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentration demonstrated a partial placental barrier to Metformin.

Nonteratogenic Effects
Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a Sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. It is not recommended that Glucovance be used during pregnancy. However, if it is used, Glucovance should be discontinued at least two weeks before the expected delivery date.

Lactation
Although it is not known whether Glibenclamide is excreted in human milk, some Sulfonylurea drugs are known to be excreted in human milk. Studies in lactating rats show that Metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue Glucovance, taking into account the importance of the drug to the mother. If Glucovance is discontinued, and if diet alone is inadequate for controlling blood glucose, Insulin therapy should be considered.

3.7 Undesirable Effects
During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take Glucovance in 2 or 3 daily doses and to increase slowly the doses. Transient visual disturbances may occur at the start of treatment due to a decrease in glycaemia levels.

The following adverse reactions may occur under treatment with Glucovance. 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.

Blood and Lymphatic System Disorders
These are reversible upon treatment discontinuation.
Rare: Leukopenia, thrombocytopenia.
Very rare: Agranulocytosis, haemolytic anaemia, bone marrow aplasia and pancytopenia.

Metabolism and Nutrition Disorders
Hypoglycaemia (*see section Special Warnings and Special Precautions for Use*).
Common: Vitamin B12 decrease/deficiency (*see section Special Warnings and Special Precautions for Use*).
Uncommon: Crises of hepatic porphyria and porphyria cutanea.
Very rare: Lactic acidosis (*see section Special Warnings and Special Precautions for Use*).
Disulfiram-like reaction with alcohol intake.

Nervous System Disorders
Common: Taste disturbance.

Eye Disorders
Transient visual disturbances may occur at the start of treatment due to a decrease in glycaemia levels.

Gastrointestinal disorders:
Very common: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur more frequently during treatment initiation and resolve spontaneously in most cases. To prevent them, it is recommended that Glucovance be taken in 2 or 3 daily doses. A slow increase of the dose may also improve gastrointestinal tolerability.

Skin and Subcutaneous Tissue Disorders
A cross reactivity to sulfonamide(s) and their derivatives may occur.
Rare: Skin reactions such as pruritus, urticaria, maculopapular rash.
Very rare: Cutaneous or visceral allergic angiitis, erythema multiforme, exfoliative dermatitis, photosensitization, urticaria evolving to shock.

Hepatobiliary Disorders
Very rare: Liver function test abnormalities or hepatitis requiring treatment discontinuation.

Investigations
Uncommon: Average to moderate elevations in serum urea and creatinine concentrations.
Very rare: Hyponatremia.

3.8 Overdose
Glibenclamide
Overdosage of Sulfonylureas, including Glibenclamide tablets, can produce hypoglycemia. Mild hypoglycemic symptoms, without loss of consciousness or neurological findings, should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnoses or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery.

Metformin hydrochloride
Hypoglycemia has not been seen even with ingestion of up to 85 grams of Metformin hydrochloride, although lactic acidosis has occurred in such circumstances. Metformin is dialyzable with a clearance

of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom Metformin overdosage is suspected.

4. PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamic Properties

Metformin is a biguanide with anti-hyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate Insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:
(1) by reducing hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
(2) in muscle, by increasing Insulin sensitivity, improving peripheral glucose uptake and utilisation
(3) and by delaying intestinal glucose absorption.

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

In humans, independently of its action on glycaemia, Metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: Metformin reduces total cholesterol, LDL-cholesterol and triglyceride levels. In clinical trials conducted so far with combination therapy with Metformin and Glibenclamide, these favourable effects on lipid metabolism have not been shown.

Glibenclamide is a second generation Sulfonylurea with a medium half-life: it causes acute lowering of blood glucose by stimulating the release of Insulin by the pancreas, this effect being dependent on the presence of functioning beta cells in the islets of Langerhans.

The stimulation of Insulin secretion by Glibenclamide in response to a meal is of major importance.

The administration of Glibenclamide to diabetics induces an increase in the postprandial Insulin-stimulating response. The increased postprandial responses in Insulin and C-peptide secretion persist after at least 6 months of treatment.

Metformin and Glibenclamide have different mechanisms and sites of action, but their action is complementary. Glibenclamide stimulates the pancreas to secrete Insulin, while Metformin reduces cell resistance to Insulin by acting on peripheral (skeletal muscle) and hepatic sensitivity to Insulin.

Results from controlled, double blind clinical trials versus reference products in the treatment of type 2 diabetes inadequately controlled by monotherapy with Metformin or Glibenclamide combined with diet and exercise, have demonstrated that the combination had an additive effect on glucose regulation.

Paediatric Patients

In a 26-week, active controlled, double-blind, clinical study performed in 167 paediatric patients aged 9 to 16 years with type 2 diabetes not adequately controlled with diet and exercise, with or without an oral antidiabetic treatment, a fixed combination of Metformin hydrochloride 250 mg and Glibenclamide 1.25 mg was not shown more effective to either Metformin hydrochloride or Glibenclamide in reducing HbA1c from baseline. Therefore, Glucovance should not be used in paediatric patients.

