**Product Monograph**

**Including Patient Medication Information**

# Pr**GLUCOPHAGE®**

Metformin Hydrochloride Tablets

For oral use

500 mg and 850 mg of Metformin Hydrochloride

Oral Antihyperglycemic Agent

sanofi-aventis Canada Inc.

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Date of Authorization:
2026-04-07

Submission Control No.: 304566

**Recent Major Label Changes**

| | |
|---|---|
| 7. Warnings and Precautions, Endocrine and Metabolism | 2026-04 |

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*Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.*


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## Part 1: Healthcare Professional Information

### 1. Indications

GLUCOPHAGE® (metformin HCl) is indicated for:

- the improvement of glycemic control in adult patients with responsive, stable, mild, non-ketosis prone, type 2 diabetes mellitus as an adjunct to proper dietary management, exercise, and weight reduction, or when insulin therapy is not appropriate.
- use as monotherapy or in combination with other antidiabetic agents.

### 1.1. Pediatrics

**(< 18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 7. **Warnings and Precautions**, **7.1.3. Special Populations**, **Pediatrics**).

### 1.2. Geriatrics

**(≥ 65 years of age)**: Controlled clinical studies of GLUCOPHAGE did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients. GLUCOPHAGE is substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, GLUCOPHAGE should only be used in patients with normal renal function (see 2. **Contraindications** and **7. Warnings and Precautions, Renal**). Because aging is associated with reduced renal function, GLUCOPHAGE should be used with caution in geriatric patients. GLUCOPHAGE treatment should not be initiated in patients older than 80 years of age, unless measurement of creatinine clearance demonstrates that renal function is not reduced (see **7. Warnings and Precautions, Endocrine and Metabolism**, Lactic Acidosis, **7.1.4. Special Populations, Geriatrics**, and **4. Dosage and Administration**).

### 2. Contraindications

GLUCOPHAGE (metformin HCL) is contraindicated in:

- unstable and/or insulin-dependent (Type I) diabetes mellitus.
- acute or chronic metabolic acidosis, diabetic ketoacidosis, with or without coma, history of ketoacidosis with or without coma. Diabetic ketoacidosis should be treated with insulin.
- patients with a history of lactic acidosis, irrespective of precipitating factors.
- the presence of renal impairment or when renal function is not known, and also in patients with serum creatinine levels above the upper limit of normal range. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 136 µmol/L (males), ≥124 µmol/L (females) or abnormal creatinine clearance <60 mL/min)) which may result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see also **7. Warnings and Precautions**).

- excessive alcohol intake, acute or chronic.
- patients suffering from severe hepatic dysfunction, since severe hepatic dysfunction has been associated with some cases of lactic acidosis, GLUCOPHAGE should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.
- patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials. GLUCOPHAGE should be temporarily discontinued because use of such products may result in acute alteration of renal function (see **7. Warnings and Precautions**).
- cases of cardiovascular collapse and in disease states associated with hypoxemia such as cardiorespiratory insufficiency, which are often associated with hyperlactacidemia.
- stress conditions, such as severe infections, trauma or surgery and the recovery phase thereafter.
- patients suffering from severe dehydration or shock.
- known hypersensitivity or allergy to metformin HCl or any of the excipients. For a complete listing, see the **6. Dosage Forms, Strengths, Composition and Packaging** section of the product monograph.
- pregnancy and breastfeeding.

## 3. Serious Warnings and Precautions Box

- Lactic acidosis is a rare, but serious, metabolic complication that occurs due to metformin accumulation during treatment with GLUCOPHAGE (see **7 Endocrine and Metabolism**, Lactic Acidosis section).
- Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking GLUCOPHAGE, since alcohol intake potentiates the effect of metformin on lactate metabolism (see **7 Endocrine and Metabolism**, Lactic Acidosis section).

## 4. Dosage and Administration

### 4.1. Dosing Considerations

In diabetic patients, individual determination of the minimum dose that will lower blood glucose adequately should be made, aiming for glycemic targets as close to normal as possible. A lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms (see **8 Adverse Reactions, Clinical Trial Adverse Drug Reactions, Gastrointestinal Reactions**).

Over a period of time, patients may become progressively less responsive to therapy with oral hypoglycemic agents because of the deterioration of their diabetic state. Patients should therefore be monitored with regular clinical and laboratory evaluations, including blood glucose and glycosylated hemoglobin ($A_{IC}$) determinations, to determine the minimum effective dosage and to detect primary failure or secondary failure (see **7. Warnings and Precautions, Endocrine and Metabolism**, Loss of control of blood glucose and **7. Monitoring and Laboratory Tests**).

In patients in whom the maximum dose fails to lower the blood glucose adequately, therapeutic alternatives should be considered.

GLUCOPHAGE is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. GLUCOPHAGE is contraindicated in patients with serum creatinine levels above the upper limit of the normal range for their age (see **2. Contraindications**).

In elderly patients, GLUCOPHAGE should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function and the risk of developing lactic acidosis (see **7. Warnings and Precautions, Endocrine and Metabolism**, Lactic Acidosis). GLUCOPHAGE treatment should not be initiated in patients older than 80 years of age, unless measurement of creatinine clearance demonstrates that renal function is not reduced, as elderly patients are more susceptible to developing lactic acidosis (see **7.1.4. Special Populations, Geriatrics**, and 7 **Monitoring and Laboratory Tests**).

Caution should be exercised when using concomitant medication(s) that may decrease renal function (like diuretics, particularly loop diuretics) or may interfere with the disposition of GLUCOPHAGE, such as cationic drugs that are eliminated by renal tubular secretion, due to the increased risk of developing lactic acidosis during co-administration (see **9. Drug Interactions, Cationic Drugs** and **Other**).

Consideration for GLUCOPHAGE dosage adjustment, as necessary, should be made when GLUCOPHAGE is simultaneously administered with cationic drugs that are excreted via renal tubular secretion, or with drugs that produce hyperglycemia or hypoglycaemia, especially at the initiation of treatment with the interfering drug and upon its discontinuation (see **9. Drug Interactions, Cationic Drugs** and **Other**).

