PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrGLUMETZA®

Metformin Hydrochloride Extended- Release Tablets, Mfr. Std.
500 mg and 1000 mg

PrGLUMETZA® (SB)

Metformin Hydrochloride Extended- Release Tablets, Mfr. Std.
1000 mg

Oral Antihyperglycemic Agent

Bausch Health, Canada Inc.
2150 St-Elzear Blvd. West
Laval, Quebec
H7L 4A8

Date of Initial Authorization:
November 03, 2015

Date of Revision:
February 15, 2023

Submission Control number: 264310

RECENT MAJOR LABEL CHANGES

N/A	

TABLE OF CONTENTS

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

PART 1: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

GLUMETZA and GLUMETZA (SB) (metformin hydrochloride) extended-release tablets are indicated for:

- the control of hyperglycemia in adult patients with type 2 (non-insulin-dependent, mature onset) diabetes, as an adjunct to dietary management, exercise, and weight reduction, or when insulin therapy is not appropriate.

- may be used as monotherapy, or concomitantly with a sulfonylurea.

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

Controlled clinical studies of metformin hydrochloride 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 hydrochloride 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 treatment should not be initiated in patients greater 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, because aging is associated with reduced renal function **(see** 7 WARNINGS AND PRECAUTIONS, Renal). Metformin is contraindicated in patients with severe renal impairment (see 2 CONTRAINDICATION). 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 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Lactic Acidosis, 7.1.4 Geriatrics)

2. CONTRAINDICATIONS

GLUMETZA and GLUMETZA (SB) (metformin hydrochloride) extended-release tablets are contraindicated for patients:

- Who are hypersensitive to this drug 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, Strengths, Composition and Packaging section of the Product Monograph.

- With unstable and/or Type 1 (insulin-dependent) diabetes mellitus.

- With acute or chronic metabolic acidosis, including 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.

- In the presence of 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).

- 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, metformin hydrochloride 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. 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 stressful conditions, such as severe infections, trauma or surgery and the recovery phase thereafter.
- Suffering from severe dehydration.
- During pregnancy and breast feeding (see 7.1.1 Pregnant Women and 7.1.2 breastfeeding).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Lactic acidosis is a rare, but serious, metabolic complication that may occur during treatment with GLUMETZA and GLUMETZA (SB) (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Lactic Acidosis).

Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking GLUMETZA and GLUMETZA (SB), 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

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. GLUMETZA and GLUMETZA (SB) treatment should not be initiated in patients older than 80 years of age, unless their renal function is not significantly reduced (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, 7.1.4 Geriatrics).

GLUMETZA and GLUMETZA (SB) extended-release tablets must be taken once daily with food to ensure optimum delivery of the metformin dose to the systemic circulation. (see 10 Clinical Pharmacology, Pharmacokinetics). In adult type 2 diabetic patients, individual determination of the minimum GLUMETZA and GLUMETZA (SB) dose that will adequately lower blood glucose 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.

During treatment initiation and dose titration, fasting plasma glucose should be used to determine the therapeutic response to GLUMETZA and GLUMETZA (SB), 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. GLUMETZA is contraindicated in patients with severe renal impairment [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2)], 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 GLUMETZA in patients with renal impairment.

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 GLUMETZA dosage adjustment, as necessary, should be made when GLUMETZA 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 recommended dose fails to lower the blood glucose adequately, the drug should be discontinued.

4.2 Recommended Dose and Dose Adjustment

GLUMETZA and GLUMETZA (SB) therapy should usually be initiated at 1000 mg once daily, taken with the evening meal. GLUMETZA and GLUMETZA (SB) extended-release tablets must be taken with food to ensure optimum delivery of the metformin dose to the systemic circulation. Gradual dose escalation in increments of 500 mg weekly are recommended, to reduce gastrointestinal side effects, and to permit identification of the minimum dose required for adequate glycemic control.

The maximum recommended dose is 2000 mg once daily, taken with the evening meal.

Renal function must be assessed prior to initiation of GLUMETZA 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 (see 7 WARNINGS AND PRECAUTIONS, Renal). The maximum daily dose of GLUMETZA in patients with an eGFR ≥30 mL/min/1.73 m^2 to <45 mL/min/1.73 m^2 is 1000 mg.

Transfer Other Antidiabetic Therapy

When transferring patients from standard oral hypoglycemic agents, other than chlorpropamide, to GLUMETZA or GLUMETZA (SB), no transition period generally is necessary. Patients treated with immediate release metformin have been switched to GLUMETZA or GLUMETZA (SB) once daily without incident (see 14 CLINICAL TRIALS) Following switching, from the IR formulation to GLUMETZA or GLUMETZA (SB), glycemic control should be closely monitored, and dosage adjustments made accordingly**.** 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 hypoglycemia.

Concomitant GLUMETZA or GLUMETZA (SB) and Oral Sulfonylurea Therapy in Adult Patients

If patients have not responded to four weeks of the maximum dose of GLUMETZA or GLUMETZA

(SB) monotherapy, consideration should be given to gradual addition of oral sulfonylurea while continuing GLUMETZA or GLUMETZA (SB) at the maximum dose, even if prior primary or secondary failure to a sulfonylurea has occurred. With concomitant metformin and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. In a clinical trial of patients with type 2 diabetes and prior treatment with glyburide, 15 mg/day, the efficacy of GLUMETZA in combination with glyburide was compared to the efficacy of glyburide alone (placebo), to achieve glycemic control as measured by significant reductions from baseline in FPG, HbA_{1c}, fructosamine and blood glucose response (see 14 CLINICAL TRIALS**).** The minimum effective dose of each drug should be identified. With concomitant GLUMETZA or GLUMETZA (SB) and sulfonylurea therapy, there is risk of hypoglycemia. Appropriate precautions should be taken. If patients have not satisfactorily responded to one to three months of concomitant therapy with the maximum dose of GLUMETZA or GLUMETZA (SB) and the maximum dose of an oral sulfonylurea, consider therapeutic alternatives including switching to insulin.

4.4 Administration

Tablets should be taken whole, with a glass of water. During treatment initiation and dose titration, fasting plasma glucose should be used to determine the therapeutic response to GLUMETZA and GLUMETZA (SB), and to identify the minimum effective dose for the patients
GLUMETZA and GLUMETZA (SB) extended-release tablets must be taken once daily with food, and should be taken whole, with a glass of water. Do not break or crush tablets.
.

4.5 Missed Dose

If a dose of GLUMETZA or GLUMETZA (SB) is missed, it should be taken as soon as possible, with food. However, if it is less than ten hours before the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses. If patients do not feel well, or home glucose testing shows elevated levels, a physician should be contacted.

5 OVERDOSAGE

Overdose with GLUMETZA and GLUMETZA (SB) has not been reported. 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, the presence of lactic acidosis should be excluded. The drug should be discontinued and proper supportive therapy should be instituted.