4.2 Pharmacokinetic Properties

Related to the Combination
The bioavailability of Metformin and Glibenclamide in the combination is similar to that noted when one tablet of Metformin and one tablet of Glibenclamide are taken simultaneously. The bioavailability of Metformin in the combination is unaffected by the ingestion of food. The bioavailability of Glibenclamide in the combination is unaffected by the ingestion of food, but the absorption speed of Glibenclamide is increased by eating.

Related to Metformin
Absorption
After an oral dose of Metformin, maximum plasma concentration (C_{max}) is reached in 2.5 hours (t_{max}). Absolute bioavailability of a 500 mg or 850 mg Metformin 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 absorption is saturable and incomplete. It is assumed that the pharmacokinetics of Metformin absorption is non-linear. At the usual Metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 mcg/mL. In controlled clinical trials, maximum Metformin plasma levels (C_{max}) did not exceed 4 mcg/mL, even at maximum doses.

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 from 63 to 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.

Related to Glibenclamide
Absorption
Glibenclamide is very readily absorbed (>95%) following oral administration. The peak plasma concentration is reached in about 4 hours.

Distribution
Glibenclamide is extensively bound to plasma albumin (99%), which may account for certain drug interactions.

Metabolism
Glibenclamide is completely metabolised in the liver to two metabolites. Hepatocellular failure decreases Glibenclamide metabolism and appreciably slows down its excretion.

Excretion
Glibenclamide is excreted in the form of metabolites via biliary route (60%) and urine (40%), elimination being complete within 45 to 72 hours. Its terminal elimination half-life is 4 to 11 hours.

Biliary excretion of the metabolites increases in cases of renal insufficiency, according to the severity of renal impairment until a creatinine clearance at 30 mL/min. Thus, Glibenclamide elimination is unaffected by renal insufficiency as long as the creatinine clearance remains above 30 mL/min.

Special Populations

Patients with Type 2 Diabetes

Multiple-dose studies with Glibenclamide in patients with type 2 diabetes demonstrate drug level concentration-time curves similar to single-dose studies, indicating no buildup of drug in tissue depots.

In the presence of normal renal function, there are no differences between single-or multiple-dose pharmacokinetics of Metformin between patients with type 2 diabetes and normal subjects (*see Table 1*), nor is there any accumulation of Metformin in either group at usual clinical doses.

Hepatic Insufficiency

No pharmacokinetic studies have been conducted in patients with hepatic insufficiency for either Glibenclamide or Metformin.

Renal Insufficiency

No information is available on the pharmacokinetics of Glibenclamide in patients with renal insufficiency.

In patients with decreased renal function (based on creatinine clearance), the plasma and blood half-life of Metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance (*see Table 1; also see Special Warnings and Precautions for Use*).

Geriatrics

There is no information on the pharmacokinetics of Glibenclamide in elderly patients.

Limited data from controlled pharmacokinetic studies of Metformin in healthy elderly subjects suggest that total plasma clearance is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in Metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (*see Table 1*).

Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

Table 1. Select Mean (±SD) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of Metformin

Subject Groups: Metformin Dose[a] (number of subjects)	Cmax[b] (mcg/mL)	Tmax[c] (hrs)	Renal Clearance (mL/min)
Healthy, nondiabetic adults:			
500 mg SD[d] (24)	1.03 (±0.33)	2.75 (±0.81)	600 (±132)
850 SD (74)[e]	1.60 (±0.38)	2.64 (±0.82)	552 (±139)
850 mg t.i.d. for 19 doses[f] (9)	2.01 (±0.42)	1.79 (±0.94)	642 (±173)
Adults with type 2 diabetes:			
850 SD (23)	1.48 (±0.5)	3.32 (±1.08)	491 (±138)
50 mg t.i.d. for 19 doses[f] (9)	1.90 (±0.62)	2.01 (±1.22)	550 (±160)
Elderly[g], healthy nondiabetic adults:			
850 mg SD (12)	2.45 (±0.70)	2.71 (±1.05)	412 (±98)
Renal-impaired adults: 850 mg SD			
Mild (CL_{cr}[h] 61-90 mL/min) (5)	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Moderate (CL_{cr} 31-60 mL/min) (4)	4.12 (±1.83)	3.75 (±0.50)	108 (±57)

Severe (CL_{cr} 10-30 mL/min) (6)	3.93 (±0.92)	4.01 (±1.10)	130 (±90)

[a]All doses given fasting except the first 18 doses of the multiple-dose studies
[b]Peak plasma concentration
[c]Time to peak plasma concentration
[d]SD = single dose
[e]Combined results (average means) of five studies: mean age 32 years (range 23-59 years)
[f]Kinetic study done following dose 19, given fasting
[g]Elderly subjects, mean age 71 years (range 65 – 81 years)
[h]CL_{cr} = creatinine clearance normalized to body surface area of 1.73 m^2

Pediatrics
There were no differences in pharmacokinetics of Glibenclamide and Metformin between paediatric patients and weight-and gender-matched healthy adults.

Gender
There is no information on the effect of gender on the pharmacokinetics of Glibenclamide.

Metformin pharmacokinetic parameters did not differ significantly in subjects with or without type 2 diabetes when analyzed according to gender (males = 19, females = 16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of Metformin was comparable in males and females.

Race
No information is available on race differences in the pharmacokinetics of Glibenclamide

No studies of Metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of Metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51), and Hispanics (n=24).

