PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]PRZ-METFORMIN

metformin hydrochloride tablets

Tablets, 1000 mg, Oral

Manufacturer's standard

Oral Antihyperglycemic Agent

Pharmaris Canada Inc.
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Surrey, British Columbia
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RECENT MAJOR LABEL CHANGES

Not applicable

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PRZ-METFORMIN (metformin) tablets are indicated for use to:

- improve 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. PRZ-METFORMIN can be used 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.

1.2 Geriatrics (> 65 years of age)

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients. Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged and C_{max} is increased, compared to healthy young subjects (see 10 CLINICAL PHARMACOLOGY, Pharmacokinetic). From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function. Metformin 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, PRZ-METFORMIN is contraindicated in patients with severe renal impairment (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2) (see 2 CONTRAINDICATIONS). Because aging is associated with reduced renal function, PRZ-METFORMIN should be used with caution in geriatric patients. PRZ-METFORMIN treatment should not be initiated in patients older than 80 years of age, unless their renal function is not significantly reduced. In patients with advanced age, metformin should be carefully titrated to establish the minimum dose for adequate glycemic effect. More careful and frequent monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis (see 4.1 Dosing considerations, 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

PRZ-METFORMIN is contraindicated in patients:

- With unstable and/or insulin-dependent (Type I) diabetes mellitus.
- With 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.
- With a history of lactic acidosis, irrespective of precipitating factors.
- With severe renal impairment [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2)], end-stage renal disease, in patients on dialysis or when renal

function is not known (see 7 WARNINGS AND PRECAUTIONS, Renal).

- With excessive alcohol intake, acute or chronic.
- Suffering from severe hepatic dysfunction, since severe hepatic dysfunction has been associated with some cases of lactic acidosis, PRZ-METFORMIN should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.
- Undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. PRZ-METFORMIN should be temporarily discontinued during period around administration of iodinated contrast materials (see 7 WARNINGS AND PRECAUTIONS).
- In cases of cardiovascular collapse and in disease states associated with hypoxemia such as cardiorespiratory insufficiency, which are often associated with hyperlactacidemia.
- During stress conditions, such as severe infections, trauma or surgery and the recovery phase thereafter.
- Suffering from severe dehydration or shock.
- Who are hypersensitive to metformin or to any ingredient in the formulation, including any non-medical ingredient or component of the container. For a complete listing, see 6 DOSAGE FORMS, COMPOSITION AND PACKAGING.
- During pregnancy and breastfeeding (see 7.1.1 Pregnant Women and 7.1.2 Breast-feeding).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

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

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

PRZ-METFORMIN 1000 mg is not intended for use as the starting dose not for initial therapy.

A lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms (see 8.1 Clinical Trial Adverse Reactions, Gastrointestinal Reactions).

During treatment initiation and dose titration, fasting plasma glucose should be used to determine the therapeutic response to PRZ-METFORMIN and to identify the minimum effective dose for the patients

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. PRZ-METFORMIN is contraindicated in patients with severe renal impairment [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2)], end-stage renal disease, in patients on dialysis or when renal function is not known (see 2 CONTRAINDICATIONS). Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of PRZ-METFORMIN in patients with renal impairment.

Care should be taken in dose selection for the elderly and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of metformin. PRZ-METFORMIN treatment should not be initiated in patients older than 80 years of age, unless their renal function is not significantly reduced (see 7.1.4 Geriatrics).

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 metformin, such as cationic drugs, that are eliminated by renal tubular secretion, due to the increased risk of developing lactic acidosis during co-administration. Consideration for PRZ-METFORMIN dosage adjustment, as necessary, should be made when PRZ-METFORMIN is simultaneously administered with cationic drugs or with drugs that produce hyperglycemia or hypoglycaemia, especially at the initiation of treatment with the interfering drug and upon its discontinuation (see 9.4 Drug-Drug Interactions, Cationic Drugs and Other).

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

4.2 Recommended Dose and Dosage Adjustment

PRZ-METFORMIN 1000 mg tablets should be taken orally once or twice daily with meals. PRZ-METFORMIN therapy should be initiated at 1000 mg orally once daily. Gradual dose escalation is recommended to reduce gastrointestinal side effects, and to permit identification of the minimum dose required for adequate glycemic control.

The usual dose of metformin is 500 mg three or four times a day, or 850 mg two or three times a day. Maximal dose of metformin should not exceed 2.55 g a day. In patients receiving a high

metformin dose (1000 mg or 2000 mg), it is possible to replace two metformin 500 mg tablets with one PRZ-METFORMIN 1000 mg tablet. Doses above 2000 mg may be better tolerated if given as 3 divided doses. The maximum daily dose of PRZ-METFORMIN in patients with an eGFR ≥30 mL/min/1.73 m^2 to <45 mL/min/1.73 m^2 is 1000 mg.