Overdose of metformin hydrochloride has been reported, including ingestion of amounts greater than 50 grams. Hypogylcemia 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 3 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Lactic Acidosis). Metformin is dialyzable with clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.
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 1: Summary Product Information

Route of Administration	Dosage Form/Strength	All - Nonmedicinal Ingredients
Oral	GLUMETZA Extended-release Tablets: 500 mg	Hypromellose, Microcrystalline Cellulose, Magnesium Stearate, Polyethylene Glycol, Polyethylene Oxide, Polysorbate, Titanium Dioxide.
	GLUMETZA (SB)	Colloidal Silicon Dioxide, Crospovidone, Dibutyl Sebacate, Ethylcellulose, Glyceryl Behenate,
	Extended-release Tablets: 1000 mg	Polyvinyl Alcohol, Povidone.
	GLUMETZA Extended-release Tablets: 1000 mg	Colloidal Silicon Dioxide, Crospovidone, Glyceryl Behenate, Polyvinyl Alcohol, Polyacrylate Dispersion, Hypromellose, Talc, Polyethylene Glycol, Titanium Dioxide, Simethicone Emulsion, Polysorbate, Shellac Glaze, Iron Oxide Black, Macrogol, N-butyl Alcohol, Propylene Glycol, FD&C Blue #2, FD&C Yellow#6 and FD&C Red #40.

GLUMETZA 500 mg: bottle of 500 tablets
GLUMETZA 1000 mg: bottle of 90 tablets
GLUMETZA (SB) 1000 mg: bottle of 1000 tablets

7 WARNINGS AND PRECAUTIONS

General

Use of GLUMETZA and GLUMETZA (SB) 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 GLUMETZA and GLUMETZA (SB) are not given when a contraindication exists. If during 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 GLUMETZA and GLUMETZA (SB) therapy, the drug should be promptly discontinued.

Driving and Operating Machinery

Patients should be warned about driving or operating a vehicle or potentially dangerous machinery under conditions where a risk of hypoglycemia is present (see 7 WARNINGS AND PRECAUTIONS). When GLUMETZA and GLUMETZA (SB) is used in combination with a sulfonylurea or in combination with insulin patients should be advised to take precautions to avoid hypoglycaemia while driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism

Change in clinical status of previously controlled type 2 diabetes patient:

A diabetic patient previously well controlled on GLUMETZA and GLUMETZA (SB) 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 GLUMETZA and GLUMETZA (SB) must be stopped immediately and appropriate corrective measures initiated **(**see WARNINGS AND PRECAUTIONS**)**.

Hypoglycemia

Hypoglycemia does not occur in patients receiving metformin hydrochloride 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 alcohol.
Elderly debilitated or malnourished patients and those with adrenal or pituitary insufficiency are particularly susceptible to hypoglycemic effect.
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, 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 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 may occur during treatment with GLUMETZA and GLUMETZA (SB). 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, deceased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin has been implicated in lactic acidosis, metformin plasma levels > 5ug/mL have been generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (0.03 cases/1000 patient years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion. Patients with congestive heart failure requiring pharmacologic management are at increased risk of lactic acidosis. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. 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 GLUMETZA and GLUMETZA (SB), and by use of the minimum effective dose of GLUMETZA and GLUMETZA (SB). In addition, GLUMETZA and GLUMETZA (SB) 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, GLUMETZA and GLUMETZA (SB) should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake when taking GLUMETZA and GLUMETZA (SB), since alcohol intake potentiates the effect of metformin hydrochloride on lactate metabolism. The onset of lactic acidosis often is subtle, and accompanied only by non- specific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and non-specific abdominal distress. Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking GLUMETZA and GLUMETZA (SB), the drug should be discontinued immediately. Because metformin hydrochloride is dialysable, 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, GLUMETZA or GLUMETZA (SB) 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 GLUMETZA and temporarily administer insulin. GLUMETZA be reinstituted after the acute episode is resolved.

Vitamin B12 levels

Impairment of vitamin B12 absorption has been reported in some patients. Therefore, measurements of serum vitamin B12 are advisable at least every one to two years in patients on long-term treatment with GLUMETZA and GLUMETZA (SB).
A decrease to subnormal levels of previously normal serum Vitamin B12 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 B12 absorption from B12 -intrinsic factor complex is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on 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 B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Long-term treatment with metformin has been associated with a decrease in serum vitamin B12 levels

which may cause peripheral neuropathy. Serious cases of peripheral neuropathy have been reported with metformin treatment in the context of vitamin B12 deficiency. Monitoring of serum vitamin B12 levels is recommended.

Hematologic

Serious cases of metformin-induced hemolytic anemia, some with a fatal outcome, have been reported. 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, GLUMETZA and GLUMETZA (SB) should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. GLUMETZA and GLUMETZA (SB) are contraindicated in patients suffering from severe hepatic dysfunction (see 2 CONTRAINDICATIONS).

Serious cases of pancreatitis have been reported in patients receiving metformin. The reported pancreatitis cases occurred either in the context of an acute metformin overdose (see 5 OVERDOSAGE, 8.5 Post-Market Adverse Reactions) 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 GLUMETZA and GLUMETZA (SB) should be monitored by periodic measurement 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 dose response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control.

More frequent glucose monitoring should be considered when GLUMETZA and GLUMETZA (SB) are 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 GLUMETZA 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). GLUMETZA must be discontinued if the eGFR decreased to ≤ 30mL/min/1.73 m^2 (see 2 CONTRAINDICATIONS).

Initial and periodic monitoring of hematologic parameters (e.g. hemoglobin/hematocrit and red blood cell indices). While megaloblastic anemia has rarely been seen with metformin hydrochloride therapy, if this is suspected, vitamin B_{12} deficiency should be excluded (see 7 WARNINGS AND PRECAUTIONS, Hematologic)

Particular attention should be paid to short range and long-range complications which are peculiar to

diabetes. Periodic cardiovascular, ophthalmic, hepatic and are advisable **(**see 7 WARNINGS AND PRECAUTIONS**)**.

Regular monitoring of thyroid-stimulating hormone (TSH) levels is recommended in patients with hypothyroidism (see 7 WARNINGS AND PRECAUTIONS, Hypothyroidism).

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 GLUMETZA and GLUMETZA (SB) and phenprocoumon or other antivitamin K anticoagulants, a close monitoring of the International Normalized Ratio (INR) is recommended (see 9.4 DRUG-DRUG INTERACTIONS).

Neurologic

Serious cases of metformin-induced encephalopathy have been reported (see 8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Drug Reactions). Some of these cases were reported without association with lactic acidosis, hypoglycemia, or renal impairment.

Peri-operative Considerations

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

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 GLUMETZA (see 2 CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned, GLUMETZA 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.