Interaction Studies
Furosemide
A single-dose, Metformin-Furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the Metformin plasma and blood Cmax by 22% and blood AUC by 15%, without any significant change in Metformin renal clearance. When administered with Metformin, the Cmax and AUC of Furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in Furosemide renal clearance. No information is available about the interaction of Metformin and Furosemide when co-administered chronically.

Nifedipine
A single-dose, Metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma Metformin Cmax and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine Tmax and half-life were unaffected. Nifedipine appears to enhance the absorption of Metformin. Metformin had minimal effects on nifedipine.

Cationic drugs
Cationic drugs (e.g. Amiloride, Digoxin, Morphine, Procainamide, Quinidine, Quinine, Ranitidine, Triamterene, Trimethoprim, or Vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with Metformin by competing for common renal tubular transport systems. Such interaction between Metformin and oral Cimetidine has been observed in normal healthy

volunteers in both single-and multiple-dose, Metformin-Cimetidine drug interaction studies, with a 60% increase in peak Metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood Metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on Cimetidine pharmacokinetics. Although such interactions remain theoretical (except for Cimetidine), careful patient monitoring and dose adjustment of Glucovance and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other
In healthy volunteers, the pharmacokinetics of Metformin and propranolol and Metformin and Ibuprofen were not affected when co-administered in single-dose interaction studies.

4.3 Preclinical Safety Data
No preclinical studies have been performed on the combination product. Preclinical evaluation of the constituents Metformin and Glibenclamide revealed no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential.

Animal studies on Metformin and Glibenclamide do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (*see section Fertility, Pregnancy and Lactation*).

Carcinogenesis, Mutagenesis, Impairment of Fertility
No animal studies have been conducted with the combined products in Glucovance. The following data are based on findings in studies performed with the individual products.

Glibenclamide
Studies in rats with Glibenclamide alone at doses up to 300 mg/kg/day (approximately 145 times the maximum recommended human daily dose of 20 mg for the Glibenclamide component of Glucovance based on body surface area comparisons) for 18 months revealed no carcinogenic effects. In a two-year oncogenicity study of Glibenclamide in mice, there was no evidence of treatment-related tumors.

There was no evidence of mutagenic potential of Glibenclamide alone in the following *in vitro* tests: Salmonella microsome test (Ames test) and in the DNA damage/alkaline elution assay.

Metformin hydrochloride
Long-term carcinogenicity studies were performed with Metformin alone in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg of the Metformin component of Glucovance based on body surface area comparisons. No evidence of carcinogenicity with Metformin alone was found in either male or female mice. Similarly, there was no tumorigenic potential observed with Metformin alone in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day of Metformin alone.

There was no evidence of a mutagenic potential of Metformin alone in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by Metformin alone when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose of the Metformin component of Glucovance based on body surface area comparisons.

5. PHARMACEUTICAL PARTICULARS

5.1 List of excipients

Tablet core

Microcrystalline cellulose, Sodium croscarmellose, Povidone K30, Magnesium stearate.

Film-coating

Glucovance® 250 mg/1.25 mg: Opadry OY-L-22903 (yellow) (Lactose monohydrate, Hypromellose, Titanium dioxide, Macrogol, Talc, Yellow iron oxide)

Glucovance® 500 mg/2.5 mg: Opadry OY-L-24808 (orange) (Lactose monohydrate, Hypromellose, Titanium dioxide, Macrogol, Yellow iron oxide, Red iron oxide, Black iron oxide).

Glucovance® 500 mg/5 mg: Opadry 31-F-22700 (yellow) (Lactose monohydrate, Hypromellose, Titanium dioxide, Macrogol, Yellow iron oxide, Red iron oxide, Quinoline Yellow Lake).

Glucovance® 1000 mg/5 mg: Opadry II OY-L-28900 (white) (Lactose monohydrate, Hypromellose, Titanium dioxide, Macrogol).

5.2 Shelf-life

The expiry date is indicated on the packaging.

5.3 Storage Condition

Store below 30ºC.

5.4 Package Quantities and Registration Numbers

Glucovance® 250 mg/1.25 mg	Box, 8 blisters @ 15 film-coated tablets Reg. No. DKL1715809217A1
Glucovance® 500 mg/2.5 mg	Box, 8 blisters @ 15 film-coated tablets Reg. No. DKL1715809217B1
Glucovance® 500 mg/5 mg	Box, 8 blisters @ 15 film-coated tablets Reg. No. DKL1715809217C1
Glucovance® 1000 mg/5 mg	Box, 4 blisters @ 15 film-coated tablets Reg. No. DKI1801600117D1

On medical prescription only
HARUS DENGAN RESEP DOKTER

Glucovance® 250 mg/1.25 mg, Glucovance® 500 mg/2.5 mg, Glucovance® 500 mg/5 mg
Manufactured by
PT Merck Tbk, Jakarta, Indonesia

Under licence from
Merck Sante S.A.S., Lyon, France

Glucovance® 1000 mg/5 mg
Manufactured by
Merck Sante S.A.S., Semoy, France

Imported and secondary packed by

PT Merck Tbk, Jakarta, Indonesia

PI based on CCDS ver 7.0
BPOM Approval of the Update 15Dec2022

DW/ia/3Nov2022

Glucovance®

Metformin hydrochloride - Glibenclamide

Baca petunjuk ini dengan seksama sebelum mulai minum obat ini karena mengandung informasi penting untuk Anda.
- 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 Glucovance dan apa kegunaannya

Glucovance terdiri dari dua obat antidiabetes, yang termasuk dalam kelompok obat-obatan yang disebut Biguanide (Metformin hydrochloride) dan Sulfonylurea (Glibenclamide).

