PRODUCT MONOGRAPH

[Pr]AG-METFORMIN

Metformin Hydrochloride Tablets, USP
500 mg, 850 mg

Oral Antihyperglycemic Agent

Angita Pharma Inc.
1310 rue Nobel
Boucherville, Quebec
J4B 5H3

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet 500 mg and 850 mg	Unflavoured and blackberry flavoured tablets contain magnesium stearate, hydroxyl propyl methylcellulose, titanium dioxide, polyethylene glycol and povidone. Blackberry Flavoured Tablets additionally contain artificial blackberry flavour.

INDICATIONS AND CLINICAL USE

AG-METFORMIN (metformin HCl) are indicated 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. AG-METFORMIN can be used as monotherapy or in combination with other antidiabetic agents.

Pediatrics (< 18 years of age): The safety and effectiveness of AG-METFORMIN have not been studied in patients under 18 years of age. AG-METFORMIN should not be used in pediatric patients (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Pediatrics**).

Geriatrics (> 65 years of age): Controlled clinical studies of metformin hydrochloride did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients. Metformin hydrochloride 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, AG-METFORMIN should only be used in patients with normal renal function (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Renal**). Because aging is associated with reduced renal function, AG-METFORMIN should be used with caution in geriatric patients. AG-METFORMIN treatment should not be initiated in patients older than 80 years of age, unless measurement of creatinine clearance demonstrates that renal function is not reduced (see **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism**, Lactic Acidosis, **Special Populations**, **Geriatrics**, and **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

- Unstable and/or insulin-dependent (Type I) diabetes mellitus.
- Acute or chronic metabolic acidosis, diabetic ketoacidosis, with or without coma, history of ketoacidosis with or without coma. Diabetic ketoacidosis should be treated with insulin.
- In patients with a history of lactic acidosis, irrespective of precipitating factors.
- In the presence of renal impairment or when renal function is not known, and also in patients with serum creatinine levels above the upper limit of normal range. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 136 µmol/L (males), ≥124 µmol/L (females) or abnormal creatinine clearance <60 mL/min)) which may result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see also **WARNINGS AND PRECAUTIONS**).
- In excessive alcohol intake, acute or chronic.
- In patients suffering from severe hepatic dysfunction, since severe hepatic dysfunction has been associated with some cases of lactic acidosis, AG-METFORMIN should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.
- AG-METFORMIN should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function (see **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.
- In patients suffering from severe dehydration or shock.
- Known hypersensitivity or allergy to metformin HCl or any of the excipients. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.
- During pregnancy and breastfeeding.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

Driving and Operating Machinery

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

General

Patient Selection and Follow-up

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

If vomiting occurs, withdraw drug temporarily, exclude lactic acidosis, and then resume dosage cautiously (see **ADVERSE REACTIONS**).

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

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

If during AG-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, the drug should be discontinued.

Change in clinical status of previously controlled diabetes patients

A diabetic patient previously well controlled on AG-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, AG-

METFORMIN must be stopped immediately and appropriate corrective measures must be initiated.

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 AG-METFORMIN therapy, the drug should be promptly discontinued.

Endocrine and Metabolism

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 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 **ADVERSE REACTIONS**, **Post-Market Adverse Drug Reactions**). Regular monitoring of TSH levels is recommended in patients with hypothyroidism (see **Monitoring and Laboratory Tests**).

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

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

Lactic Acidosis

Lactic acidosis is a rare, but serious, metabolic complication that occurs due to metformin accumulation during treatment with AG-METFORMIN. 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 HCl is very low (approximately 0.03 cases / 1000 patient-years, with approximately 0.015 fatal cases / 1000 patient-years) and occurs primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications.
Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. AG-METFORMIN treatment should not be initiated in patients ≥80 years of age, unless measurement of creatinine clearance demonstrates that renal function is not reduced, as the patients are more susceptible to developing lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking AG-METFORMIN and by use of the minimum effective dose of AG-METFORMIN. In addition, AG-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, AG-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 AG-METFORMIN (metformin HCl), since alcohol intake potentiates the effect of metformin HCl on lactate metabolism. In addition, AG-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. AG-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 AG-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 AG-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 AG-METFORMIN, the drug should be discontinued immediately and general supportive measures should be promptly instituted. Because metformin HCl is dialyzable (with clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Physicians should instruct their patients to recognize the symptoms which could be signal onset of lactic acidosis. If acidosis of any kind develops, AG-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 AG-METFORMIN and temporarily administer insulin. AG-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 of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy.