Renal

Metformin hydrochloride is excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. GLUMETZA and GLUMETZA (SB) is contraindicated in patients with severe renal impairment; eGFR <30 mL/min/1.73 m^2 (see 2 CONTRAINDICATIONS). Renal function must be assessed prior to initiation of GLUMETZA or GLUMETZA (SB) and periodically thereafter, with more frequent monitoring in patients whose eGFR decreases to less than 60 mL/min/1.73 m^2. In patients with advanced age, 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 GLUMETZA or GLUMETZA (SB) should not be titrated to the maximum dose (see 4.1 Dosing Considerations and 4.2 Recommended Dose and Dose Adjustment). In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and GLUMETZA and GLUMETZA (SB) 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.

Radiologic studies involving the use of iodinated contrast materials can lead to acute renal failure and have been associated with lactic acidosis in patients receiving metformin. Metformin should be discontinued 2 days before radiologic studies and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Use of concomitant medications that may affect renal function or metformin disposition: Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see 9.4 Drug-Drug Interactions), should be used with caution.

7.1 Special Populations

7.1.1 Pregnant Women

GLUMETZA and GLUMETZA (SB) are contraindicated during pregnancy (see 2 CONTRAINDICATIONS). Safety of metformin in pregnant women has not been established. There are no adequate and well- controlled studies in pregnant women. Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. It is recommended that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

The combined fertility and developmental toxicity study in rats, (0, 150, 450, or 900 mg/kg/day orally) showed no adverse effects on fertility or embryofetal development, although a decrease in male reproductive organ weights was observed at a dose of 900 mg/kg/day. An embryofetal development study in rabbits revealed no effects on gross external, soft tissue, or skeletal malformation or variations at dose up to 90 mg/kg/day (see 16 TOXICOLOGY).

7.1.2 Breast-feeding

GLUMETZA and GLUMETZA (SB) are contraindicated in breast-feeding women (see 2 CONTRAINDICATIONS).Studies in lactating rats have shown 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.

7.1.4 Geriatrics: (> 80 years of age)

Metformin treatment should not be initiated in patients greater 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, 7.1.4 Geriatrics). Care should be taken in dose selection which should be based on careful and more frequent monitoring of renal function. In patients with advance age, metformin should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is

associated with reduced renal function **(**See 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics and Special Populations**)**. Generally, elderly patients should not be titrated to the maximum dose of GLUMETZA and GLUMETZA (SB) (see 4.1 Dosing Considerations, 4.2 Recommended Dose and Dosage Adjustment).

8. ADVERSE REACTIONS

8.1 Adverse Drug Reaction Overview

Lactic acidosis is a rare, but serious adverse reaction associated with GLUMETZA and GLUMETZA (SB) treatment. Lactic acidosis is fatal in approximately 50% of cases (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Lactic Acidosis).

Gastrointestinal symptoms (GI) (diarrhea, nausea, vomiting, abdominal pain, abdominal distention, dyspepsia, and flatulence.) are common reactions to metformin hydrochloride treatment. These symptoms are generally transient and resolve spontaneously during continued treatment.

Additionally, as GI symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take their medication with meals.

8.2 Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In clinical trials conducted in the U.S., over 1000 patients with type 2 diabetes mellitus have been treated with GLUMETZA 1500 – 2000 mg/day in active-controlled and placebo-controlled studies.

Gastrointestinal disorders were the most frequently occurring events in all trials. **Table 2** shows the combined incidence of gastrointestinal adverse events occurring in one Phase 2 study and one Phase 3 study comparing GLUMETZA to immediate- release metformin, coupled with the open label extension of the Phase 3 study.

Table 2 Combined Gastrointestinal Adverse Events Occurring in at least 5% of Patients, in Three Clinical Trials*

System organ class/preferred term	GLUMETZA 1500 mg QD N=176 (%)	GLUMETZA 2000 mg QD N=279 (%)	Metformin IR 1500 mg am/pm N=174 (%)
Patients with at least one AE	133 (75.6)	222 (79.6)	136 (78.2)
Gastrointestinal disorders	85 (48.3)	134 (48.0)	73 (42.0)
Diarrhea	32 (18.2)	63 (22.6)	30 (17.2)
Nausea	30 (17)	41 (14.7)	24 (13.8)
Dyspepsia	15 (8.5)	35 (12.5)	13 (7.5)

Vomiting	14 (8.0)	15 (5.4)	6 (3.5)
Abdominal distention	5 (2.8)	22 (7.9)	1 (0.6)
Constipation	8 (4.5)	14 (5)	5 (2.9)
Abdominal pain	13 (7.4)	12 (4.3)	7 (4.0)

* Combined data is from one Phase 2 study and one Phase 3 study comparing GLUMETZA to immediate- release metformin coupled with the open label extension of the Phase 3 study.

In the Phase 3 trial comparing the safety and efficacy of GLUMETZA to metformin immediate-release tablets, all four treatment regimens (GLUMETZA at 1500 mg QD, 1500 mg BID, 2000 mg QD and Metformin IR 1500 mg BID) had comparable safety profiles. Patients in the once-daily treatment groups did not report any higher occurrence of adverse events than the twice daily treatment groups. The occurrence of GI adverse events was comparable between all treatment groups. All GLUMETZA treatment groups reported fewer occurrences of diarrhea and nausea than did the immediate-release treatment group during the first week of the titration period [1000 mg dose].

In the placebo-controlled study, patients receiving background glyburide (SU; sulfonylurea) therapy were randomized to receive add-on treatment of either one of three different regimens of GLUMETZA or placebo. In total, 431 patients received GLUMETZA + SU and 144 patients placebo + SU. Adverse events reported in greater than 5% of patients treated with GLUMETZA, that were more common in the combined GLUMETZA + SU group, than in the placebo + SU group, are shown in Table 3.

In 0.7% of patients treated with GLUMETZA + SU, diarrhea was responsible for discontinuation of study medication compared to zero in the placebo + SU group.