Insulin adalah hormon yang memungkinkan jaringan tubuh mengambil glukosa (gula) dari darah dan menggunakannya untuk menghasilkan energi atau menyimpannya untuk penggunaan di waktu mendatang. Pasien dengan diabetes mellitus tipe 2 (yaitu diabetes tidak tergantung insulin) tidak menghasilkan insulin yang cukup di pankreas atau tubuhnya tidak merespon dengan benar terhadap insulin yang dihasilkannya. Hal ini menyebabkan peningkatan kadar glukosa dalam darah. Glucovance membantu mengurangi gula darah pasien ke tingkat normal.

Glucovance digunakan untuk pengobatan oral (melalui mulut, diminum) diabetes mellitus tipe 2 pada pasien dewasa apabila pengaturan pola makan, olah raga dan pengobatan dengan Sulfonylurea atau Metformin tidak menghasilkan pengontrolan kadar gula darah yang cukup. Pengobatan ini digunakan untuk menggantikan pemberian kombinasi dua zat aktif Glucovance (Metformin hydrochloride dan Glibenklamide) secara terpisah pada pasien yang sebelumnya diobati dengan kombinasi ini, dan efektif dalam mengendalikan kadar glukosa darah pasien.

2 Apa yang perlu Anda ketahui sebelum Anda minum Glucovance

Jangan minum Glucovance jika Anda:
- Alergi (hipersensitif) terhadap Metformin hydrochloride, Glibenklamide atau Sulfonamide lainnya atau bahan lain dari Glucovance (tercantum dalam bagian 6).
- Memiliki masalah fungsi ginjal atau hati.
- Memiliki diabetes tak terkontrol, disertai, contohnya, hiperglikemia parah (glukosa darah tinggi), mual, muntah, diare, asidosis laktat (lihat 'Risiko asidosis laktat' di bawah) atau ketoasidosis. Ketoasidosis adalah kondisi di mana senyawa 'Ketone tubuh' terakumulasi dalam darah yang dapat menyebabkan

diabetetik pra koma. Gejalanya meliputi nyeri dalam perut, napas terengah-engah, mengantuk, atau napas menjadi bau buah yang tidak biasa.
- Memiliki infeksi berat (misalnya infeksi saluran pernapasan atau infeksi saluran kemih).
- Mengalami dehidrasi (misalnya karena diare persisten atau berat, muntah yang berulang)
- Sedang dirawat karena gagal jantung akut, baru saja mengalami serangan jantung, mengalami masalah peredaran darah yang parah atau kesulitan bernapas. Kondisi ini dapat menyebabkan kekurangan pasokan oksigen ke jaringan tubuh sehingga membuat Anda terkena risiko asidosis laktat.
- Menderita porfiria (penyakit keturunan yang jarang terjadi karena kekurangan enzim yang menyebabkan tubuh memproduksi dan mengeluarkan porfirin berlebih, yaitu komponen yang digunakan untuk pembuatan pigmen darah pembawa oksigen).
- Sedang menggunakan Miconazole (obat untuk mengobati infeksi jamur tertentu) bahkan untuk penggunaan lokal.
- Minum alkohol secara berlebihan (baik setiap hari atau hanya dalam waktu tertentu)
- Sedang menyusui.

Pastikan untuk meminta saran dokter jika Anda:
- Perlu melakukan pemeriksaan seperti sinar-X atau scan yang melibatkan suntikan obat kontras yang mengandung iodium ke dalam aliran darah Anda.
- Perlu menjalani operasi di bawah anestesi total, spinal, atau peridural.

Anda harus berhenti meminum Glucovance untuk jangka waktu tertentu sebelum dan sesudah pemeriksaan atau tindakan operasi. Dokter Anda akan memutuskan apakah Anda memerlukan perawatan lain untuk saat ini. Penting bagi Anda mengikuti instruksi dokter dengan tepat.

Peringatan dan tindakan pencegahan
Bicarakan dengan dokter Anda sebelum meminum Glucovance.

Risiko asidosis laktat
Glucovance dapat menyebabkan komplikasi yang sangat jarang, namun serius yang disebut asidosis laktat, terutama jika ginjal Anda tidak berfungsi dengan baik. Risiko asidosis laktat juga meningkat dengan diabetes yang tidak terkontrol, puasa berkepanjangan atau asupan alkohol, dehidrasi (lihat informasi lebih lanjut di bawah), gangguan hati atau kondisi medis apapun yang mana salah satu bagian tubuh kekurangan pasokan oksigen (misalnya penyakit jantung akut parah).

Jika salah satu kondisi di atas terjadi pada Anda, hubungi dokter untuk instruksi lebih lanjut.

Hentikan penggunaan Glucovance untuk sesaat jika Anda memiliki kondisi yang berkaitan dengan dehidrasi (kehilangan cairan tubuh yang signifikan) seperti muntah berat, diare, demam, atau Anda minum air kurang dari normal. Bicarakan dengan dokter untuk instruksi lebih lanjut.