*Transfer from Other Antidiabetic Therapy*

When transferring patients to GLUCOPHAGE from standard oral hypoglycaemic agents, other than chlorpropamide, no transition period is generally necessary. When transferring patients from chlorpropamide, care should be exercised during the first two weeks because of the prolonged retention of chlorpropamide in the body, leading to overlapping drug effects and possible hypoglycaemia.

### 4.2. Recommended Dose and Dosage Adjustment

The usual dose is 500 mg three or four times a day, or 850 mg two or three times a day. Maximal dose should not exceed 2.55 g a day.

### 4.4. Administration

To minimize gastric intolerance such as nausea and vomiting, GLUCOPHAGE (metformin HCl) should be taken with food whenever possible.

**Dosing in Special Populations:**

**Pediatrics (< 18 years of age):** Health Canada has not authorized an indication for pediatric use; therefore GLUCOPHAGE should not be used in the pediatric population (see 1.1 Pediatrics and **7. Warnings and Precautions, 7.1.3.** Special Populations, Pediatrics).

**Geriatrics (> 65 years of age):** GLUCOPHAGE should be carefully titrated in geriatric patients to establish the minimum dose for adequate glycemic effect, because of reduced renal function associated with aging and the risk of developing lactic acidosis (see **7. Warnings and Precautions, Endocrine and Metabolism**, Lactic Acidosis). In elderly patients, the initial and maintenance dose of GLUCOPHAGE should be conservative, and any dose adjustment should be based on careful assessment of renal function. Renal function should be monitored regularly and generally; GLUCOPHAGE should not be titrated to the maximum dose (see **7. Warnings and Precautions, 7.1.4.** Special Populations, Geriatrics).

**Renal Impairment:** GLUCOPHAGE is contraindicated in patients with impaired renal function, unknown renal function, or in patients with serum creatinine levels above the upper limit of the normal range for their age, due to the risk of lactic acidosis (see **2. Contraindications**).

**Hepatic Impairment:** GLUCOPHAGE is contraindicated in patients with severe hepatic dysfunction (see **2. Contraindications**). Since impaired hepatic function has been associated with some cases of lactic acidosis, GLUCOPHAGE should not be used in patients with clinical or laboratory evidence of hepatic disease (see **7. Warnings and Precautions,** Hepatic/Biliary/Pancreatic).

### 4.5. Missed Dose

If a dose of GLUCOPHAGE tablets is missed, the patient should wait for the next dose at the usual time. The dose should not be doubled to make up for the forgotten dose.

## 5. Overdose

Available information concerning treatment of a massive overdosage of GLUCOPHAGE

(metformin HCl) is very limited. It would be expected that adverse reactions of a more intense character including epigastric discomfort, nausea and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen. Should those symptoms persist, lactic acidosis should be excluded. The drug should be discontinued, and proper supportive therapy should be instituted.

Overdose of Metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see **7. Warnings and Precautions, Endocrine and Metabolism**, Lactic Acidosis). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for the removal of accumulated drug from patients in whom metformin overdosage is suspected.

Pancreatitis may occur in the context of a metformin overdose (see **7. Warnings and Precautions, Hepatic/Biliary/Pancreatic**).

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

## 6. Dosage Forms, Strengths, Composition, and Packaging

**Table 1 – Dosage Forms, Strengths, and Composition**

| Route of Administration | Dosage Form/ Strength/Composition | Non-Medicinal Ingredients |
|---|---|---|
| oral | Tablet 500 mg of Metformin hydrochloride | magnesium stearate and povidone<br>Tablet coating: hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide |
| | Tablet 850 mg of Metformin hydrochloride | magnesium stearate and povidone |

**Description**

GLUCOPHAGE (metformin HCl) 500 mg tablets are white, round, biconvex film-coated tablets, scored on one face and debossed with "HMR" on the other. Available in bottles of 100 and 500 tablets.

GLUCOPHAGE (metformin HCl) 850 mg tablets are white oblong tablets, debossed with "HMR" on one face and 850 on the other. Available in bottles of 100 tablets.

## 7. Warnings and Precautions

**See 3 Serious Warnings and Precautions Box**

### General

Patient Selection and Follow-up
Careful selection of patients is important. It is imperative that there be rigid attention to diet and careful adjustment of dosage. Regular thorough follow-up examinations are necessary.

If vomiting occurs, withdraw drug temporarily, exclude lactic acidosis, and then resume dosage cautiously (see **7. Lactic Acidosis** and **8. Adverse Reactions**).

Particular attention should be paid to short range and long range complications which are peculiar to diabetes (see **7. Monitoring and Laboratory Tests**).

Use of GLUCOPHAGE must be considered as treatment in addition to proper dietary regimen and not as a substitute for diet.

If during GLUCOPHAGE therapy the patient develops acute intercurrent disease such as clinically significant hepatic dysfunction, cardiovascular collapse, congestive heart failure, acute myocardial infarction, or other conditions complicated by hypoxemia, the drug should be discontinued.

Change in clinical status of previously controlled diabetes patients
A diabetic patient previously well controlled on GLUCOPHAGE 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, GLUCOPHAGE must be stopped immediately, and appropriate corrective measures must be initiated. See 7 Lactic Acidosis

Hypoxic states: Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on GLUCOPHAGE therapy, the drug should be promptly discontinued.

### Driving and Operating Machinery

Patients should be warned about driving a vehicle or operating machinery under conditions where risks of hypoglycemia are present (see **7. Warnings and Precautions, Endocrine and Metabolism**, Hypoglycemia).

### Endocrine and Metabolism

*Hypoglycemia*
Hypoglycemia does not occur in patients receiving GLUCOPHAGE alone under usual circumstances of use, but could occur 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. Elderly debilitated or malnourished patients and patients with adrenal, pituitary, or hepatic

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.

*Hypothyroidism*
Metformin induces a reduction in thyrotropin (thyroid stimulating hormone (TSH)) levels in patients with treated or untreated hypothyroidism (see **8. Adverse Reactions, Post-Market Adverse Drug Reactions**). Regular monitoring of TSH levels is recommended in patients with hypothyroidism (see **Monitoring and Laboratory Tests**).