Transfer from Other Antidiabetic Therapy
When transferring patients to PRZ-METFORMIN 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.

Pediatrics (< 18 years of age): Safety and effectiveness of PRZ-METFORMIN in pediatric and adolescent patients have not been established. Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

Geriatrics (> 65 years of age): PRZ-METFORMIN 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 PRZ-METFORMIN should be conservative, and any dose adjustment should be based on careful assessment of renal function. Renal function should be monitored more frequent and generally, PRZ-METFORMIN should not be titrated to the maximum dose (see 4.1 Dosing Considerations and 7.1.4 Geriatrics).

Renal Impairment: PRZ-METFORMIN is contraindicated in patient with severe renal impairment [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2)], end-stage renal disease, in patients on dialysis or when renal function is not known. (see 2 CONTRAINDICATIONS). Renal function must be assessed prior to initiation of PRZ-METFORMIN and periodically thereafter, at least once a year in patients with normal renal function, and more frequent monitoring in patients with renal impairment (eGFR<60 mL/min/1.73 m^2) and in elderly patients (see 7 WARNINGS AND PRECAUTIONS, Renal).

The maximum daily dose of PRZ-METFORMIN in patients with an eGFR ≥30 mL/min/1.73 m^2 to <45 mL/min/1.73 m^2 is 1000 mg.

Hepatic Impairment: PRZ-METFORMIN is contraindicated in patients with severe hepatic dysfunction (see 2 CONTRAINDICATIONS). Since impaired hepatic function has been associated with some cases of lactic acidosis, PRZ-METFORMIN should not be used in patients with clinical or laboratory evidence of hepatic disease (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

4.4 Administration

To minimize gastric intolerance such as nausea and vomiting, PRZ-METFORMIN (metformin) tablets should be taken orally with meals and should be taken whole, with a glass of water. Do not break or crush tablets.

4.5 Missed Dose

In case the patient forgets to take PRZ-METFORMIN tablets, he/she should wait for the next dose at the usual time. He/she should not double the dose to make up for the forgotten dose.

5 OVERDOSAGE

Available information concerning treatment of a massive overdosage of metformin 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 has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin 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 management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet / 1000 mg metformin hydrochloride	Crospovidone, Hypromellose, Magnesium stearate, Polyethylene Glycol, Povidone and Starch Pregelatinised, Titanium Dioxide.

PRZ-METFORMIN (metformin hydrochloride) 1000 mg tablets are white to off-white, deep convex film coated tablets, debossed one side 'S' and another side 'M3'. Available in bottles of 100 tablets.

7 WARNINGS AND PRECAUTIONS

See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

PRZ-METFORMIN should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Use of PRZ-METFORMIN must be considered as treatment in addition to proper dietary and exercise regimen, and not as a substitute for either. Care should be taken to ensure that PRZ-METFORMIN is not given when a contraindication exists. If during PRZ-METFORMIN 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 which may also cause prerenal azotemia, the drug should be discontinued. If vomiting occurs, withdraw drug temporarily, exclude lactic acidosis, and then resume dosage cautiously.

Cardiovascular

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 PRZ-METFORMIN 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

Change in clinical status of previously controlled diabetes patients

A diabetic patient previously well controlled on PRZ-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, PRZ-METFORMIN must be stopped immediately, and appropriate corrective measures must be initiated.

Hypoglycemia

Hypoglycemia does not occur in patients receiving metformin 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 8.5 Post-Market Adverse Drug Reactions). Regular monitoring of TSH levels is recommended in patients with hypothyroidism (see 7 WARNINGS AND PRECAUTIONS, 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 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 9.4 Drug-Drug Interactions, Levothyroxine).

Lactic Acidosis

Lactic acidosis is a rare, but serious, metabolic complication that occurs due to metformin accumulation during treatment with PRZ-METFORMIN (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX). 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.

The reported incidence of lactic acidosis in patients receiving metformin 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. PRZ-METFORMIN treatment should not be initiated in patients ≥80 years of age, unless their 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 PRZ-METFORMIN and by use of the minimum effective dose of PRZ-METFORMIN. In addition, PRZ-METFORMIN 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, PRZ-METFORMIN 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 PRZ-METFORMIN (metformin), since alcohol intake potentiates the effect of metformin on lactate metabolism. In addition, PRZ-METFORMIN 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. PRZ-METFORMIN 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 PRZ-METFORMIN, 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 PRZ-METFORMIN, 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 PRZ-METFORMIN, the drug should be discontinued immediately, and general supportive measures should be promptly instituted. Because metformin 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, PRZ-METFORMIN should be discontinued immediately, and the patient should be immediately hospitalized.