Table 3 Treatment-Emergent Adverse Events Reported By >5%* of Patients for the Combined GLUMETZA Group Versus Placebo Group

Adverse Event (MedDRA Preferred Term)	GLUMETZA + SU (n = 431)	Placebo + SU (n = 144)
Hypoglycemia	13.7%	4.9%
Diarrhea	12.5%	5.6%

Adverse Event (MedDRA Preferred Term)	GLUMETZA + SU (n = 431)	Placebo + SU (n = 144)
Nausea	6.7%	4.2%

***AE's that were more common in the GLUMETZA-treated than in the placebo-treated patients.**

In the same study, the following adverse events were reported by 1-5% of patients for the combined GLUMETZA group and these events occurred more commonly in the GLUMETZA-treated than in the placebo-treated patients:

- Ear and labyrinth disorders: ear pain
- Gastrointestinal disorders: vomiting, dyspepsia, flatulence, abdominal pain upper, abdominal distension, abdominal pain, toothache, loose stools
- General disorders and administration site conditions: asthenia, chest pain
- Immune system disorders: seasonal allergy
- Infections and infestations: gastroenteritis viral, tooth abscess, tonsillitis, fungal infection
- Injury, poisoning and procedural complications: muscle strain
- Musculoskeletal and connective tissue disorders: pain in limb, myalgia, muscle cramp Nervous system disorders: dizziness, tremor, sinus headache, hypoaesthesia Respiratory, thoracic and mediastinal disorders: nasal congestion
- Skin and subcutaneous tissue disorders: contusion
- Vascular disorders: hypertension

8.3 Less common Clinical Trial Adverse Drug Reactions (< 1%)

The following adverse drug reactions were reported with <1% incidence in patients in any GLUMETZA treatment group in the placebo-controlled trial:

- Blood Disorders**:** thrombocytopenia, neutropenia
- Eye disorders: vision blurred
- Gastrointestinal disorders**:** flatulence, gastric, gastrointestinal upset, loose stools, vomiting
- General disorders and administration site conditions: adverse drug reaction, asthenia, chest pain, fatigue, lethargy, oedema aggravated, oedema peripheral, rigors
- Infection and Infestations: gastroenteritis viral
- Investigations: blood glucose decreased, liver function test abnormal, muscle cramp, white blood cell count increased
- Metabolism and Nutrition Disorders: hyperglycemia.
- Nervous System Disorders: dizziness, migraine, parasthesia, syncope, tremor
- Reproductive System and Breast Disorders: sexual dysfunction
- Respiratory Disorders: rhinorrhea, sinus congestion

8.5 Post-Market Adverse Reactions

Post Market Adverse Reaction as per GLUCOPHAGE include the following:

- Blood and Lymphatic System Disorders: Hemolytic anemia, some with a fatal outcome
- 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.
- Investigations: Blood lactic acid increased, hypomagnesemia in the context of diarrhea, reduction of thyrotropin level in patients with treated or untreated hypothyroidism.
- Metabolism and Nutrition Disorders: Lactic acidosis, decrease of vitamin B12 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.
- 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 metformin in the treatment of diabetes, particularly sulfonylureas.The simultaneous administration of GLUMETZA with sulfonylureas must be carefully monitored to prevent hypoglycemic reaction, especially if they are given to patients also receiving other drugs which can potentiate their effect. For example, the effect of sulfonylureas can be potentiated by long-acting sulfonamides, tuberculostatics, phenylbutazone, clofibrate, monoamine oxidase inhibitors, salicylates, probenecid and propranolol.

9.3 Drug-Behavioural Interactions

Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking GLUMETZA and GLUMETZA (SB), since alcohol intake potentiates the effect of metformin hydrochloride on lactate metabolism (see 2 CONTRAINDICATIONS).

9.4 Drug-Drug Interactions

GLUMETZA and sulfonylurea: With concomitant GLUMETZA and sulfonylurea (SU) therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. The influence of glyburide on GLUMETZA pharmacokinetics was assessed in a single-dose interaction study in healthy subjects. Co-administration of GLUMETZA and glyburide did not result in any changes in metformin pharmacokinetics, as AUC, C_{max}, and T_{max}, were unchanged. Changes in pharmacodynamics were not evaluated in this study **(**see 4 DOSAGE AND ADMINISTRATION, Concomitant GLUMETZA and Oral Sulphonylurea Therapy**)**. In a clinical trial of patients with type 2 diabetes and prior treatment with glyburide, GLUMETZA plus glyburide combined therapy yielded a significant decrease from baseline to endpoint in mean HbA_{1c}, relative to SU treatment alone (see 10 CLINICAL PHARMACOLOGY, 14 CLINICAL TRIALS). With concomitant GLUMETZA and sulfonylurea therapy, the risk of hypoglycemia associated with sulfonylurea therapy exists. Appropriate precautions should be taken. If patients have not satisfactorily responded to one to three months of concomitant therapy with the maximum dose of GLUMETZA and the maximum dose of an oral sulfonylurea, consider therapeutic alternatives including switching to insulin.

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.

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

Drugs that have a tendency to produce hyperglycemia and may lead to a loss of blood sugar control include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, estrogen plus proestrogen, oral contraceptive, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs and isoniazid. When such drugs are administered to patients receiving GLUMETZA and GLUMETZA (SB), the patient should be closely observed to maintain adequate glycemic control.

Furosemide
A single dose metformin - furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood 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 when co-administered chronically.

Nifedipine
A single dose metformin - nifedipine drug interaction study in healthy subjects demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, and increased the amount excreted in the urine. T_{max} and half life were unaffected.

Cationic Drugs
(amiloride, cimetidine, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, vancomycin) These drugs theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction has been observed between metformin and oral cimetidine in normal healthy volunteers in both single and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC was observed. The H2-blocker cimetidine competitively inhibits renal tubular secretion of metformin, significantly decreasing its clearance and increasing its bioavailability. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Therefore, careful patient monitoring and dose adjustment of metformin or the interfering drug is recommended in patients who are taking cationic medications that are excreted via renal tubular secretion (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests)

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 GLUMETZA dosage adjusted as necessary.

Anticoagulant phenprocoumon: Elimination rate of the anticoagulant phenprocoumon has been reported to be increased by 20% when used concurrently with metformin. Patients receiving phenprocoumon or other antivitamin K anticoagulants should be monitored carefully when both types of drugs are used simultaneously. In such cases, an important increase of prothrombin time

may occur upon cessation of metformin therapy, with an increased risk of hemorrhage (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

9.5 Drug-Food Interactions

GLUMETZA and GLUMETZA (SB) extended-release tablets have been formulated to be dosed with food. Both GLUMETZA and GLUMETZA (SB) extended-release tablets must be taken with food to ensure complete release and absorption of the metformin dose. In a single-dose study with the 500 mg tablet, when the product was given to healthy volunteers while fasting or with a high fat, or a AHA 30% low fat meal, AUC was increased significantly and a delay in T_{max} was observed when compared to the fasted state. The increase in AUC was significantly greater when the product was given with the high fat meal. There was no significant difference in C_{max}. In an open label pharmacoscintigraphic pharmacokinetic study in healthy volunteers, GLUMETZA 500 mg dosed with different fat content meals was evaluated. Both the gastric retention time and the systemic exposure of metformin were higher following the high fat meal than following the AHA 30% fat meal, demonstrating that prolonged gastric retention enables extended delivery of metformin (see 4 DOSAGE AND ADMINISTRATION).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory 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, **(**see 7 WARNINGS AND PRECAUTIONS**)** 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.

DETAILED PHARMACOLOGY

The mechanism of the antihyperglycemic effect of metformin is not completely understood and probably several actions are involved. The following mechanisms of action have been suggested: 1) increased insulin receptor binding; 2) decreased intestinal glucose absorption; 3) increased cellular glucose uptake; 4) decreased hepatic gluconeogenesis; 5) stimulation of anaerobic glycolysis; and 6) potentiation of insulin action at the receptor or post-receptor level.