Studies have shown that metformin reduces plasma TSH levels, often to subnormal levels, when it is administered to patients with untreated hypothyroidism or to hypothyroid patients effectively treated with Levothyroxine. The metformin-induced reduction of plasma TSH levels is not observed when metformin is administered to patients with normal thyroid function. Metformin has been suggested to enhance the inhibitory modulation of thyroid hormones on TSH secretion**.**

Levothyroxine can reduce the hypoglycemic effect of metformin. Careful monitoring of blood glucose levels is recommended in patients with hypothyroidism treated with Levothyroxine, especially when thyroid hormone therapy is initiated, changed, or stopped (see **Monitoring and Laboratory Tests** and **9. Drug Interactions, Levothyroxine**).

*Lactic Acidosis*
Lactic acidosis is a rare, but serious, metabolic complication that occurs due to metformin accumulation during treatment with GLUCOPHAGE. When it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (> 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. See 2 Contraindications and 3 Serious Warnings and Precautions.

The reported incidence of lactic acidosis in patients receiving metformin HCl is very low (approximately 0.03 cases / 1000 patient-years, with approximately 0.015 fatal cases / 1000 patient-years) and occurs 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. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Glucophage treatment should not be initiated in patients ≥80 years of age, unless measurement of creatinine clearance demonstrates that renal function is not reduced, as the patients are more susceptible to developing 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 GLUCOPHAGE and by use of the minimum effective dose of GLUCOPHAGE. In addition, GLUCOPHAGE 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, GLUCOPHAGE 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 GLUCOPHAGE (metformin HCl), since alcohol intake potentiates the effect of metformin HCl on lactate metabolism. In addition, GLUCOPHAGE should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis is often subtle, and accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and non-specific abdominal distress. There may be associated hypothermia, hypotension and resistance 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. GLUCOPHAGE 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 GLUCOPHAGE, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. In patients taking GLUCOPHAGE, levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L, 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 GLUCOPHAGE, the drug should be discontinued immediately, and general supportive measures should be promptly instituted. Because metformin HCl is dialyzable (with clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Physicians should instruct their patients to recognize the symptoms which could be signal onset of lactic acidosis. If acidosis of any kind develops, GLUCOPHAGE should be discontinued immediately, and the patient should be immediately hospitalized.

*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 Maternally inherited diabetes and deafness (MIDD), GLUCOPHAGE 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 GLUCOPHAGE, immediate withdrawal of GLUCOPHAGE should be considered, and prompt diagnostic evaluation should be performed.

*Loss of control of blood glucose*
When a patient stabilized on any antidiabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold GLUCOPHAGE and temporarily administer insulin. GLUCOPHAGE may be reinstituted after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in

many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy.

Should secondary failure occur with GLUCOPHAGE, therapeutic alternatives should be considered.

*Vitamin $B_{12}$ levels*
Impairment of vitamin $B_{12}$ absorption has been reported in some patients. Therefore, measurements of serum vitamin $B_{12}$ are advisable at least every one to two years in patients on long-term treatment with GLUCOPHAGE.

A decrease to subnormal levels of previously normal serum Vitamin $B_{12}$ levels, without clinical manifestations, is observed in approximately 7% of patients receiving GLUCOPHAGE in controlled clinical trials of 28 weeks duration. Such decrease, possibly due to interference with $B_{12}$ absorption from $B_{12}$-intrinsic factor complex is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of GLUCOPHAGE or vitamin $B_{12}$ supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on GLUCOPHAGE (see **Monitoring and Laboratory Tests**), and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin $B_{12}$ or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin $B_{12}$ levels.

Long-term treatment with GLUCOPHAGE has been associated with a decrease in serum vitamin $B_{12}$ levels which may cause peripheral neuropathy. Serious cases of peripheral neuropathy have been reported with GLUCOPHAGE treatment in the context of vitamin $B_{12}$ deficiency (see 8. **Adverse Reactions, Post-Market Adverse Drug Reactions**). Monitoring of serum vitamin $B_{12}$ levels is recommended (see **Monitoring and Laboratory Tests**).

### Hematologic

Serious cases of metformin-induced hemolytic anemia, some with a fatal outcome, have been reported (see 8. **Adverse Reactions, Post-Market Adverse Drug Reactions**). Two mechanisms were described for the metformin-induced immune hemolytic anemia; formation of an antibody against the erythrocyte-metformin complex and autoantibody formation. Monitoring of hematologic parameters is recommended (see 7 **Monitoring and Laboratory Tests**).

### Hepatic/Biliary/Pancreatic

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

GLUCOPHAGE is contraindicated in patients suffering from severe hepatic dysfunction (see **2. Contraindications**).

Serious cases of pancreatitis have been reported in patients receiving metformin (see 8. **Adverse Reactions, Post-Market Adverse Drug Reactions**). The reported pancreatitis cases occurred either in the context of an acute metformin overdose (see **5. Overdose**) or in patients receiving therapeutic doses of metformin with concurrent renal failure and/or lactic acidosis, indicating metformin accumulation.

### Monitoring and Laboratory Tests

Response to all antidiabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control. Periodic monitoring of blood and/or urinary glucose is necessary to detect primary and secondary failure (see **7. Warnings and Precautions, Endocrine and Metabolism,** Loss of control of blood glucose).

More frequent glucose monitoring should be considered when GLUCOPHAGE is simultaneously administered with cationic drugs that are excreted via renal tubular secretion, or with drugs that produce hyperglycemia or hypoglycaemia, especially at the initiation of treatment with the interfering drug(s) (see **9. Drug Interactions, Cationic Drugs** and **Other**).

Periodic cardiovascular, ophthalmic, hematological, hepatic, and renal assessments are advisable (see **7. Warnings and Precautions**).

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis (see **7. Warnings and Precautions, Hematologic** and **Renal**). While megaloblastic anemia has rarely been seen with GLUCOPHAGE (metformin HCl) therapy, if this is suspected, vitamin $B_{12}$ deficiency should be excluded.

Impairment of vitamin $B_{12}$ absorption has been reported in some patients, and long-term treatment with GLUCOPHAGE has been associated with reductions in vitamin $B_{12}$ serum levels. Periodic measurements of serum vitamin $B_{12}$ levels should be performed in patients on long-term treatment with GLUCOPHAGE, especially in patients with anemia or neuropathy (see **7. Warnings and Precautions, Endocrine and Metabolism,** Vitamin $B_{12}$ levels).