Hentikan penggunaan Glucovance dan hubungi dokter atau rumah sakit terdekat jika Anda mengalami gejala asidosis laktat, yang mana kondisi ini dapat menyebabkan koma. Gejala asidosis laktat meliputi muntah, sakit perut (nyeri perut), kram otot, merasa tidak sehat disertai kelelahan berlebih, kesulitan bernapas, serta suhu tubuh dan detak jantung turun.

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

Jika Anda akan mendapatkan tindakan operasi besar, Anda harus menghentikan Glucovance selama dan setelah tindakan dalam beberapa waktu. Dokter Anda akan memutuskan kapan Anda harus berhenti dan memulai kembali pengobatan menggunakan Glucovance.

Risiko Hipoglikemia

- Jika Anda mengalami gejala gula darah rendah (hipoglikaemia). Tanda peringatan bisa terjadi tiba-tiba dan bisa termasuk keringat dingin, kulit dingin dan pucat, pusing, sakit kepala, denyut jantung cepat, merasa sakit, merasa sangat lapar, perubahan penglihatan sementara, kantuk, kelelahan dan lemah yang tidak biasa dan merasa lemah, gugup dan tremor, merasa cemas, merasa bingung, kesulitan berkonsentrasi.
- Pasien berusia 65 tahun ke atas sangat sensitif terhadap reaksi hipoglikemik dari Glibenclamide dan karena itu lebih berisiko mengalami hipoglikemia. Pada lansia, gula darah rendah mungkin agak sulit dikenali. Dosis awal dan dosis pemeliharaan Glibenclamide, harus diatur oleh dokter secara cermat untuk menghindari reaksi hipoglikemik.

Jika Anda menyadari gejala-gejala tersebut:
- Pertama, makan tablet glukosa atau makanan dengan kadar gula tinggi (madu, permen, biskuit, jus buah)
- **BERHENTI minum obat ini SEGERA dan HUBUNGI DOKTER Anda secepatnya** di mana Anda mungkin perlu dirawat di rumah sakit untuk mengembalikan glukosa darah Anda, lalu beristirahatlah.

Saran umum: Menginformasikan keluarga, teman, dan kolega Anda untuk membantu Anda dan untuk langsung mencarikan pertolongan medis jika Anda pingsan. Mereka seharusnya tidak memberi Anda makanan atau minuman saat Anda dalam keadaan tidak sadar. Hal tersebut dapat membuat Anda tersedak.

Tingkat gula darah rendah bisa terjadi jika:
- Anda makan terlalu sedikit atau melewatkan makan.
- Diet Anda mengandung kadar gula yang tidak mencukupi atau tidak seimbang.
- Anda minum alkohol.
- Anda berolahraga lebih dari biasanya.
- Anda memiliki masalah hati, ginjal, atau hormon tertentu.
- Dosis obat Anda terlalu tinggi.
- Anda adalah pasien lanjut usia.
- Anda meminum obat-obatan tertentu dan Glucovance pada saat bersamaan (lihat bagian *2 Obat-obatan lainnya dan Glucovance*).

Diskusikan dengan dokter Anda apakah Glucovance adalah pengobatan yang tepat untuk diabetes Anda jika Anda sering mengalami gejala berat gula darah rendah atau jika Anda merasa sulit untuk mengenalinya.
- Jika Anda menderita penyakit menular seperti flu, infeksi saluran pernapasan atau infeksi saluran kemih.
- Jika Anda memiliki kondisi turunan dimana sel darah merah Anda tidak menghasilkan cukup banyak enzim G6PD (kekurangan G6PD), meminum Glucovance dapat menyebabkan sel darah merah Anda dihancurkan terlalu cepat (anemia hemolitik). Beritahu dokter Anda jika Anda memiliki kondisi ini, karena Glucovance mungkin tidak sesuai untuk Anda.
- Lanjutkan untuk mengikuti saran diet yang diberikan dokter Anda dan berolahraga secara teratur saat Anda minum obat ini.
- Konsultasikan dengan dokter Anda secara teratur untuk menguji kadar gula darah Anda dan fungsi ginjal Anda.

Konsultasikan dengan dokter Anda, jika ada situasi di atas yang berlaku untuk Anda dan jika Anda merasa tidak yakin tentang penggunaan obat ini.

Obat-obatan lain dan Glucovance
Saat meminum Glucovance, Anda tidak boleh menggunakan obat berikut ini:
- Miconazole bahkan untuk penggunaan lokal (lihat bagian *2 Jangan minum Glucovance jika Anda*)

- Jika Anda membutuhkan injeksi media kontras ke aliran darah yang mengandung iodium, misalnya akan dilakukan pemeriksaan sinar-X atau scan, Anda harus berhenti minum Glucovance sebelum dan saat proses injeksi. Dokter Anda akan memutuskan kapan Anda harus berhenti dan memulai kembali pengobatan menggunakan Glucovance.