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 PRZ-METFORMIN and temporarily administer insulin. PRZ-METFORMIN 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. 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 PRZ-METFORMIN, 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 PRZ-METFORMIN.

A decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, is observed in approximately 7% of patients receiving metformin 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 metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on PRZ-METFORMIN (see 7 WARNINGS AND PRECAUTIONS, 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 metformin 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 metformin treatment in the context of vitamin B_{12} deficiency (see 8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Drug Reactions). Monitoring of serum vitamin B_{12} levels is recommended (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Hematologic
Serious cases of metformin-induced hemolytic anemia, some with a fatal outcome, have been reported (see 8.5 Post-Market Adverse 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 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Hepatic/Biliary/Pancreatic
Since impaired hepatic function has been associated with some cases of lactic acidosis, PRZ-METFORMIN should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

PRZ-METFORMIN is contraindicated in patients suffering from severe hepatic dysfunction (see 2 CONTRAINDICATIONS).

Serious cases of pancreatitis have been reported in patients receiving metformin (see 8.5 Post-Market Adverse Reactions). The reported pancreatitis cases occurred either in the context of an acute metformin overdose (see 5 OVERDOSAGE) 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 PRZ-METFORMIN 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 9.4 Drug-Drug Interactions, Cationic Drugs and Other).

Renal function must be assessed prior to initiation of PRZ-METFORMIN and periodically thereafter, at least once a year in patients with normal renal function, and more frequent monitoring in patients with renal impairment (eGFR<60 mL/min/1.73m^2) and in elderly patients. In patients with eGFR less than 60 mL/min/1.73 m^2, more intensive monitoring for glycemic and renal biomarkers and signs and symptoms of renal dysfunction is recommended, especially if the eGFR is less than 45 mL/min/1.73 m^2 (see 4.2 Recommended Dose and Dose Adjustment, 7 WARNINGS AND PRECAUTIONS, Renal). PRZ-METFORMIN must be discontinued if the eGFR decreased to ≤ 30mL/min/1.73 m^2 (see 2 CONTRAINDICATIONS)

Periodic cardiovascular, ophthalmic and hepatic 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 (see 7 WARNINGS AND PRECAUTIONS, Hematologic). While megaloblastic anemia has rarely been seen with metformin 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 metformin 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 PRZ-METFORMIN, 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, 8.5 Post-Market Adverse 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 9.4 Drug-Drug Interactions Levothyroxine).

For patients concurrently administering PRZ-METFORMIN and phenprocoumon or other antivitamin K anticoagulants, a close monitoring of the International Normalized Ratio (INR) is recommended (see 9.4 Drug-Drug Interactions, Anticoagulants).

Neurologic
Serious cases of metformin-induced encephalopathy have been reported (see 8.5 Post-Market Adverse Reactions). Some of these cases were reported without association with lactic acidosis, hypoglycemia, or renal impairment.

Peri-Operative Considerations
PRZ-METFORMIN therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids). PRZ-METFORMIN 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
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. PRZ-METFORMIN is contraindicated in patients with severe renal impairment (estimated glomerular rate (eGFR) <30 mL/min/1.73 m^2 (see 2 CONTRAINDICATIONS). In patients with advanced age, PRZ-METFORMIN 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 more frequently and generally, PRZ-METFORMIN should not be titrated to the maximum dose (see 4.1 Dosing Considerations and 4.2 Recommended Dose and Dose Adjustment).

Renal function must be assessed prior to initiation of PRZ-METFORMIN and periodically thereafter, at least once a year in patients with normal renal function and more frequent monitoring in patients with renal impairment (eGFR<60 mL/min/1.73m^2) and in elderly patients. In patients with eGFR less than 60 mL/min/1.73 m^2, more intensive monitoring for glycemic and renal biomarkers and signs and symptoms of renal dysfunction is recommended, especially if the eGFR is less than 45 mL/min/1.73 m^2 (see 4 DOSAGE AND ADMINISTRATION, 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). PRZ-METFORMIN must be discontinued if the eGFR decreased to ≤ 30mL/min/1.73 m^2 (see 2 CONTRAINDICATIONS)

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 PRZ-METFORMIN, such as cationic drugs that are eliminated by renal tubular secretion (see 9 DRUG INTERACTIONS), should be used with caution.

Monitoring of renal function is recommended prior to and following initiation of any concomitant drug which might have an impact on renal function.

Radiological studies involving the use of intravascular iodinated contrast materials.

Intravascular contrast studies with iodinated materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast material) 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, PRZ-METFORMIN 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.