Should secondary failure occur with AG-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 AG-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 hydrochloride 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 hydrochloride or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on AG-METFORMIN (see **Monitoring and Laboratory Tests**), and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels.

Long-term treatment with metformin hydrochloride 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 hydrochloride treatment in the context of vitamin B_{12} deficiency (see **ADVERSE REACTIONS**, **Post-Market Adverse Drug Reactions**). Monitoring of serum vitamin B_{12} levels is recommended (see **Monitoring and Laboratory Tests**).

Hematologic

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

Hepatic/Biliary/Pancreatic

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

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

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

Neurologic

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

Peri-Operative Considerations

AG-METFORMIN therapy should be temporarily suspended for any surgical procedure Metformin (except minor procedures not associated with restricted intake of food and fluids). AG-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 hydrochloride is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of the normal range for their age should not receive AG-METFORMIN. In patients with advanced age, AG-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 regularly and generally, AG-METFORMIN should not be titrated to the maximum dose (see **DOSAGE AND ADMINISTRATION**).

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

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

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

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

Radiological studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast material

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see **CONTRAINDICATIONS**). Therefore, in patients in whom any such study is planned, AG-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.

Special Populations

Pregnant Women: Safety of metformin hydrochloride in pregnant women has not been established. There are no adequate and well-controlled studies of AG-METFORMIN in pregnant women. AG-METFORMIN is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

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

Breast-feeding: Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Metformin hydrochloride is also excreted into human breast milk in very small amounts. AG-METFORMIN is contraindicated in breast-feeding women (see **CONTRAINDICATIONS**).

Pediatrics (< 18 years of age): Safety and effectiveness in pediatric patients have not been established. Therefore, AG-METFORMIN should not be used in this population (see **INDICATIONS AND CLINICAL USE**).

Geriatrics (> 65 years of age): Controlled clinical studies of metformin hydrochloride did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients. Metformin hydrochloride is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, AG-METFORMIN should only be used in patients with normal renal function (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**, **Renal**). Because aging is associated with reduced renal function, AG-METFORMIN should be used with caution as age increases. AG-METFORMIN treatment should not be initiated in patients older than 80 years of age, unless measurement of creatinine clearance demonstrates that renal function is not reduced, as elderly patients are more susceptible to developing lactic acidosis (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism,** Lactic Acidosis). Care should be taken in dose selection which should be based on careful and regular monitoring of renal function. AG-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 AG-METFORMIN (see **DOSAGE AND ADMINISTRATION**, **Geriatrics**).

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 **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism,** Loss of control of blood glucose).

More frequent glucose monitoring should be considered when AG-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 **DRUG INTERACTIONS**, **Cationic Drugs** and **Other**).

Periodic cardiovascular, ophthalmic, hematological, hepatic, and renal assessments are advisable (see **WARNINGS AND PRECAUTIONS).**

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis (see **WARNINGS AND PRECAUTIONS**, **Hematologic** and **Renal**). While megaloblastic anemia has rarely been seen with metformin hydrochloride 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 hydrochloride 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 AG-METFORMIN, especially in patients with anemia or neuropathy (see **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 **WARNINGS AND PRECAUTIONS**, **Hypothyroidism** and **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

For hypothyroid patients treated with Levothyroxine, careful monitoring of blood glucose levels is recommended, especially when thyroid hormone therapy is initiated, changed, or stopped (see **WARNINGS AND PRECAUTIONS**, **Hypothyroidism** and **DRUG INTERACTIONS**, **Levothyroxine**).

For patients concurrently administering AG-METFORMIN and phenprocoumon or other antivitamin K anticoagulants, a close monitoring of the International Normalized Ratio (INR) is recommended (see **DRUG INTERACTIONS**, **Other**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Lactic acidosis is a rare, but serious adverse reaction associated with AG-METFORMIN (metformin HCl) treatment. Lactic acidosis is fatal in approximately 50% of cases (see **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism**, Lactic Acidosis).

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

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

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug 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.

The clinical trials which formed the basis of approval for the original metformin hydrochloride submission are not available (see **CLINICAL TRIALS**).

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

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

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

Because gastrointestinal symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take AG-METFORMIN with meals (see **DOSAGE AND ADMINISTRATION**, **Dosing Considerations**).