Regular monitoring of thyroid-stimulating hormone (TSH) levels is recommended in patients with hypothyroidism (see **7. Warnings and Precautions, Hypothyroidism** and 8. **Adverse Reactions, Post-Market Adverse Drug Reactions**).

For hypothyroid patients treated with Levothyroxine, careful monitoring of blood glucose levels is recommended, especially when thyroid hormone therapy is initiated, changed, or stopped (see **7. Warnings and Precautions, Hypothyroidism** and **9. Drug Interactions, Levothyroxine**).

For patients concurrently administering GLUCOPHAGE and phenprocoumon or other antivitamin K anticoagulants, a close monitoring of the International Normalized Ratio (INR) is recommended (see **9. Drug Interactions**, **Other**).

### Neurologic

Serious cases of metformin-induced encephalopathy have been reported (see 8. **Adverse Reactions, Post-Market Adverse Drug Reactions**). Some of these cases were reported without association with lactic acidosis, hypoglycemia, or renal impairment.

### Perioperative Considerations

GLUCOPHAGE therapy should be temporarily suspended for any surgical procedure Metformin (except minor procedures not associated with restricted intake of food and fluids). GLUCOPHAGE should be discontinued 2 days before surgical intervention and should not be restarted or until the patient's oral intake has resumed and renal function has been evaluated as normal.

### Renal

GLUCOPHAGE 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 the normal range for their age should not receive GLUCOPHAGE. In patients with advanced age, GLUCOPHAGE should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, renal function should be monitored regularly and generally, GLUCOPHAGE should not be titrated to the maximum dose (see **4. Dosage and Administration**).

Before initiation of GLUCOPHAGE therapy, and every 6 months while on GLUCOPHAGE therapy, renal function should be assessed and verified as being within normal range.

In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and GLUCOPHAGE must be discontinued if evidence of renal impairment is present.

Special caution should be exercised in situations where renal function may become impaired, for example in the elderly, in the case of dehydration, when initiating antihypertensive therapy or diuretic therapy, or when starting therapy with an NSAID.

*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 GLUCOPHAGE, such as cationic drugs that are eliminated by renal tubular secretion (see **9. Drug Interactions**), should be used with caution.

*Radiological studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography [CT] scans with intravascular contrast material)*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 (see **2. Contraindications**). Therefore, in patients in whom any such study is planned, GLUCOPHAGE should be temporarily discontinued at the time of or prior to the procedure, withheld for 48 hours subsequent to the procedure, and reinstituted only after renal function has been re-evaluated and found to be normal.

### Reproductive Health

Please refer to 2 Contraindications, 7.1.1 Pregnancy, 10.3 Pharmacokinetics, 16 Non-clinical Toxicology

### Fertility

No data related to human fertility is available.

## 7.1. Special Populations

### 7.1.1. Pregnancy

GLUCOPHAGE is contraindicated during pregnancy (see **2. Contraindications**).

Safety of metformin hydrochloride during pregnancy has not been established. There are no adequate and well-controlled studies of GLUCOPHAGE during pregnancy.

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, or about two times the maximum recommended human daily dose on a body surface area basis. Determination of fetal concentrations demonstrated a partial placental barrier to metformin. Because animal reproduction studies are not always predictive of human response, GLUCOPHAGE is contraindicated during pregnancy (see **2. Contraindications**).

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

### 7.1.2. Breastfeeding

GLUCOPHAGE is contraindicated during breast-feeding (see **2. Contraindications**).

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Metformin hydrochloride is also excreted into human breast milk in very small amounts.

### 7.1.3. Pediatrics

**(< 18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see **1. Indications**).

### 7.1.4. Geriatrics

**(> 65 years of age)**: Controlled clinical studies of GLUCOPHAGE (metformin HCl) did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients. GLUCOPHAGE 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, GLUCOPHAGE should only be used in patients with normal renal function (see **2 Contraindications** and **7. Warnings and Precautions, Renal**). Because aging is associated with reduced renal function, GLUCOPHAGE should be used with caution as age increases. GLUCOPHAGE treatment should not be initiated in patients older than 80 years of age, unless measurement of creatinine clearance demonstrates that renal function is not reduced, as elderly patients are more susceptible to developing lactic acidosis (see **7. Warnings and Precautions, Endocrine and Metabolism,** Lactic Acidosis). Care should be taken in dose selection which should be based on careful and regular monitoring of renal function. GLUCOPHAGE should be carefully titrated to establish the minimum dose for adequate glycemic effect. Generally,

elderly patients should not be titrated to the maximum dose of GLUCOPHAGE (see **4. Dosage and Administration, Geriatrics**).

## 8. Adverse Reactions

### 8.1. Adverse Reaction Overview

Lactic acidosis is a rare, but serious adverse reaction associated with GLUCOPHAGE (metformin HCl) treatment. Lactic acidosis is fatal in approximately 50% of cases (see 7. Warnings and Precautions, Endocrine and Metabolism, Lactic Acidosis).

The adverse reactions most commonly associated with GLUCOPHAGE treatment are diarrhea, nausea, vomiting, abdominal pain, abdominal distention, dyspepsia, and flatulence.

The most common adverse reactions resulting in discontinuation of GLUCOPHAGE treatment are gastrointestinal disturbances described as diarrhea, nausea, vomiting, abdominal pain, and dyspepsia.

### 8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

The clinical trials which formed the basis of approval for the original GLUCOPHAGE submission are not available (see **14. Clinical Trials**).

The following adverse drug reactions (a combination of clinical trials and post-marketing data) were reported for Glucophage:

**Lactic Acidosis:** Very rare (<1/10,000 and isolated reports) (see **7. Warnings and Precautions**, and **5. Overdose**).

**Gastrointestinal Reactions:** Very common (>1/10). Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to GLUCOPHAGE and are approximately 30% more frequent in patients on GLUCOPHAGE monotherapy than in placebo-treated patients, particularly during initiation of GLUCOPHAGE therapy. These symptoms are generally transient and resolve spontaneously during continued treatment. Occasionally, temporary dose reduction may be useful.

Because gastrointestinal symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take GLUCOPHAGE with meals (see **4. Dosage and Administration, 4.1** Dosing Considerations).

Because significant diarrhea and/or vomiting can cause dehydration and prerenal azotemia, GLUCOPHAGE should be temporarily discontinued under such circumstances.