At therapeutic doses, metformin does not lower plasma glucose levels in non-diabetic animals or humans. However, oral administration of metformin was shown to effectively lower plasma glucose levels in several different animal models of hyperglycemia, including streptozotocin-induced diabetic mice, genetically diabetic KK mice, obese female fa/fa rats, and alloxan-induced diabetic rats. Metformin does not reduce basal glucose concentrations below the normal physiological range, either in diabetic animals or humans.

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.

Animal studies have demonstrated that metformin inhibits intestinal glucose absorption in both normal and diabetic animals, although the concentrations necessary to produce this effect are usually higher than the therapeutic range. The inhibition of intestinal glucose absorption does not appear to account for the full ability of metformin to reduce glycemia, indicating that other mechanisms of action play a role. The effect of metformin on glucose absorption has not been confirmed in diabetic patients.

Several studies have been conducted, both in vitro and in vivo, to determine the effects of metformin on glucose uptake into tissues, glucose oxidation, and glycogen synthesis. In general, metformin potentiates insulin-mediated glucose uptake into tissues, with the skeletal muscle being the most important site. This effect of metformin appears to be due to facilitation of a post-receptor sensitivity to insulin. Metformin was shown to have no effect on basal or insulin-stimulated glucose oxidation in muscle from non-diabetic mice but potentiated glucose oxidation in muscle from streptozotocin-diabetic mice in the presence of insulin. Metformin also increased basal glucose oxidation in adipocytes from non-diabetic rats. The results of studies on glycogen synthesis have been less consistent, with metformin producing either no effect or an increase in insulin-stimulated glycogen synthesis in skeletal muscle of non-diabetic and diabetic animals.

Many studies in diabetic animals and human diabetic patients have demonstrated that metformin improves glucose tolerance, an effect that is less pronounced or absent in non- diabetic individuals. Studies at the cellular level indicate that metformin potentiates insulin action and results from in vitro studies support a post-receptor mechanism of action.

In addition to antihyperglycemic effects, metformin has been shown to have hypolipidemic effects and to significantly improve the progression and regression of atherosclerotic lesions. Metformin has been shown to be effective in inhibiting fructose- and fat-induced hypertriglyceridemia; it appears that metformin inhibits the transfer of dietary triglyceride from the gastrointestinal tract into plasma and reduces the uptake of the absorbed lipid by adipose tissue.

Several studies were conducted to determine the effects of metformin on the lipoprotein composition of VLDL from normal and cholesterol-fed animals. The results indicated that metformin produced changes in the lipoprotein composition in cholesterol-fed animals toward a more normal composition. In addition, it produced structural modifications of VLDL that led to a rapid turnover and a decreased interaction with arterial wall binding components.
Metformin also altered lipid metabolism in the aortic wall, inhibiting intramural lipid biosynthesis.

Metformin has been shown to reduce blood pressure in spontaneously hypertensive rats. The suggested mechanisms involved in this effect include a sympathoinhibitory effect, a direct effect on vascular smooth muscle responsiveness to norepinephrine, and attenuation of hyperinsulinemia.

Several drug interaction studies with metformin were available in the scientific literature. Metformin was shown to enhance the elimination of phenprocoumon in diabetic patients. Because studies in rats did not demonstrate any effect of metformin on liver microsomal enzymes, it was postulated that an increase in liver blood flow might explain the drug interaction between metformin and phenprocoumon. Metformin was also shown to counteract the hyperglycemic effects of diazepam and nifedipine.

10.2 Pharmacodynamics

The Glumetza® tablet utilises a delivery technology, an aqueous-coating Smart-coat™ version of the extended-release tablet formulation. Since the tablet coating controls the release of metformin, the tablet does not need to dissolve or break down in order to deliver the specified dose of metformin. Therefore, the tablet coating may be retrieved in the stool.

Metformin hydrochloride is a biguanide anti-hyperglycemic agent, which is widely used for the treatment of type 2 diabetes mellitus (non-insulin-dependent diabetes mellitus [NIDDM]. Metformin improves glycemic control by enhancing insulin sensitivity in liver and muscle and reducing gastrointestinal glucose absorption and hepatic glucose production. However, it does not stimulate insulin secretion and, therefore, is not associated with hypoglycemia. Improved metabolic control with metformin does not induce weight gain and may cause weight loss. It has been demonstrated that the favorable effects of metformin also include improvements in factors associated with cardiovascular risk including lipids, fibrinolysis and body weight.
The Glumetza® tablet utilises a delivery technology, an aqueous-coating Smart-coat™ version of the extended-release tablet formulation. Since the tablet coating controls the release of metformin, the tablet does not need to dissolve or break down in order to deliver the specified dose of metformin. Therefore, the tablet coating may be retrieved in the stool.

10.3 Pharmacokinetics

GLUMETZA pharmacokinetics have been characterized after oral administration of single and multiple doses to adult healthy volunteers, in eleven separate studies.

Table 4: Summary of Mean Pharmacokinetic Parameters

Pharmacokinetic Parameters (n-=35)	A Metformin HCl ER 500 mg Tablets 500 mg (YT5402)	B Metformin HCl ER 500 mg Tablets 2 x 500 mg (YT5402)	C Metformin HCl ER 500 mg Tablets 3 x 500 mg (YT5402)	D Metformin HCl ER 500 mg Tablets 5 x 500 mg (YT5402)
AUC_{0-t} (ng*hr/mL)	3348 ± 830	6392 ± 1839	8911 ± 2828	13463 ± 4719
$AUC_{0-\infty}$ (ng*hr/mL)	3501 ± 796	6705 ± 1918	9299 ± 2833	14161 ± 4432
C_{max} (ng/mL)	473.1 ± 145.4	867.5 ± 223.4	1171.0 ± 297.4	1629.9 ± 398.7
T_{max} (hr)	3.9 ± 0.5	4.1 ± 0.5	3.9 ± 0.3	3.8 ± 0.4
t½ (hr)	6.9 ± 3.1	7.2 ± 2.5	7.5 ± 3.2	9.9 ± 8.6

Absorption
Following a single oral dose of 1000 mg GLUMETZA extended-release Tablets once-daily after a meal, the time to reach maximum plasma metformin concentration (T_{max}) is approximately 7 - 8 hours. In both single and multiple dose studies in healthy subjects, once daily 1000 mg dosing provides equivalent systemic exposure, as measured by area-under-the-curve (AUC), of metformin relative to the immediate release given as 500 mg twice daily.