Beritahukan dokter jika Anda sedang menggunakan, baru saja atau akan menggunakan obat lain. Anda mungkin akan lebih memerlukan pemeriksaan kadar gula darah atau fungsi ginjal, atau dokter Anda akan melakukan penyesuaian dosis Glucovance. Penting untuk diperhatikan jika Anda sedang, baru saja, atau akan menggunakan:
- Obat yang meningkatkan produksi urin (diuretic)
- Obat untuk mengobati nyeri dan inflamasi (anti inflamasi non-steroid dan inhibitor COX-2)
- Obat tertentu untuk pengobatan tekanan darah tinggi (inhibitor pengubah angiotensin)
- Beta-blocker (digunakan untuk mengobati berbagai kondisi kardiovaskular, seperti tekanan darah tinggi dan beberapa penyakit lainnya)
- Agonis Beta-2 (digunakan untuk pengobatan asma, seperti Ritodrine, Salbutamol, atau Terbutaline)
- Bosentan (digunakan untuk mengobati hipertensi pulmonal)
- Kortikosteroid dan Tetracosactide (satu kelas hormon yang digunakan untuk mengobati berbagai kondisi, misalnya peradangan parah pada kulit atau asma)
- Fluconazole (digunakan untuk mengobati infeksi jamur tertentu)
- Chlorpromazine (obat neuroleptik, yang mempengaruhi kerja otak Anda)
- Desmopressin (umumnya digunakan untuk mengurangi produksi urin)
- Danazol (digunakan untuk mengobati endometriosis, suatu kondisi dimana lapisan jaringan rahim berada di luar rahim)
- Bile acid sequestrant (obat penurun kolesterol yang digunakan untuk mengurangi kadar kolesterol dalam darah)
- Obat yang dapat mengubah kadar Glucovance dalam darah Anda, terutama jika fungsi ginjal Anda menurun (seperti Verapamil, Rifampicin, Cimetidine, Dolutegravir, Ranolazine, Trimethoprime, Vandetanib, Isavucanazole, Crizotinib, Olaparib)

Tindakan pencegahan khusus dapat mencakup pemantauan glukosa darah sendiri, tes darah, dan modifikasi dosis.

Glucovance dengan Alkohol
Hindari alkohol saat mengkonsumsi Glucovance karena alkohol dapat meningkatkan risiko asidosis laktat (lihat bagian *4 Efek samping yang mungkin terjadi*).

Kehamilan dan Menyusui
Jika Anda hamil atau menyusui, merasa akan hamil atau berencana untuk hamil, mintalah saran dokter Anda sebelum minum obat ini. Selama kehamilan, diabetes harus diobati dengan insulin. Jika Anda tahu bahwa Anda hamil saat minum Glucovance, berkonsultasilah dengan dokter sehingga memungkinkan dokter mengubah pengobatan Anda.

Jangan minum Glucovance jika Anda sedang menyusui atau berencana menyusui bayi Anda.

Mengemudi dan Menjalankan Mesin
Jangan mengemudi atau menjalankan mesin:
- Jika penglihatan Anda kabur. Hal ini bisa terjadi pada awal pengobatan karena kadar gula darah Anda turun.
- Jika Anda merasa gejala gula darah rendah mulai muncul.

Informasi Penting Tentang Kandungan Glucovance

Setiap tablet Glucovance mengandung laktosa. Jika dokter Anda mengatakan bahwa Anda memiliki intoleransi gula tertentu, hubungi dokter sebelum minum obat ini.

3 Bagaimana meminum Glucovance

Selalu minum obat ini sesuai dengan anjuran dokter. Tanyakan kepada dokter atau apoteker jika Anda tidak yakin.

Hanya orang dewasa yang dapat minum obat ini.

Dokter akan menyesuaikan dosis pengobatan Anda tergantung pada pengaruhnya terhadap uji darah Anda.

Terus ikuti saran diet yang diberikan dokter Anda. Glucovance tidak dapat menggantikan manfaat dari gaya hidup sehat.

Makanlah secara teratur dengan asupan gula yang cukup dan seimbang. Hal ini akan menurunkan risiko gula darah yang rendah.

Glucovance sebagai Pengobatan Awal
Dosis awal yang direkomendasikan adalah Glucovance 250 mg/1.25 mg satu atau dua kali sehari.

Glucovance untuk Pasien yang Sebelumnya Telah Menerima Pengobatan Dosis Tunggal
Dosis awal yang biasa sama dengan dosis tunggal Metformin hydrochloride dan Glibenclamide yang telah Anda terima sebelum pengobatan dengan Glucovance. Jika Anda sudah diobati dengan kombinasi Metformin hydrochloride dan Glibenclamide, satu tablet Glucovance 1000 mg/5 mg dapat digunakan untuk menggantikan dua tablet Metformin hydrochloride/Glibenclamide 500 mg/2.5 mg. Jika Anda adalah pasien lanjut usia, dosis awal yang biasa adalah satu tablet Glucovance 500 mg/2.5 mg per hari.

Dosis Harian Maksimum
Dosis harian maksimum Metformin/Glibenclamide yang direkomendasikan adalah 2000 mg/20 mg.

Dokter akan menentukan dosis Glucovance serta jumlah tablet harian yang Anda perlukan.

Penyesuaian Dosis pada Pasien Lanjut Usia
Berhati-hatilah jika Anda adalah pasien lanjut usia. Dosis Glucovance akan dinaikkan dengan hati-hati tergantung kadar gula darah dan fungsi ginjal Anda. Pastikan Anda berkonsultasi dengan dokter secara teratur.