For patients who have been stabilized on GLUCOPHAGE, nonspecific gastrointestinal symptoms should not be attributed to therapy unless intercurrent illness or lactic acidosis has been excluded.

**Special Senses:** Common (≥1/100). During initiation of GLUCOPHAGE therapy complaints of taste disturbance are common, i.e. metallic taste.

**Dermatologic Reactions:** Very rare (<1/10,000 and isolated reports). The incidence of rash/dermatitis in controlled clinical trials was comparable to placebo for GLUCOPHAGE monotherapy and to sulfonylurea for GLUCOPHAGE/sulfonylurea therapy. Reports of skin reactions such as erythema, pruritus, and urticaria are very rare.

**Hematologic:** During controlled clinical trials of 29 weeks duration, approximately 9% of patients on GLUCOPHAGE monotherapy and 6% of patients on GLUCOPHAGE/sulfonylurea therapy developed asymptomatic subnormal serum vitamin B12 levels; serum folic acid levels did not decrease significantly. However, only five cases of megaloblastic anemia have been reported with metformin administration (none during U.S. clinical studies), and no increased incidence of neuropathy has been observed in clinical trials. However, serious cases of peripheral neuropathy have been reported with GLUCOPHAGE treatment in the post-marketing experience in patients with vitamin $B_{12}$ deficiency (see **7. Warnings and Precautions**, Endocrine and Metabolism, Vitamin $B_{12}$ levels).

Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin is rare (≥1/10,000 and <1/1,000). Consideration of such aetiology is recommended if a patient presents with megaloblastic anemia.

**Hepatic:** Very rare (<1/10,000 and isolated reports). Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation has been documented in isolated reports.

### 8.5. Post-Market Adverse Reactions

**Blood and Lymphatic System Disorders:** Hemolytic anemia, some with a fatal outcome (see **7. Warnings and Precautions, Hematologic**).

**Gastrointestinal Disorders**: Abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper, constipation, diarrhea, dry mouth, dyspepsia, flatulence, gastric disorder, gastric ulcer, gastrointestinal disorder, nausea, vomiting.

**Hepatobiliary Disorders**: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation, autoimmune hepatitis, drug-induced liver injury, hepatitis, pancreatitis (see **7. Warnings and Precautions, Hepatic/Biliary/Pancreatic**).

**Investigations**: Blood lactic acid increased.

Reduction of thyrotropin level in patients with treated or untreated hypothyroidism (see **7. Warnings and Precautions, Hypothyroidism** and **Monitoring and Laboratory Tests**).

**Nervous System Disorders:** Encephalopathy (see **7. Warnings and Precautions, Neurologic**).

**Metabolism and Nutrition Disorders**: Lactic acidosis, decrease of vitamin $B_{12}$ absorption with decrease of serum levels during long-term use of metformin, weight decreased, decreased appetite.

Peripheral neuropathy in patients with vitamin B12 deficiency (see **7. Warnings and Precautions, Endocrine and Metabolism**, Vitamin B12 levels).

Hypomagnesemia in the context of diarrhea.

**Skin and Subcutaneous Tissue Disorders**: Photosensitivity, erythema, pruritus, rash, skin lesion, and urticaria.

## 9. Drug Interactions

### 9.1. Drug Interactions Overview

Certain drugs may potentiate the effect of GLUCOPHAGE, particularly sulfonylurea type of drugs in the treatment of diabetes. The simultaneous administration of these two types of drugs could produce a hypoglycemic reaction, especially if they are given in patients already receiving other drugs which, themselves, can potentiate the effect of sulfonylureas. These drugs can be: long-acting sulfonamides, tubercolostatics, phenylbutazone, clofibrate, monoamine oxidase inhibitors, salicylates, probenecid and propanolol.

In healthy volunteers, the pharmacokinetics of propranolol and ibuprofen were not affected by metformin when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to sulfonylureas, which are extensively bound to serum proteins.

### 9.2. Drug-Behaviour Interactions

Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking GLUCOPHAGE, since alcohol intake potentiates the effect of metformin on lactate metabolism (see **2. Contraindications**). 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 avoided.

### 9.3. Drug-Drug Interactions

**Glyburide:** In a single-dose interaction study in NIDDM subjects, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and $C_{max}$ were observed, but were highly

variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamics effects, make the clinical significance of this interaction uncertain.

**Furosemide:** A single-dose study, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased metformin plasma and blood $C_{max}$ by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the $C_{max}$ 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 healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin $C_{max}$ and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. $T_{max}$ 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, and 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 an interaction has been observed between metformin and oral cimetidine in normal healthy volunteers. In both single and multiple-dose metformin-cimetidine drug interaction studies, there was a 60% increase in peak metformin plasma and whole blood concentrations, as well as 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. Therefore, careful patient monitoring (see **7. Warnings and Precautions, Monitoring and Laboratory Tests**) and dose adjustment of GLUCOPHAGE or the interfering drug is recommended in patients who are taking cationic medications that are excreted via renal tubular secretion (see **4. Dosage and Administration, Dosing Considerations**).

**Levothyroxine:** Levothyroxine can reduce the hypoglycemic effect of metformin. Monitoring of blood glucose levels is recommended, especially when thyroid hormone therapy is initiated, changed, or stopped (see **7. Warnings and Precautions, Monitoring and Laboratory Tests**), and GLUCOPHAGE dosage adjusted as necessary (see **4. Dosage and Administration, Dosing Considerations**).

**Other**

Other drugs tend to produce hyperglycemia and may lead to a loss of blood sugar control. These include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid hormone replacement drugs e.g. levothyroxine, estrogens, estrogen plus progestogen, oral contraceptives,

phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, isoniazid, and beta-2-agonists. ACE-inhibitors may decrease the blood glucose levels. When such drugs are administered to patients receiving GLUCOPHAGE, the patient should be closely observed to maintain adequate glycemic control. More frequent blood glucose monitoring may be required, especially at the beginning of treatment (see **7. Warnings and Precautions, Monitoring and Laboratory Tests**). If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation (see **4. Dosage and Administration, Dosing Considerations**).

Diuretics, especially loop diuretics, may increase the risk of lactic acidosis due to their potential to decrease renal function (see **4. Dosage and Administration, Dosing Considerations**).