Once daily oral doses of GLUMETZA 500 mg to 2500 mg doses resulted in less than proportional increases in both AUC and C_{max}. The mean C_{max} values were 473 ± 145, 868 ± 223, 1171 ± 297, and 1630 ± 399 ng/mL for once daily doses of 500, 1000, 1500, and 2500 mg, respectively. For AUC, the mean values were 3501 ± 796, 6705 ± 1918, 9299 ± 2833, and 14161 ± 4432 ng.hr/mL for once daily doses of 500, 1000, 1500, and 2500 mg, respectively.

Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from GLUMETZA extended-release tablets by about 38% and 73%, respectively, relative to fasting. Both meals prolonged metformin T_{max} by approximately 3 hours, but C_{max} was not affected. In an open label pharmacoscintigraphic pharmacokinetic study in healthy volunteers, GLUMETZA 500 mg dosed with different fat content meals was evaluated. Both the gastric retention time and the systemic exposure of metformin were higher following the high fat meal than following the AHA 30% fat meal, demonstrating that extended gastric retention enables extended delivery of metformin. For transit times less than 7 hours as sometimes seen in AHA 30% fat meal administration, absorption of metformin may be decreased almost linearly with decreasing upper GI transit time.

Distribution
The apparent volume of distribution (V/F) of metformin, following single oral doses of 850 mg immediate- release metformin hydrochloride averaged 654 ± 358 L. At doses of 500 to 1500 mg, metformin has an absolute oral bioavailability of 50% to 60%. The drug is not protein bound and therefore has a wide volume of distribution, with maximal accumulation in the small intestine wall. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally < 1 mcg/mL.

Metabolism

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Elimination
Metformin undergoes no modifications in the body and is secreted unchanged by rapid kidney excretion (through glomerular filtration and, possibly, tubular secretion). Impaired kidney function slows elimination and may cause metformin accumulation.

The apparent plasma elimination half-life of metformin following a single dose of GLUMETZA tablets is approximately 8 hours. Results from a dose proportionality study involving once daily oral doses of GLUMETZA 500 mg to 2500 mg, indicate a lack of dose proportionality with increasing doses, as both AUC and C_{max} increased nonlinearly within the investigated dose range.

Concomitant administration with glyburide (DIABETA®) does not lead to a change in the peak and systemic exposures of metformin. **(PART II: SCIENTIFIC INFORMATION, CLINICAL TRIALS)**

Special Populations and Conditions

Pediatrics
No pharmacokinetic studies of GLUMETZA or GLUMETZA (SB) in pediatric subjects were conducted.

Geriatrics
Limited data from controlled pharmacokinetic studies of metformin hydrochloride 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. 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 WARNINGS AND PRECAUTIONS, Special Populations).

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 $t_{1/2}$(males = 229, females = 260). However, C_{max} for metformin were somewhat higher in female subjects (Female/Male C_{max} Ratio = 1.4). The gender differences for C_{max} are unlikely to be clinically important.

Race and Ethnic Origin
There were no definitive conclusions on the differences between the races with respect to the pharmacokinetics of GLUMETZA because of the imbalance in the respective sizes of the racial groups. However, the data suggest a trend towards higher metformin C_{max} and AUC values for metformin are obtained in Asian subjects when compared to Caucasian, Hispanic and Black subjects. The differences between the Asian and Caucasian groups are unlikely to be clinically important.

Hepatic Insufficiency
No pharmacokinetic studies of GLUMETZA or GLUMETZA (SB) have been conducted in patients

with hepatic insufficiency.

Renal Insufficiency
In patients with decreased renal function (based on measured serum creatinine) the blood half-life of metformin is prolonged, and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

11. STORAGE AND STABILITY

GLUMETZA and GLUMETZA (SB) (metformin hydrochloride extended- release) tablets are to be stored at 15 ºC - 30˚C.

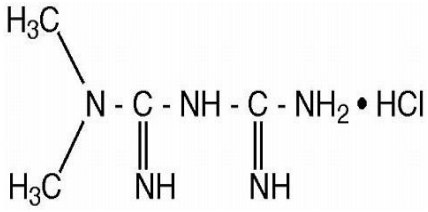
PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	metformin hydrochloride
Chemical Name:	1,1-dimethylbiguanide hydrochloride
Molecular Formula:	$C_4H_{11}N_5$•HCl
Molecular Mass:	165.63 g/mol

Structural formula:



Physiochemical Properties

Description:	Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63 g/mol.
Solubility:	Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform.
pKa:	The pK_a of metformin is 12.4.
pH:	The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

GLUMETZA and GLUMETZA (SB) tablets are modified release dosage forms that contain 500 mg or 1000 mg of metformin hydrochloride.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Four clinical studies were conducted in patients with type 2 diabetes, to establish the safety and efficacy of GLUMETZA extended-release tablets, as shown in the following **Table 5**.

Table 5 GLUMETZA Safety and Efficacy Trials

Trial Design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (range)	Gender
Phase 2, randomized, double-blind, parallel-group, active-controlled, dose-escalation, multicentre	1000 - 2,000 mg/day, orally for 4 weeks	163	54.6 (31-77)	83 M/ 80 F
Phase 3, randomized, double-blind, parallel-group, active-controlled, non-inferiority, multicentre	1500 - 2000 mg/day, orally for 24 weeks	706	54 (24-79)	380 M/ 326 F
Open-label, phase 3 extension to Study 81-0003,randomized, double-blind, active uncontrolled, multicentre	2000 mg orally for 24 weeks	245	56 (26-78)	135 M / 110 F
Phase 3, randomized, double-blind, parallel- group, active placebo-controlled (add-on), multicentre	1500 - 2000 mg/day, orally for 24 weeks	575	53 (25-80)	314M/ 261F

14.2 Study results

In a multicenter, randomized, double-blind, active-controlled, dose-ranging, parallel group study of GLUMETZA 1500 mg once a day, GLUMETZA 1500 per day in divided doses (500 mg in the morning and 1000 mg in the evening), and GLUMETZA 2000 mg once a day were compared to immediate release (IR) metformin 1500 mg per day in divided doses (500 mg in the morning and 1000 mg in the evening) (**Table 6**). Metformin IR treatment was initiated as 500 mg BID for 1 week followed by 500 mg with breakfast and 1000 mg with dinner from the second week. The 3-week titration period was followed by an additional 21-week period at the randomized dose. Each of the GLUMETZA regimens, were at least as effective as metformin IR in all measures of glycemic control. Once daily dosing of GLUMETZA was as effective as the commonly prescribed twice daily dosing of the immediate-release product.