Penggunaan Obat
Minum tablet dengan makanan. Telan tiap tablet utuh dengan segelas air. Jangan menghancurkan atau mengunyah obat sebelum menelan.

Minum tablet
- sekali sehari, di pagi hari (saat sarapan) jika Anda diresepkan 1 tablet per hari
- dua kali sehari, di pagi hari (saat sarapan) dan malam (saat makan malam) jika Anda diresepkan 2 atau 4 tablet per hari
- tiga kali sehari, di pagi hari (saat sarapan), siang (saat makan siang) dan malam (saat makan malam), jika Anda diresepkan 3 tablet per hari

Dokter akan memberitahu Anda bagaimana cara minum Glucovance jika Anda harus meminumnya bersamaan dengan obat penurun kolesterol (bile acid sequestrant), Glucovance harus diminum minimal 4 jam sebelum minum obat penurun kolesterol (bile acid sequestrant).

Jika Anda Minum Glucovance Berlebih dari Seharusnya
Jika Anda telah minum lebih banyak tablet Glucovance dari pada seharusnya, Anda mungkin mengalami asidosis laktat atau gula darah rendah (untuk gejala asidosis laktat dan gula darah rendah, lihat bagian 2, Peringatan dan tindakan pencegahan). **SEGERA HUBUNGI DOKTER ANDA**.

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

Jika Anda Berhenti Minum Glucovance
Biasanya tidak ada efek samping saat Anda berhenti minum obat ini. Namun, karena diabetes Anda tidak diobati lagi, komplikasi akibat kekurangan pengobatan dapat terjadi.

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

4 Efek samping yang mungkin terjadi

Seperti halnya obat lain, obat ini dapat menyebabkan efek samping, meskipun tidak semua pasien mengalaminya. Efek samping berikut ini teramati saat uji klinik atau saat manajemen pasien rutin.

Glucovance dapat menyebabkan kondisi yang sangat langka (berdampak pada 1 dari 10.000 pasien), namun suatu efek samping yang sangat serius yaitu asidosis laktat (lihat bagian 'Peringatan dan tindakan pencegahan'). Jika hal ini menimpa Anda, **hentikan minum Glucovance dan segera hubungi dokter atau rumah sakit terdekat**, karena asidosis laktat dapat menyebabkan koma.

Gangguan penglihatan: Saat Anda mulai minum obat ini, mungkin dapat menyebabkan gangguan penglihatan Anda karena kadar gula darah yang lebih rendah. Namun, kondisi ini biasanya hilang setelah beberapa saat.

Gula darah rendah: Untuk gejala gula darah rendah, lihat bagian 2, Peringatan dan tindakan pencegahan.

Efek samping yang sangat umum terjadi (dapat mempengaruhi lebih dari 1 dari 10 pasien)
- Gangguan gastrointestinal seperti mual, muntah, diare, nyeri perut, dan kehilangan nafsu makan. Efek samping ini paling sering terjadi setelah memulai pengobatan. Anda akan terbantu jika Anda minum obat siang hari dan disertai makan. **Jika gejala ini berlanjut, HENTIKAN minum obat ini dan KONSULTASIKAN dengan DOKTER Anda.**

Efek samping yang umum terjadi (dapat mempengaruhi hingga 1 dari 10 pasien)
- Gangguan indera perasa
- 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.

Efek samping yang tidak umum terjadi (dapat mempengaruhi hingga 1 dari 100 pasien)
- Kadar urea dan kreatinin dalam darah abnormal, yang menunjukkan perubahan kinerja ginjal.
- Krisis kondisi tertentu dari porfiria (porfiria hepatika atau porfiria kutanea; Penjelasan tentang porfiria, lihat bagian 2, 'Jangan minum Glucovance') dapat terjadi pada pasien dengan kekurangan enzim tertentu.

Efek samping yang jarang terjadi (dapat mempengaruhi hingga 1 dari 1.000 pasien)

- Penurunan jumlah sel darah putih, yang menyebabkan infeksi lebih mungkin terjadi
- Penurunan platelet darah yang meningkatkan risiko perdarahan atau memar
- Reaksi kulit termasuk gatal, gatal-gatal, ruam kulit

Efek samping yang sangat jarang terjadi (bisa mempengaruhi hingga 1 dari 10.000 pasien)
- Asidosis laktat (lihat bagian 2, Peringatan dan tindakan pencegahan)
- Pengurangan jumlah sel darah putih (agranulocytosis), anemia akibat pemecahan sel darah merah berlebih (anemia hemolitik), kurang atau tidak cukupnya jumlah sel darah baru yang diproduksi oleh sumsum tulang (aplasia sumsum tulang belakang) dan pengurangan jumlah sel darah yang sangat parah (pansitopenia, yang mana dapat membuat kulit terlihat pucat, dapat menyebabkan lemah atau sesak napas, bisa meningkatkan risiko pendarahan atau memar atau menyebabkan infeksi lebih mungkin terjadi)
- Kelainan pada uji fungsi hati atau radang hati (hepatitis, hal ini dapat menyebabkan kelelahan, kehilangan nafsu makan, penurunan berat badan, dengan atau tanpa kekuningan pada kulit atau mata). Jika hal ini terjadi pada Anda, **berhentilah minum Glucovance dan bicarakan dengan dokter Anda.**
- Sensitivitas kulit yang berlebihan terhadap sinar matahari, reaksi alergi serius pada kulit atau pembuluh darah.
- Intoleransi terhadap alkohol (dengan gejala seperti perasaan tidak nyaman, wajah memerah, denyut jantung cepat)
- Rendahnya tingkat sodium, yang bisa menyebabkan kelelahan dan kebingungan, otot berkedut, atau koma

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. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5 Bagaimana menyimpan Glucovance
Simpan obat Glucovance jauh dari penglihatan dan jangkauan anak-anak.