Elimination rate of the anticoagulant phenprocoumon has been reported to be increased by 20% when used concurrently with GLUCOPHAGE. Therefore, a close monitoring of the International Normalized Ratio (INR) is recommended in patients concurrently administering GLUCOPHAGE and phenprocoumon or other antivitamin K anticoagulants (see **7. Warnings and Precautions, Monitoring and Laboratory Tests**). In such cases, an important increase of prothrombin time may occur upon cessation of GLUCOPHAGE therapy, with an increased risk of hemorrhage.

### 9.4. Drug-Food Interactions

Interactions with food have not been established.

### 9.5. Drug-Herb Interactions

Interactions with herbal products have not been established.

### 9.6. Drug-Laboratory Test Interactions

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 (see **2. Contraindications** **and 7. Warnings and Precautions, Renal**).

## 10. Clinical Pharmacology

### 10.1. Mechanism of Action

GLUCOPHAGE (metformin HCl) is a biguanide derivative producing an antihyperglycemic effect which can only be observed in man or in the diabetic animal and only when there is insulin secretion.

Metformin, at therapeutic doses, does not cause hypoglycemia when used alone in man or in the non-diabetic animal, except when using a near lethal dose. Metformin has no effects on the pancreatic beta cells. The mode of action of metformin is not fully understood. It has been postulated that metformin might potentiate the effect of insulin or that it might enhance the effect of insulin on the peripheral

receptor site. This increased sensitivity seems to follow an increase in the number of insulin receptors on cell surface membranes.

## 10.2. Pharmacodynamics

Few data are available on the relationship between pharmacodynamics and pharmacokinetics, and therefore the effect of metformin on glucose control cannot be predicted from pharmacokinetic data alone. Tissue concentrations of metformin in the dual target sites of the liver and muscle appear to be more informative, and the deep metformin compartment supplying these tissues is critical and related to plasma concentrations. This view substantiates the clinical observation that the glucose-lowering action of metformin takes time to be fully expressed and also that activity is not lost immediately on drug withdrawal.

## 10.3. Pharmacokinetics

**Absorption**

Metformin absorption is relatively slow and may extend over about 6 hours.

**Distribution**

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged between 63-276 1.

**Metabolism**

Metformin is not metabolized. Its main sites of concentration are the intestinal mucosa and the salivary glands. The plasma concentration at steady-state ranges about 1 to 2 mcg/mL. Certain drugs may potentiate the effects of metformin.

**Elimination**

The drug is excreted in urine at high renal clearance rate of about 450 mL/minThe initial elimination of metformin is rapid with a half-life varying between 1.7 and 3 hours. The terminal elimination phase accounting for about 4 to 5 % of the absorbed dose is slow with a half-life between 9 and 17 hours.

## 11. Storage, Stability, and Disposal

Store at room temperature (15°to 30°C) in well closed containers.

## Part 2: Scientific Information

## 13. Pharmaceutical Information

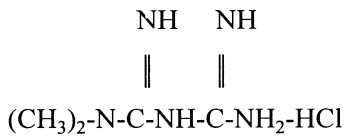
### Drug Substance

Non-proprietary name of the drug substance(s): Metformin HCl

Chemical name: N, N-dimethyl biguanide hydrochloride

Molecular formula and molecular mass: 165.6

Structure (for biologics)/Structural formula: [image]




**Physicochemical properties:**

Metformin HCl is a white crystalline powder.

Metformin HCl is soluble in water and in 95% ethyl alcohol. It is practically insoluble in ether and in chloroform.

**Product Characteristics:**

Melting Point: 218-220°C.

## 14. Clinical Trials

### 14.1. Clinical Trials by Indication

The data which formed the basis of approval for the original GLUCOPHAGE submission are not available. Rather, this section presents data from a published study which investigated the safety and efficacy of metformin.

The prospective randomised (UKPDS) study 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. There was no significant difference between the metformin group and those assigned intensive therapy with sulfonylurea or insulin.

- 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). There was no significant difference between the metformin group and those assigned intensive therapy with sulfonylurea or insulin.

- There were no significant differences between the metformin group and the diet alone in the other aggregate endpoints (stroke, peripheral vascular disease and microvascular complications.

## 16. Non-Clinical Toxicology

**General toxicology**

1. Animal Toxicity

| | Acute Toxicity ($LD_{50}$) | |
|---|---|---|
| Animal | Subcutaneously | Orally |
| Mouse | 225 mg/kg | 3500 mg/kg |
| Chicken | 150 mg/kg | |
| Rat | 300 mg/kg | 1000 mg/kg |
| Rabbit | 150 mg/kg | 350 mg/kg |
| Guinea Pig | 150 mg/kg | 500 mg/kg |

Chronic Toxicity

A) The following doses of metformin produced no organ toxicity:

| | | |
|---|---|---|
| Rats | 125 mg/kg | per os for one year |
| Rabbits | 100 mg/kg | per os for one year |
| Dogs | 50 mg/kg | subcutaneously for 2 years |

Acute or chronic organ toxicity was not produced in the animal species involved.

B) A study was carried out during 9 months with 80 rats, male and female, divided in 4 groups, with the following dosage regimen:

| | |
|---|---|
| 1st Group | control |
| 2nd Group | 150 mg/kg per os |
| 3rd Group | 300 mg/kg per os |

4th Group 300 mg/kg per os, dose increased by 100 mg/kg/day every 15 days

In summary, the authors report the excellence tolerance of metformin by rats, even when administered in very high doses. No drug related lesion has been observed.

C) Chronic toxicity studies of 9 months duration were carried through with 16 beagle dogs,

although the complete intolerance of this animal species to oral hypoglycemic agents is a well established fact. Trophic and neurologic disorders with cachexia rapidly lead to the dog's death. During the periods of metformin administration, laboratory findings were within normal limits. The levels of enzymes were somewhat elevated, but it is difficult to ascribe a pathological significance to their values, since subjects in the control group were at the same level as treated animals.

Pathological studies show an extreme degree of undernutrition in all metformin treated animals. Profound wasting especially marked in fat tissues was evident in all organs. Cachexia appears as the common cause of death of these animals.

2. Human Toxicity

In man, no adverse effect has been reported on liver or kidney function, the hematopoietic system or on the blood vessels.

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 patients/years).