7.1 Special Populations

7.1.1 Pregnant Women

PRZ-METFORMIN is contraindicated in pregnant women (see 2 CONTRAINDICATIONS). Safety of metformin in pregnant women has not been established. There are no adequate and well-controlled studies of metformin in pregnant women.

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.

7.1.2 Breast-feeding

PRZ-METFORMIN is contraindicated in breast-feeding women (see 2 CONTRAINDICATIONS). Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Metformin 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 1.1 Pediatrics).

7.1.4 Geriatrics (> 65 years of age)

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients. Metformin 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, PRZ-METFORMIN is contraindicated in patient with severe renal impairment (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Renal). Because aging is associated with reduced renal function, PRZ-METFORMIN should be used with caution as age increases. PRZ-METFORMIN treatment should not be initiated in patients older than 80 years of age, unless their renal function is not significantly 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 more frequent monitoring of renal function. PRZ-METFORMIN 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 PRZ-METFORMIN (see 4.1 Dosing Considerations and 4.2 Recommended Dose and Dosage Adjustment).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Lactic acidosis is a rare, but serious adverse reaction associated with metformin 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 metformin treatment are diarrhea, nausea, vomiting, abdominal pain, abdominal distention, dyspepsia, and flatulence.

The most common adverse reactions resulting in discontinuation of metformin 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. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The clinical trials which formed the basis of approval for the original metformin 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 metformin:

Lactic Acidosis: Very rare (<1/10,000 and isolated reports) (see 7 WARNINGS AND PRECAUTIONS, and 5 OVERDOSAGE).

Gastrointestinal Reactions: Very common (>1/10). Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to metformin and are approximately 30% more frequent in patients on metformin monotherapy than in placebo-treated patients, particularly during initiation of metformin therapy. These symptoms are generally transient and resolve spontaneously during continued treatment. Occasionally, temporary dose reduction may be useful (see 4.1 Dosing Considerations).

Special Senses: Common (≥1/100). During initiation of metformin 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 metformin monotherapy and to sulfonylurea for metformin /sulfonylurea therapy. Reports of skin reactions such as erythema, pruritus, and urticaria are very rare.

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.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Hematologic: During controlled clinical trials of 29 weeks duration, approximately 9% of patients on metformin monotherapy and 6% of patients on metformin /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 metformin treatment in the post-marketing experience in patients with vitamin B12 deficiency.

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.

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, hypomagnesemia in the context of diarrhea, reduction of thyrotropin level in patients with treated or untreated hypothyroidism (see 7 WARNINGS AND PRECAUTIONS, Hypothyroidism and Monitoring and Laboratory Tests).

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.

Nervous System Disorders: Encephalopathy, peripheral neuropathy in patients with vitamin B12 deficiency (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Vitamin B12 levels).

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

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Certain drugs may potentiate the effect of PRZ-METFORMIN, 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, tuberculostatic, phenylbutazone, clofibrate, monoamine oxidase inhibitors, salicylates, probenecid, and propranolol.

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.

9.3 Drug-Behavioural Interactions

Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking PRZ-METFORMIN, 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.

9.4 Drug-Drug Interactions

The drugs listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Anticoagulant:
Elimination rate of the anticoagulant phenprocoumon has been reported to be increased by 20% when used concurrently with metformin. Therefore, a close monitoring of the International Normalized Ratio (INR) is recommended in patients concurrently administering metformin and phenprocoumon or other antivitamin K anticoagulants (see 7 WARNINGS AND PRECAUTIONS). In such cases, an important increase of prothrombin time may occur upon cessation of PRZ-METFORMIN with an increased risk of hemorrhage.

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 PRZ-METFORMIN or the interfering drug is recommended in patients who are taking cationic medications that are excreted via renal tubular secretion (see 4.1 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 PRZ-METFORMIN dosage adjusted as necessary (see 4.1 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 PRZ-METFORMIN, 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 4.1 Dosing Considerations).

Diuretics, especially loop diuretics, may increase the risk of lactic acidosis due to their potential to decrease renal function (see 4.1 Dosing Considerations).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 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

Metformin is an antihyperglycemic agent, which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may actually decrease.

At therapeutic doses, metformin does not lower plasma glucose levels in non-diabetic animals or humans. Oral administration of metformin was demonstrated to effectively lower plasma glucose levels in streptozocine-induced diabetic mice, genetically diabetic KK mice, obese female fa/fa rats, and alloxan-induced diabetic rats. In addition to its antihyperglycemic effects, metformin has been shown to have hypolipidemic effects and to significantly improve the progression and regression of atherosclerotic lesions. Metformin has also been shown to reduce blood pressure in spontaneously hypertensive rats, either through sympathoinhibitory effects, a direct effect on vascular smooth muscle responsiveness to norepinephrine, and/or attenuation of hyperinsulinemia.