Table 6 Mean±SE Changes from Baseline to Final Visit in HbA_{1c}, Fasting Plasma Glucose and Body Weight for the GLUMETZA and Metformin IR Treatment Groups (24-Week Study)

Parameter	GLUMETZA			Metformin IR 1500 mg AM/PM (n = 174)	Overall Treatment p-Value
	1500 mg QD (n = 178)	1500 mg AM/PM (n = 182)	2000 mg QD (n = 172)		
HbA_{1c} (%)					
n	169	175	159	170	
Baseline	8.22 ± 0.25	8.50 ± 0.24	8.26 ± 0.24	8.70 ± 0.25	0.483
Mean Change ± SE at Final Visit	-0.73 ± 0.12	-0.74 ± 0.12	-1.06 ± 0.12	-0.70 ± 0.12	0.013
Mean Difference ± SE from Metformin IR	-0.03 ± 0.12	-0.04 ± 0.12	-0.36 ± 0.12	N/A	
98.4% CI for Difference	(-0.32, 0.26)	(-0.33, 0.25)	(-0.65, -0.06)		
Fasting Plasma Glucose (mg/dL)					
n	175	179	170	172	
Baseline	190.0 ± 9.9	192.5 ± 9.9	183.9 ± 9.9	196.5 ± 11.2	0.855
Mean Change ± SE at Final Visit	-38.5 ± 4.4	-31.8 ± 4.4	-42.0 ± 4.5	-32.1 ± 4.5	0.051
Mean Difference ± SE from Metformin IR	-6.4 ±4.4	0.2 ± 4.3	-9.9 ± 4.4	N/A	
95% CI for Difference	(-15.0, 2.1)	(-8.3, 8.7)	(-18.5, -1.3)		
Body Weight (kg)					
n	176	180	171	173	
Baseline	88.17 ± 3.66	90.50 ± 3.66	87.73 ± 3.66	88.72 ± 3.87	0.954
Mean Change ± SE at Final Visit	-0.93 ± 0.40	-0.68 ± 0.40	-1.10 ± 0.40	-0.85 ±0.41	0.753
Mean Difference ± SE from Metformin IR	-0.09 ± 0.40	0.17 ± 0.39	-0.26 ± 0.40	N/A	
95% CI for Difference	(-0.86, 0.69)	(-0.61, 0.94)	(-1.04, 0.52)		

Patients who completed this 24-week study were placed on GLUMETZA 2000 mg/day treatment during a 24-week open-label trial in order to evaluate the long-term safety and duration of effectiveness of GLUMETZA. This resulted in the exposure of 158 patients to continuous treatment with GLUMETZA 1500-2000 mg/day (56 on 2000 mg/day) for a cumulative period of 48 weeks. GLUMETZA treatment maintained steady levels of HbA1c, FPG and plasma fructosamine over the 24-week period from the open-label baseline to the open-label endpoint. All treatment groups irrespective of previous treatment in the double-blind study, showed similar decreases in HbA1c, FPG and plasma fructosamine levels over the cumulative 48-week period from the double-blind baseline to the open-label phase.

In a double-blind, randomized, placebo-controlled (add-on), multicentre study, patients with type 2 diabetes mellitus who were newly diagnosed or treated with diet and exercise, or who were receiving monotherapy with metformin, sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, or meglinitides, or treated with combination therapy consisting of metformin/glyburide at doses up to 1000 mg metformin + 10 mg glyburide per day (or equivalent doses of glipizide or glimepiride up to half the maximum therapeutic dose) were enrolled. They were stabilized on glyburide for a 6-week period, and then randomized to 1 of 4 treatments: placebo + glyburide (glyburide alone); GLUMETZA 1500 mg once a day + glyburide, GLUMETZA 2000 mg once a day + glyburide, or GLUMETZA 1000 mg twice a day + glyburide. A 3-week GLUMETZA titration phase was followed by a 21-week maintenance treatment phase. There was a decrease from Baseline to Endpoint in mean HbA1c levels in the GLUMETZA + glyburide groups (mean change, -0.74%; 95% CI, -0.85, -0.64), but almost no change in the glyburide only group (mean change 0.08%; 95% CI, -0.08, 0.25). (See Table 6). The difference in the change from Baseline in HbA1c levels between the combined M-ER+ SU groups and the SU only group was statistically significant (p<0.001). The changes in glycemic control across the three GLUMETZA + glyburide groups were comparable.

Table 7 Mean±SE Changes from Baseline to Final Visit in HbA_{1c}, Fasting Plasma Glucose and Body Weight for the Combined GLUMETZA/Glyburide and Placebo/Glyburide Treatment Groups (24-Week Study)

Parameter	Combined GLUMETZA /Glyburide Groups (n = 431)	Placebo/Glyburide Group (n = 144)	Overall Treatment p-Value
HbA_{1c} (%)			
n	416	141	
Baseline	7.79 ±□0.07	8.08 ± 0.13	0.051
Mean Change ± SE at Final Visit	-0.74 ± 0.05	-0.08 ± 0.08	
Mean Difference ± SE from Glyburide Alone	-0.82 ± 0.09	N/A	
95% CI for Difference	(-1.00, -0.65)		
p-value for pairwise comparison	< 0.001		
Fasting Plasma Glucose (mg/dL)			
n	429	144	
Baseline	162.0 ± 2.7	164.0 ± 4.7	0.719
Mean Change ± SE at Final Visit	-13.0 ± 2.4	15.4 ± 3.7	
Mean Difference ± SE from Glyburide Alone	-28.4 ± 4.0	N/A	
95% CI for Difference	(-36.2, -20.6)		
p-value for pairwise comparison	< 0.001		
Body Weight (kg)			
n	430	144	
Baseline	98.66 ± 6.46	95.56 ± 7.94	0.762
Mean Change ± SE at Final Visit	0.16 ± 1.01	0.77 ± 1.04	
Mean Difference ± SE from Glyburide	-0.60 ± 0.43	N/A	

Parameter	Combined GLUMETZA /Glyburide Groups (n = 431)	Placebo/Glyburide Group (n = 144)	Overall Treatment p-Value
Alone			
95% CI for Difference	(-1.45, 0.24)		
p-value for pairwise comparison	0.16		

* Glyburide was administered as 10 mg at breakfast and 5 mg at dinner.

15. MICROBIOLOGY

No microbiological information is required for this drug product.

16. NON-CLINICAL TOXICOLOGY

A comprehensive nonclinical toxicology program was conducted with metformin, including repeat-dose toxicity studies in rats and dogs, a battery of genotoxicity studies, two carcinogenicity studies, and a full assessment of reproductive toxicity studies.

General 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.

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. No evidence of carcinogenicity was observed in male or female mice.

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. These doses are approximately two and five times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. The No-observed-effect level in this study was 450 mg/kg/day. No evidence of carcinogenicity with metformin was found in either male or female rats. There was, however, an increased incidence of adenomas and diffuse hyperplasia in the parathyroids of treated males. 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.

Genotoxicity

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.

Reproductive Toxicity

Fertility of male and female rats was unaffected by metformin when administered at doses as high as 900 mg/kg/day, which is approximately four times the recommended human daily dose based on body surface area comparisons **(see 16 NON- CLINICAL TOXICOLOGY)**

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.