The consecutive administration of both phenformin and metformin to the same patient has allowed for the demonstration of a fundamental difference between these two biguanides in relation to lactacidemia. In some instances, patients developed hyperlactacidemia with phenformin when the same patients were presenting normal lactic acid levels while being treated with metformin. In other instances, hyperlactacidemia observed during a treatment with phenformin did regress when metformin was substituted for phenformin. Metformin may increase lactacidemia but to a degree that is clinically less significant than the elevation seen after phenformin.

**Special toxicology**

Teratology

Teratological studies were carried out in albino rats divided in three groups:

No abnormalities were found, even when high doses were administered. The number of animals was the same in each group.

Death rate in the three groups of treated animals and controls was approximately the same. However, the number of living animals in each group treated was slightly lower than in the control group. Also, the frequency of litters exceeding 10 live animals was slightly higher in the control group. A loss of weight at the time of weaning has been observed when compared to the control group.

Nevertheless, on a statistical basis, differences were shown to be non-significant. There is no difference between the groups of treated animals and the control group regarding the number of stillborn. The number of deaths after birth was slightly higher in metformin treated groups than in the control group, but the comparison of average death rates is not significant ($p < 0.05$).

## Patient Medication Information

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PrGLUCOPHAGE®**

**Metformin Hydrochloride Tablets**

This Patient Medication Information is written for the person who will be taking **GLUCOPHAGE**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **GLUCOPHAGE**, talk to a healthcare professional.

**Serious warnings and precautions box**

- GLUCOPHAGE may rarely cause a serious, life-threatening condition called lactic acidosis (see **Lactic Acidosis** section below).
- You should not drink a lot of alcohol if you take GLUCOPHAGE (see **Lactic Acidosis** section below)

**What GLUCOPHAGE is used for:**

GLUCOPHAGE is used, in addition to proper diet, exercise and weight loss, to treat high blood sugar in adults with type 2 diabetes mellitus. GLUCOPHAGE can be used by itself or in combination with other diabetes medicines.

**How GLUCOPHAGE works:**

GLUCOPHAGE is a medicine that contains metformin to help control your blood sugar level.

GLUCOPHAGE only helps people who already have some insulin in their bodies. It makes the insulin work better, but it can't replace insulin completely.

GLUCOPHAGE may work by creating more insulin receptors on your cells where insulin can attach and work to control blood sugar levels.

**The ingredients in GLUCOPHAGE are:**

Medicinal ingredient: metformin hydrochloride

Non-medicinal ingredients: magnesium stearate and povidone. Tablet coating for the 500 mg tablet includes hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide.

**GLUCOPHAGE comes in the following dosage form:**

Tablets; 500 mg, 850 mg

**Do not use GLUCOPHAGE if:**

- you are allergic to metformin hydrochloride any of the other ingredients in this medicine
- you have Type I diabetes mellitus that is unstable and/or insulin-dependent
- you have metabolic acidosis (when your blood becomes too acidic)
- you have diabetic ketoacidosis (when your body cannot use sugar properly and it starts breaking down fat for energy instead) with or without coma
- you have had ketoacidosis with or without coma
- you have had lactic acidosis (too much acid in the blood)
- you drink a lot of alcohol (regularly drink alcohol or sometimes drink a lot of alcohol ("binge drinking")
- you have severe liver problems
- you have kidney problems
- you are stressed, have a severe infection, or are experiencing trauma
- you have severe dehydration (have lost a lot of water from your body)
- you are pregnant or planning to become pregnant
- you are breastfeeding
- you have heart system collapse (when blood circulation fails abruptly)
- you have a disease that can cause hypoxemia (low oxygen in the blood) such as when the heart and lungs do not deliver enough oxygen to the body (cardiorespiratory insufficiency).

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take GLUCOPHAGE. Talk about any health conditions or problems you may have, including if you:**

- are 80 years of age or older and you have not had your kidney function tested
- have liver problems
- develop a serious medical condition, such as heart attack, severe infection, or a stroke
- develop or experience a worsening of heart disease or heart failure
- have thyroid problems
- have low blood levels of vitamin B12 or calcium

**Other warnings you should know about:**

**Low vitamin B12:** GLUCOPHAGE can cause your vitamin B12 level to be low. This can cause you to feel pins and needles in your hands and feet (called **peripheral neuropathy**).

**Lactic Acidosis:** This can happen if metformin, the active ingredient in GLUCOPHAGE, builds up in your blood. It is a rare but serious side effect. The build up of lactic acid can cause serious damage and can be fatal in up to half of the people who develop it. If you experience lactic acidosis you might need to be hospitalized for treatment.

**If you get the following symptoms, stop taking GLUCOPHAGE and contact a healthcare professional right away:**

- Feel very weak and tired
- Have unusual muscle pain

- Have trouble breathing
- Have stomach pain with nausea and vomiting, or diarrhea
- Feel cold, especially in your arms and legs
- Feel dizzy or lightheaded
- Have a slow or irregular heartbeat
- Your medical condition suddenly changes

**You have a higher chance of getting lactic acidosis if you:**

- have severe kidney or liver problems,
- have congestive heart failure that requires treatment with medicines,
- are over the age of 80
- get dehydrated
- have low blood oxygen levels
- have a serious infection
- drink a lot of alcohol (very often or short-term "binge" drinking)
- have surgery
- have x-ray tests with injectable dyes or contrast agents.
- have or think you have a mitochondrial disease (a disease that is passed down at birth affecting mitochondria). For these patients, taking GLUCOPHAGE increases the risk for lactic acidosis and can lead to worsening of the mitochondrial disease.

**Hypoglycemia** (low blood sugar levels): GLUCOPHAGE rarely causes hypoglycemia. It can happen if you:

- are elderly
- do not eat enough
- drink alcohol
- exercise heavily and do not eat enough
- take other medications that lower blood sugar
- also have adrenal, pituitary or liver problems

**Driving and using machines**: Do not drive or operate machines if you develop low blood sugar (hypoglycemia).

**Surgery:** If you need to have major surgery, stop taking GLUCOPHAGE 2 days before the procedure. You will restart again once you are eating and drinking again as you normally would.

**Scans or X-rays needing contrast dyes:** If you need a scan for which contrast dye will be used, stop taking GLUCOPHAGE 2 days before the scan. Your healthcare professional will tell you when to restart after the scan.