The antihyperglycemic effect of metformin does not appear to be due to effects on plasma insulin or glucagon concentrations. While some studies have demonstrated that metformin produces an increase in insulin receptor binding or an increase in low-affinity receptor number, it is generally accepted that the antihyperglycemic effects of metformin are poorly correlated with insulin binding and its effects on receptor binding and number are not directly related to its metabolic and clinical effects. A direct effect of metformin on insulin secretion has been ruled out as a mechanism for the antihyperglycemic effects because metformin does not increase circulating levels of insulin, nor has it been shown experimentally to stimulate insulin secretion. Although the precise mechanism of hypoglycemic action of metformin remains unclear, it likely interrupts mitochondrial oxidative processes in the liver and corrects abnormalities of intracellular calcium metabolism in insulin-sensitive tissues (liver, skeletal muscle, and adipocytes) and cardiovascular tissues from specific studies.

PRZ-METFORMIN (metformin) 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

No clinical trials have been performed to study the pharmacokinetics of PRZ-METFORMIN.

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 63-2761.

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 (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).

Elimination
The drug is excreted in urine at high renal clearance rate of about 450 mL/min. The 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.

Special Populations and Conditions

- **Pediatrics:** No pharmacokinetic studies of PRZ-METFORMIN in pediatrics < 18 years of age were conducted. Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

- **Geriatrics:** Aging is associated with reduced renal function, PRZ-METFORMIN should be used with caution as age increases. Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients. Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged and Cmax 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 7.1.4 Geriatrics).

- **Sex:** In the pharmacokinetic studies in healthy volunteers, there were no important differences between male and female subjects with respect to metformin AUC (males = 268, females = 293) and t½ (males = 229, females = 260). However, Cmax for metformin were somewhat higher in female subjects (Female/Male Cmax Ratio = 1.4). The gender

differences for Cmax are unlikely to be clinically important.

- **Pregnancy and Breast-feeding:** Safety of metformin in pregnant and breast-feeding women has not been established. PRZ-METFORMIN is contraindicated during pregnancy and breast-feeding (see 2 CONTRAINDICATIONS).

- **Hepatic Insufficiency:** No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment. Metformin has little effect on liver glycogen of the healthy animal. In low and average doses, no change occurs. In high doses nearing lethal levels, liver glycogen decreases. This lowering precedes the fall in blood sugar. This reaction represents a defense mechanism tending to mobilize body reserves in order to combat hypoglycemia.

  In the diabetic animal with a low liver glycogen reserve, the opposite occurs, and metformin builds up glycogen stores of the liver.

- **Renal Insufficiency:** Metformin is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2). In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Renal).

11 STORAGE, STABILITY AND DISPOSAL

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

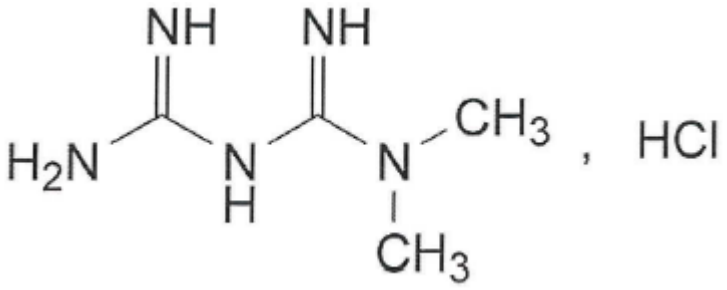
Drug Substance

Proper name: Metformin hydrochloride

Chemical name: 1, 1-dimethylbiguanide hydrochloride

Molecular formula and molecular mass: $C_4H_{11}N_5$ HCl and 165.6 g/mol

Structural formula:



Physicochemical properties: Metformin hydrochloride is white or almost crystals.

Metformin hydrochloride is freely soluble in water, slightly soluble in ethanol (96%), practically insoluble in acetone, methylene chloride.

Metformin hydrochloride pH Solubility Profile:

Sr. No.	Media	pH	Solubility (mg/mL)
1	0.1 N HCl	1.2	184.4
2	Acetate buffer	4.5	303.6
3	Water	6.3	420.1
4	Phosphate buffer	6.8	217.4

Melting Point: 222-226°C.