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

Produk obat ini tidak memerlukan kondisi penyimpanan khusus.

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 Glucovance
Zat aktif obat adalah Metformin hydrochloride dan Glibenclamide.

Glucovance® 250 mg/1.25 mg
- Satu tablet salut selaput mengandung 250 mg Metformin hydrochloride setara dengan 195 mg Metformin base dan 1.25 mg Glibenclamide.
- Bahan lainnya:
  - Tablet inti: Microcrystalline cellulose, Sodium croscarmellose, Povidone K30, Magnesium stearate.
  - Lapisan salut selaput: Opadry OY-L-22903 (kuning) (Lactose monohydrate, Hypromellose, Titanium dioxide, Macrogol, Talc, Yellow iron oxide)

Glucovance® 500 mg/2.5 mg

- Satu tablet salut selaput mengandung 500 mg Metformin hydrochloride setara dengan 390 mg Metformin base dan 2.5 mg Glibenclamide.
- Bahan lainnya:
  - Tablet inti: Microcrystalline cellulose, Sodium croscarmellose, Povidone K30, Magnesium stearate.
  - Lapisan salut selaput: Opadry OY-L-24808 (oranye) (Lactose monohydrate, Hypromellose, Titanium dioxide, Macrogol, Yellow iron oxide, Red iron oxide, Black iron oxide).

Glucovance® 500 mg/5 mg

- Satu tablet salut selaput mengandung 500 mg Metformin hydrochloride setara dengan 390 mg Metformin base dan 5 mg Glibenclamide.
- Bahan lainnya:
  - Tablet inti: Microcrystalline cellulose, Sodium croscarmellose, Povidone K30, Magnesium stearate.
  - Lapisan salut selaput: Opadry 31-F-22700 (kuning) (Lactose monohydrate, Hypromellose, Titanium dioxide, Macrogol, Yellow iron oxide, Red iron oxide, Quinoline Yellow Lake).

Glucovance® 1000 mg/5 mg

- Satu tablet salut selaput mengandung 1000 mg Metformin hydrochloride setara dengan 780 mg Metformin base dan 5 mg Glibenclamide.
- Bahan lainnya:
  - Tablet inti: Microcrystalline cellulose, Sodium croscarmellose, Povidone K30, Magnesium stearate.
  - Lapisan salut selaput: Opadry II OY-L-28900 (putih) (Lactose monohydrate, Hypromellose, Titanium dioxide, Macrogol).

Seperti Apa Glucovance dan Isi Kemasannya

Tablet diedarkan dalam kemasan blister bening atau tak tembus cahaya (PVC/Aluminium).

Tablet salut selaput Glucovance® 250 mg/1.25 mg berbentuk kapsul berwarna kuning pucat, cembung, tercetak *250* di salah satu sisi tablet dan *1.25* di sisi lainnya.

Tablet salut selaput Glucovance® 500 mg/2.5 mg berbentuk kapsul berwarna oranye pucat, cembung, tercetak *2.5* di salah satu sisi tablet.

Tablet salut selaput Glucovance® 500 mg/5 mg berbentuk kapsul berwarna kuning, cembung, tercetak *5* di salah satu sisi tablet.

Tablet salut selaput Glucovance® 1000 mg/5 mg berbentuk oval berwarna putih hingga putih pucat, cembung, tercetak *1000* di salah satu sisi tablet dan *5* di sisi lainnya.

Kemasan dan Nomor Izin Edar

Glucovance® 250 mg/1.25 mg	Dus, 8 blister @ 15 tablet salut selaput Reg No. DKL1715809217A1
Glucovance® 500 mg/2.5 mg	Dus, 8 blister @ 15 tablet salut selaput Reg. No. DKL1715809217B1
Glucovance® 500 mg/5 mg	Dus, 8 blister @ 15 tablet salut selaput Reg. No. DKL1715809217C1

Glucovance® 1000 mg/5 mg	Dus, 4 blister @ 15 tablet salut selaput Reg. No. DKI1801600117D1

HARUS DENGAN RESEP DOKTER

Glucovance® 250 mg/1.25 mg, Glucovance® 500 mg/2.5 mg, Glucovance® 500 mg/5 mg
Diproduksi oleh
PT Merck Tbk,
Jakarta, Indonesia

Atas lisensi dari
Merck Sante S.A.S.,
Lyon, Prancis

Glucovance® 1000 mg/5 mg
Diproduksi oleh
Merck Sante S.A.S.,
Semoy, Prancis

Diimpor dan dikemas sekunder oleh
PT Merck Tbk,
Jakarta, Indonesia

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