**Tests and check-ups:** Before and during your treatment with GLUCOPHAGE, your healthcare professional will do blood tests. These will be repeated regularly. The results will tell you how well your liver, kidneys and thyroid are working and will measure the amount of vitamin B12 in your blood. These tests will also check how GLUCOPHAGE affects your blood and blood sugar.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with GLUCOPHAGE:**

- Other diabetes drugs such as glyburide
- A medicine used to treat malaria called quinine
- Medicines used to treat high blood pressure including nifedipine, amlodipine, felodipine, verapamil and diltiazem (calcium channel blockers) as well as ACE inhibitors
- Medicines used to lower extra fluid in the body including furosemide, triamterene and amiloride. These are also known as diuretics or water pills.
- A medicine used to treat heart failure called digoxin
- A medicine used to treat pain called morphine
- Medicines used to treat irregular heart beat such as procainamide and quinidine
- A medicine used to lower stomach acid called ranitidine
- Medicines used to treat bacterial infections such as trimethoprim, and vancomycin
- Medicines used to prevent blood clots (called "blood thinners") including phenprocoumon and other antivitamin K anticoagulants
- Medicines that can cause high blood sugar and may lead to a loss of blood sugar control including:
    - Corticosteroid medicines like prednisone
    - Medicines used to treat mental and emotional disorders including phenothiazines
    - A thyroid hormone replacement drug called levothyroxine
    - The female hormones, estrogen or estrogen plus progestogen
    - Birth control medicines that are taken by mouth
    - A medicine used to treat epilepsy called phenytoin
    - A medicine used to prevent and treat low niacin called nicotinic acid
    - Medicines used to stimulate the sympathetic nervous system called sympathomimetics
    - A medicine used to treat active tuberculosis infections called Isoniazid
    - Medicines for asthma such as salbutamol or formoterol

**How to take GLUCOPHAGE**

- Take GLUCOPHAGE exactly as your healthcare professional has told you. Check with them if you are not sure.
- Take tablets with food to reduce nausea and vomiting.

**Usual dose:**

Your healthcare professional will tell you how much GLUCOPHAGE to take and when to take it.

**Overdose:**

If you take too much GLUCOPHAGE, you might feel stomach discomfort, nausea, vomiting, diarrhea, drowsiness, weakness, dizziness, malaise, and headache.

Lactic acidosis may also occur. This is a serious, life-threatening condition.

If you think you, or a person you are caring for, have taken too much GLUCOPHAGE, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

**Missed dose:**

If you forget to take GLUCOPHAGE tablets, skip the missed dose. Take your next dose at the usual time. Do not take two doses at the same time to make up for a missed dose.

**Possible side effects from using GLUCOPHAGE:**

These are not all the possible side effects you may have when taking GLUCOPHAGE. If you experience any side effects not listed here, tell your healthcare professional.

- diarrhea
- nausea
- vomiting
- abdominal pain, bloating
- heartburn
- taste changes
- gas
- loss of appetite
- skin redness, itching, hives

GLUCOPHAGE can cause abnormal blood test results. Your healthcare professional will do blood tests during your treatment and will interpret the results.

**Serious side effects and what to do about them**

| Frequency/Side Effect/Symptom | Talk to your healthcare professional | | Stop taking this drug and get immediate medical help |
|---|---|---|---|
| | Only if severe | In all cases | |
| **Rare** | | | |
| **Lactic Acidosis** (a build up of lactic acid in the blood that can cause death or cardiovascular mortality): feeling very weak, tired, or uncomfortable, unusual muscle pain, trouble breathing, unusual or unexpected stomach discomfort, stomach pain with nausea and vomiting, or diarrhea, feeling cold, feeling dizzy or lightheaded, | | | √ |

| Frequency/Side Effect/Symptom | Talk to your healthcare professional | | Stop taking this drug and get immediate medical help |
|---|---|---|---|
| | Only if severe | In all cases | |
| suddenly developing a slow or irregular heartbeat | | | |
| **Pancreatitis** (inflammation of the pancreas): prolonged severe abdominal pain which may be accompanied by vomiting; pain may spread out towards the back. | | | √ |
| **Hemolytic anemia** (when red blood cells are destroyed faster than bone marrow can replace them): fatigue, pale color, rapid heartbeat, shortness of breath, dark urine, chills, and backache. | | | √ |
| **Encephalopathy** (disease of the brain that severely alters thinking): muscle weakness in one area, poor decision-making or concentration, involuntary twitching, trembling, difficulty speaking or swallowing, seizures. | | | √ |
| **Peripheral neuropathy** (a result of damage to your peripheral nerves): gradual onset of numbness, prickling or tingling in your feet or hands, which can spread upward into your legs and arms, sharp, jabbing, throbbing, freezing or burning pain, extreme sensitivity to touch, lack of coordination and falling, muscle weakness or paralysis if motor nerves are affected. | | | √ |
| **Very Rare** | | | |
| **Mitochondrial Disease** (a disease affecting energy producing components within cells): seizure, reduction in a person's mental abilities (memory lapses, difficulty concentrating, trouble finding words or following conversations, poor judgment or decision-making, confusion), difficulty with body movements, muscle pain or | | | ✓ |

| Frequency/Side Effect/Symptom | Talk to your healthcare professional | | Stop taking this drug and get immediate medical help |
|---|---|---|---|
| | Only if severe | In all cases | |
| weakness, pain, numbness, migraine, deafness | | | |
| **Liver problems:** yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness | | ✓ | |
| **Unknown** | | | |
| **Hypothyroidism** (underactive/low thyroid): weight gain, tiredness, hair loss, muscle weakness, feeling cold, dry skin, constipation, puffy face, heavier than normal or irregular menstrual periods, enlarged thyroid gland | | ✓ | |
| **Photosensitivity** (sensitivity to sunlight): itchy, red skin when exposed to sunlight | | ✓ | |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

**Reporting side effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage**

Store at room temperature (15°to 30°C) in well closed containers. Throw away any medication that is outdated or no longer needed. Talk to your pharmacist about the proper disposal of your medication.

Keep out of reach and sight of children.

**If you want more information about GLUCOPHAGE:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (https://www.sanofi.com/en/canada/); or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

Date of Authorization: 2026-04-07

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