14 CLINICAL TRIALS

14.3 Comparative Bioavailability Studies

A randomized, two-way, single-dose, crossover comparative bioavailability study of PRZ-METFORMIN tablets (Pharmaris Canada Inc.) (administered as a 1 x 1000 mg dose) and ^{Pr}GLUCOPHAGE® tablets (sanofi-aventis Canada Inc., Canada) was conducted in healthy, adult, male subjects under fasting conditions. Comparative bioavailability data from 27 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Metformin (1000 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test**[1]	**Reference**[2]	**% Ratio of Geometric Means**	**90% Confidence Interval**[3]
AUC_T (ng·h/mL)	13714.95 13928.37 (16.95)	13909.77 14072.59 (15.58)	98.7	93.7 - 104.0
AUC_I (ng·h/mL)	13956.76 14169.15 (16.75)	14117.38 14278.63 (15.40)	99.0	94.0 - 104.2
C_{max} (ng/mL)	2096.62 2139.71 (19.94)	2112.22 2148.20 (18.84)	99.5	93.0 - 106.5
T_{max}[3] (h)	3.00 (1.00 - 4.50)	3.00 (1.00 - 4.00)		
$T_{½}$[4] (hr)	4.33 (21.82)	4.20 (16.97)		

[1] PRZ-METFORMIN (metformin hydrochloride) tablets, 1000 mg (Pharmaris Canada Inc.
[2] GLUCOPHAGE® (metformin hydrochloride) tablets, 2 x 500 mg (sanofi-aventis Canada Inc.)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV %) only

The data which formed the basis of approval for the original metformin 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).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Chronic Toxicity
In a 26-week oral/gavage toxicity study, 160 Sprague-Dawley rats were administered with 150, 450, 900 mg/kg/day. The No-observed-effect level in this study was 150 mg/kg/day. Decrease in body weight gains at 450 and 900 mg/kg/day, changes in clinical laboratory parameters (decreased total leukocyte, lymphocyte and neutrophil count) and in some organ weights at 900 mg/kg/day have been observed.

In another 39-week oral toxicity study, 32 Beagle dogs were administered with 20, 40, 60, 80 mg/kg/day. Only at 80 mg/kg/day, treatment-related effects in food consumption have been observed in females.

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.

Carcinogenicity:
In 26-week dermal carcinogenicity study in transgenic mice. 150 mice were administered with 500, 1000, 2000 mg/kg/day. There is no findings and none of papillomas at treatment sites. In a 104-week oral/gavage carcinogenicity study in rats, 400 rats / Sprague-Dawley were administered 150, 300, 450 mg/kg/day for males and 150, 450, 900, 1200 mg/kg/day for females. The No-observed-effect level in this study was 450 mg/kg/day. Parathyroid hyperplasia was noted in males at all doses, and not noted for females.

Non-neoplastic findings seen in females and not with males, no tumorigenicity has been observed and increase in female kidney weights at 900 and 1200 mg/kg/day. No long-term animal studies have been performed to evaluate carcinogenic potential of PRZ-METFORMIN.

Genotoxicity:
There was no evidence of a mutagenic potential of metformin in the in vitro tests. AMES Assay has been performed, doses at 100, 333, 1000, 5000 mcg/plate with Salmonella /E. coli strain. Results were all negatives.

In vitro cytogenetics – mouse lymphoma assay, doses at 1000, 2000, 3000, 4000, 5000 mcg/plate with mice /Lymphoma cells strains. Results obtained were all negatives.

In vivo cytogenetics – mouse micronucleus assay, 70 ICR mice were oral administered 500, 1000, 2000 mg/kg. Results were also all negatives. No long-term animal studies have been performed to evaluate mutagenic potential of PRZ-METFORMIN.

Reproductive and Developmental Toxicology:

Reproductive Toxicity
In rats Segment I/II toxicity study (Fertility & developmental toxicity), 200 Sprague-Dawley Rats (100 males and 100 females) were orally administered 150, 450, 900 mg/kg/day. Decrease in male reproductive organ weights at 900 mg/kg/day has been noted.
In a second rats Segment III toxicity study (Pre-and postnatal toxicity), 100 mated females Sprague-Dawley rats were orally administered 150, 300, 600 mg/kg/day. The No-observed effect level in this study was 150 mg/kg/day in this study and decrease in F1 female body weight and feed consumption at 300 and 600 mg/kg/day were observed.

In a third Segment II toxicity study in rabbits (Developmental toxicity in rabbits), 80 New Zealand white Time Pregnant females Rabbits were Orally/ Stomach tube administered 30, 60, 90 mg/kg/day. The No-observed-effect level in this study was higher than 90 mg/kg/day and no effects on gross external, soft tissue or skeletal malformation were noted.

Special Toxicology:
No long-term animal studies have been performed to evaluate any special toxicology potential of PRZ-METFORMIN.

Juvenile Toxicity:
No long-term animal studies have been performed to evaluate mutagenic potential of PRZ-METFORMIN.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrGLUCOPHAGE® tablets, 500 mg and 850 mg, submission control 211582, Product Monograph, Sanofi-Aventis Canada Inc. (March 2, 2018)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrPRZ-METFORMIN

Metformin Hydrochloride Tablets, 1000 mg

Read this carefully before you start taking **PRZ-METFORMIN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PRZ-METFORMIN**.