Bridging Study

Bridging study in dogs has been performed, 70 Beagle dogs were orally administered 250, 500, 1000 mg/day. The No-observed-effect level in this study was 250 mg/kg/day and severe weight loss and clinical signs at doses 500 mg/day and higher have been observed.

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrGLUMETZA® and PrGLUMETZA® (SB)
Metformin hydrochloride extended-release tablet**s**

Read this carefully before you start taking **GLUMETZA and GLUMETZA (SB)** 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 **GLUMETZA and GLUMETZA (SB)**.

Serious Warnings and Precautions

- **GLUMETZA and GLUMETZA (SB)** 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 **GLUMETZA and GLUMETZA (SB).**

- Stop taking **GLUMETZA and GLUMETZA (SB)** 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.

- **GLUMETZA and GLUMETZA (SB)** 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 **GLUMETZA and GLUMETZA (SB)** 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 GLUMETZA and GLUMETZA (SB) used for?

GLUMETZA and GLUMETZA (SB) are used in addition to diet and exercise to improve blood sugar levels in adults with type 2 diabetes mellitus. GLUMETZA and GLUMETZA (SB) can be used with other antidiabetic medicines or by itself.

How does GLUMETZA and GLUMETZA (SB) work?
GLUMETZA and GLUMETZA (SB) help 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 GLUMETZA and GLUMETZA (SB) continue to exercise and follow the diet advised by your doctor for your diabetes.

What are the ingredients in GLUMETZA and GLUMETZA (SB)?

Medicinal ingredients: metformin hydrochloride

Non-medicinal ingredients **GLUMETZA 500 mg:** Hypromellose, Microcrystalline Cellulose, Magnesium Stearate, Polyethylene Glycol, Polyethylene Oxide, Polysorbate, Titanium Dioxide.

Non-medicinal ingredients **GLUMETZA 1000 mg:** Colloidal Silicon Dioxide, Crospovidone, Glyceryl Behenate, Polyvinyl Alcohol, Polyacrylate Dispersion, Hypromellose, Talc, Polyethylene Glycol, Titanium Dioxide, Simethicone Emulsion, Polysorbate, Shellac Glaze, Iron Oxide Black, Macrogol, N-Butyl Alcohol, Propylene Glycol, FD&C Blue #2, FD&C Yellow #6 and FD&C Red #40.

Non-medicinal ingredients **GLUMETZA (SB) 1000 mg:** Colloidal Silicon Dioxide, Crospovidone, Dibutyl Sebacate, Ethylcellulose, Glyceryl Behenate, Polyvinyl Alcohol, Povidone.

GLUMETZA and GLUMETZA (SB) comes in the following dosage forms:
Extended Release tablets, GLUMETZA 500 mg
Extended Release tablets, GLUMETZA 1000 mg
Extended Release tablets, GLUMETZA (SB) 1000 mg

Do not use GLUMETZA and GLUMETZA (SB) if you:
- have a known allergy to metformin, or any ingredients found in GLUMETZA and GLUMETZA (SB) extended-release tablets
- have Type 1 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 problems
- have heart system collapse (blood circulation failure) or heart problems that can cause hypoxemia (low oxygen in the blood)
- have kidney problems
- regularly drink alcohol
- are going to get injection of dyes (iodinated contrast materials)
- are stressed, have a severe infection, or are experiencing trauma
- will have surgery and during recovery after your surgery
- have severe dehydration (have lost a lot of water from your body) or shock
- are pregnant or planning to become pregnant
- are breast feeding

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take GLUMETZA and GLUMETZA (SB). Talk about any health conditions or problems you may have, including if you:
- have a history of kidney problem
- are 80 years or older and you have NOT had your kidney function tested
- have liver problems
- 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:
- GLUMETZA and GLUMETZA (SB) can cause your vitamin B_{12} levels to be low. This can cause **peripheral neuropathy** (nerve damage).

Thyroid problems:
- GLUMETZA and GLUMETZA (SB) 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:
- GLUMETZA and GLUMETZA (SB) 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 every 6 months during treatment with GLUMETZA and GLUMETZA (SB).

Patients older than 65 years old:
- You should not take GLUMETZA and GLUMETZA (SB) 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 GLUMETZA and GLUMETZA (SB) 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 GLUMETZA and GLUMETZA (SB).
- Do not breastfeed while you are taking GLUMETZA and GLUMETZA (SB).

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

sugar levels).

If any of the above side effects occur, contact your healthcare professional immediately.

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 GLUMETZA or GLUMETZA (SB):

- Other diabetes drugs, such as glyburide, insulin, and rosiglitazone
- Cationic drugs which may interfere with the elimination of metformin (cimetidine) ,
- Intravenous contrast dyes (such as intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast material)
- Alcohol
- Nifedipine and calcium channel blockers, used to treat high blood pressure
- 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
- 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:
    - Furosemide (water pills)
    - 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 for asthma such as salbutamol

How to take GLUMETZA or GLUMETZA (SB):

- Follow the directions provided by your healthcare professional for using this medicine. Check with your healthcare professional if you are not sure.
- Swallow tablets whole. Do not break or crush tablets.
- Take by mouth with food or with a glass of water, and drink plenty of fluids.
- Do not miss any doses.

Usual dose:

Initial dose is 1000 mg with evening meal. Maximum daily dose is 2000 mg.

GLUMETZA or GLUMETZA (SB) contains a tablet shell (coating) that controls the amount of

medicine that is released. This shell may not always dissolve and you may occasionally pass the tablet shell or a soft mass in your stool. This is normal and it does not affect how GLUMETZA or GLUMETZA (SB) works.

Overdose:

If you think you, or a person you are caring for, have taken too much GLUMETZA or GLUMETZA (SB), 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,
- nausea and vomiting followed by diarrhea,
- drowsiness, weakness, dizziness, and headache

Missed Dose:

If you miss a dose of GLUMETZA or GLUMETZA (SB)

- Do not take a double dose
- Take the next dose at the usual time

If you do not feel well or your home glucose test shows higher levels, contact your healthcare professional.

What are possible side effects from using GLUMETZA or GLUMETZA (SB) ?

These are not all the possible side effects you may have when taking GLUMETZA or GLUMETZA (SB). Taking GLUMETZA or GLUMETZA (SB) with meals can help to reduce these side effects. If you experience any side effects not listed here, tell your healthcare professional.

- diarrhea
- nausea and vomitting
- upset stomach
- abdominal pain
- abdominal bloating
- gas
- loss of appetite
- weight loss
- skin problems; skin reaction, rash, itchy skin

GLUMETZA or GLUMETZA (SB) 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 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 levels of acid in the blood): Symptoms include: that can cause death, feeling very weak, tiered 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 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 (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 15˚C - 30˚C.
- 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 GLUMETZA or GLUMETZA (SB):

- 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://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website www.bauschhealth.ca, or by calling 1-800-361-4261.

This leaflet was prepared by Bausch Health, Canada Inc.

Last Revised: February 15, 2023