Serious Warnings and Precautions

Lactic Acidosis

- PRZ-METFORMIN may cause lactic acidosis. This is a serious condition when there is too much lactic acid in your body. It may cause death.
- The risk of lactic acidosis is higher if you have:
  - liver, kidney or heart problems, including heart failure.
  - drink a lot of alcohol. You should not drink alcohol while taking PRZ-METFORMIN.
- Stop taking PRZ-METFORMIN right away and talk to your healthcare professional if you have these symptoms:
  - discomfort, muscle pain, difficult or fast breathing, extreme tiredness, weakness, upset stomach, stomach pain, feeling cold, low blood pressure or slow heartbeat.
- PRZ-METFORMIN can also cause diarrhea, nausea, upset stomach, bloating, gas or loss of appetite.
  - If any of these side effects come back after you are on the same dose of PRZ-METFORMIN for many days or weeks, tell your healthcare professional right away. These symptoms may be due to lactic acidosis.
- Lactic acidosis must be treated in the hospital. Your healthcare professional will decide the best treatment options for you.

What is PRZ-METFORMIN used for?

PRZ-METFORMIN is used to improve blood sugar levels in adults with type 2 diabetes mellitus. It is used in addition to proper diet, exercise and weight loss. PRZ-METFORMIN can be used with other antidiabetic medicines or by itself.

How does PRZ-METFORMIN work?

- PRZ-METFORMIN helps to control your blood sugar. It is believed to help your body respond better to the insulin it makes naturally.
- High blood sugar can be lowered by diet and exercise, by a number of medicines taken by mouth, and by insulin shots.

- While you take PRZ-METFORMIN, continue to exercise and follow the diet advised by your healthcare professional for your diabetes.

What are the ingredients in PRZ-METFORMIN?
Medicinal ingredients: metformin hydrochloride
Non-medicinal ingredients: crospovidone, magnesium stearate, povidone and starch pregelatinised. Tablet coating is comprised of hypromellose, polyethylene glycol, and titanium dioxide.

PRZ-METFORMIN comes in the following dosage forms:
Tablets; 1000 mg

Do not use PRZ-METFORMIN if you:
- have Type I diabetes that is unstable and/or insulin-dependent
- have metabolic acidosis (including diabetic ketoacidosis, or a history of ketoacidosis with or without coma
- have a history of lactic acidosis (too much acid in the blood)
- have severe liver or kidney problems
- regularly drink alcohol
- are going to get an injection of dyes (iodinated contrast materials) for medical imaging.
- Have heart system collapse(blood circulation failure) or heart problems that can cause hypoxemia (low oxygen in the blood)
- are stressed, have a severe infection, or are experiencing trauma
- will have surgery and during recovery after your surgery
- suffer from severe dehydration (have lost a lot of water from your body) or shock
- are hypersensitive or allergic to metformin or any other ingredient in this medicine or component of the container
- are pregnant or planning to become pregnant
- are breastfeeding

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PRZ-METFORMIN. Talk about any health conditions or problems you may have, including if you:
- have liver or kidney problems
- have a history of kidney problem
- are 80 years or older and you have NOT had your kidney function tested
- have metabolic acidosis (e.g. diabetic ketoacidosis)
- have had a recent heart attack
- have had recent stroke
- have a serious infection
- are dehydrated
- are scheduled for surgery
- are scheduled for and x-ray or scanning procedures
- are pregnant, breast-feeding or planning to become pregnant
- have vitamin B12 or folic acid deficiency
- drink alcohol
- have hormone problems (adrenal or pituitary glands)
- have low blood sugar

- have a low daily calorie intake

Other warnings you should know about:

Vitamin B_{12} levels:
- PRZ-METFORMIN can cause your vitamin B_{12} levels to be low. This can cause **peripheral neuropathy** (nerve damage).

Thyroid problems:
- PRZ- METFORMIN can cause **hypothyroidism** (low thyroid hormone levels) if:
  - you have thyroid problems or if you are being treated with levothyroxine (a drug used to treat thyroid problems).
- Your healthcare professional will monitor your thyroid health during treatment.

See the "Serious side effects and what to do about them" table, below, for more information on these and other serious side effects.

Low Blood Sugar:
- PRZ- METFORMIN rarely causes hypoglycemia (low blood sugar) by itself.
- Hypoglycemia can happen if you:
  - do not eat enough
  - drink alcohol
  - take other medicines to lower blood sugar.
  - have hormone (adrenal or pituitary gland) or liver problems

Check-ups and testing: You will have regular visits with your healthcare professional, before, during and at the end of your treatment. They will:
- Do blood and urine tests to check your blood health and sugar levels.
- Check that your heart, eyes, thyroid and liver are working properly.
- Check your kidney health before starting treatment and during treatment with PRZ-METFORMIN.

Patients older than 65 years old:
- You should not take PRZ-METFORMIN if you are older than 80 years old unless certain tests are done to check your kidney health.

Pregnancy and breastfeeding:
Female patients
- Do not take PRZ-METFORMIN if you are pregnant. It may harm your unborn baby.
- Tell your healthcare professional right away if you become pregnant or think you may be pregnant during your treatment with PRZ-METFORMIN.
- Do not breastfeed while you are taking PRZ-METFORMIN.

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

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 PRZ-METFORMIN

- Other diabetes medicines like glyburide, insulin, and rosiglitazone
- intravenous contrast dyes (such as intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast material)
- Nifedipine, used to treat high blood pressure, chest pain and Raynaud's phenomenon
- Medicines used to treat heart failure and irregular heartbeats like digoxin
- Medicines used to treat pain like morphine
- Medicines used to treat irregular heartbeats like procainamide, quinidine
- Medicines used to lower stomach acid like ranitidine and cimetidine
- Medicine used to treat malaria like quinine
- Medicines used to treat bacterial infections (antibiotics) like trimethoprim, vancomycin
- Medicines used as blood thinners like phenprocoumon
- Medicines used to lower the extra fluid in your body (diuretics), like furosemide, amiloride, triamterene
- Medicines that create high blood sugar and may lead to a loss of blood sugar control. Examples include:
  - Thiazide and other diuretics (used to lower the extra fluid in your body)
  - Phenytoin, used to treat epilepsy
  - Nicotinic acid, used to prevent and treat low niacin
  - Isoniazid, used to treat active tuberculosis infections
  - Corticosteroids (anti-inflammatory drugs) like prednisone
  - Phenothiazines, used to treat mental and emotional disorders
  - Thyroid hormone drugs, like levothyroxine
  - Female hormones like estrogens or estrogens plus progestogen
  - Oral birth control
  - Sympathomimetics (used to stimulate the sympathetic nervous system)
  - Medicines used to lower blood pressure, like amlodipine, felodipine, veramapil and diltiazem
  - Medicines for asthma such as salbutamol or formoterol
- Medicines used to treat high blood pressure (ACE-inhibitors) like enalapril, lisinopril and quinapril

How to take PRZ-METFORMIN:

- Take exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Take by mouth with a meal.
- Swallow tablets whole with a glass of water. Do not break or crush tablets.

Usual dose:

- **Adults 18 years and older:** Your healthcare professional will decide on the best dosage for you based on your condition.
- Your healthcare professional may lower your dose, stop your treatment for a period of time or recommend that you stop treatment completely. This may happen if you:
  - experience serious side effects, or
  - your disease gets worse.

Overdose:

If you think you, or a person you are caring for, have taken too much PRZ-METFORMIN, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Symptoms of overdose may include:

- rapid breathing or trouble in breathing
- stomach pain
- nausea and vomiting followed by diarrhea
- drowsiness, weakness, dizziness
- headache

Missed Dose:

If you miss a dose of PRZ-METFORMIN:

- Do not take a double dose to make up for missed dose.
- Take the next dose at the usual time.

What are possible side effects from using PRZ-METFORMIN?

These are not all the possible side affects you may have when taking **PRZ-METFORMIN**. Taking PRZ-METFORMIN with meals can help to reduce these side effects. If you experience any side effects not listed here, tell your healthcare professional.

- diarrhea
- nausea, vomiting
- upset stomach
- abdominal pain, bloating
- gas
- loss of appetite
- weight loss
- metallic taste
- skin problems: skin reaction, rash, itchy skin

PRZ-METFORMIN can cause abnormal blood test results. Your healthcare professional will do blood tests during your treatment.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Encephalopathy (disease of the brain that severely alters thinking): Possible neurological symptoms include: muscle weakness in one			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
area, poor decision-making or concentration, involuntary twitching, trembling, difficulty speaking or swallowing, seizures.			
Hemolytic anemia (breakdown of red blood cells): symptoms may include fatigue, pale color, rapid heartbeat, shortness of breath, dark urine, chills, and backache.			√
Lactic Acidosis (high level of acid in the blood) that can cause death: 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, 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.			√
Peripheral neuropathy (a result of damage to your peripheral nerves): signs and symptoms might include 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			
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
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, talk to 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health 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°C 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 PRZ-METFORMIN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-

products/drug-product-database.html); the manufacturer's website www.pharmaris.com, or by calling 1-866-913-7955

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