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

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

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

Hematologic: During controlled clinical trials of 29 weeks duration, approximately 9% of patients on metformin hydrochloride monotherapy and 6% of patients on metformin hydrochloride /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 hydrochloride treatment in the post-marketing experience in patients with vitamin B_{12} deficiency (see **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism**, Vitamin B_{12} levels).

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

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

Post-Market Adverse Drug Reactions

Blood and Lymphatic System Disorders: Hemolytic anemia, some with a fatal outcome (see **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 **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**).

Investigations: Blood lactic acid increased.

Reduction of thyrotropin level in patients with treated or untreated hypothyroidism (see **WARNINGS AND PRECAUTIONS**, **Hypothyroidism** and **Monitoring and Laboratory Tests**).

Nervous System Disorders: Encephalopathy (see **WARNINGS AND PRECAUTIONS**, **Neurologic**).

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

Peripheral neuropathy in patients with vitamin B12 deficiency (see **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism**, Vitamin B12 levels).

Hypomagnesemia in the context of diarrhea.

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

DRUG INTERACTIONS

Overview

Certain drugs may potentiate the effect of AG-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, tubercolostatics, phenylbutazone, clofibrate, monoamine oxidase inhibitors, salicylates, probenecid and propanolol.

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

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

Drug-Drug Interactions

Glyburide: In a single-dose interaction study in NIDDM subjects, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamics effects, make the clinical significance of this interaction uncertain.

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

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

Cationic Drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion, theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such an interaction has been observed between metformin and oral cimetidine in normal healthy volunteers. In both single and multiple-dose metformin-cimetidine drug interaction studies, there was a 60% increase in peak metformin plasma and whole blood concentrations, as well as a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination

half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Therefore, careful patient monitoring (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests**) and dose adjustment of AG-METFORMIN or the interfering drug is recommended in patients who are taking cationic medications that are excreted via renal tubular secretion (see **DOSAGE AND ADMINISTRATION**, **Dosing Considerations**).

Levothyroxine: Levothyroxine can reduce the hypoglycemic effect of metformin. Monitoring of blood glucose levels is recommended, especially when thyroid hormone therapy is initiated, changed, or stopped (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests**), and AG-METFORMIN dosage adjusted as necessary (see **DOSAGE AND ADMINISTRATION**, **Dosing Considerations**).

Other

Other drugs tend to produce hyperglycemia and may lead to a loss of blood sugar control. These include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid hormone replacement drugs e.g. levothyroxine, estrogens, estrogen plus progestogen, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, isoniazid, and beta-2-agonists. ACE-inhibitors may decrease the blood glucose levels. When such drugs are administered to patients receiving AG-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 **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 **DOSAGE AND ADMINISTRATION**, **Dosing Considerations**).

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

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

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

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 **CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS**, **Renal**).

Drug-Lifestyle Interactions

Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking AG-METFORMIN, since alcohol intake potentiates the effect of metformin on lactate metabolism (see **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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

Over a period of time, patients may become progressively less responsive to therapy with oral hypoglycemic agents because of the deterioration of their diabetic state. Patients should therefore be monitored with regular clinical and laboratory evaluations, including blood glucose and glycosylated hemoglobin (A_{1C}) determinations, to determine the minimum effective dosage and to detect primary failure or secondary failure (see **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism**, Loss of control of blood glucose and **Monitoring and Laboratory Tests**).

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

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

In elderly patients, AG-METFORMIN should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function and the risk of developing lactic acidosis (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Lactic Acidosis). AG-METFORMIN treatment should not be initiated in patients older than 80 years of age, unless measurement of creatinine clearance demonstrates that renal function is not reduced, as elderly patients are more susceptible to developing lactic acidosis

(see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics, and Monitoring and Laboratory Tests).

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

Consideration for AG-METFORMIN dosage adjustment, as necessary, should be made when AG-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 and upon its discontinuation (see **DRUG INTERACTIONS**, **Cationic Drugs** and **Other**).

Recommended Dose and Dosage Adjustment

The usual dose is 500 mg three or four times a day, or 850 mg two or three times a day. Maximal dose should not exceed 2.55 g a day. To minimize gastric intolerance such as nausea and vomiting, AG-METFORMIN (metformin HCl) should be taken with food whenever possible.

Transfer from Other Antidiabetic Therapy

When transferring patients to AG-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 metformin hydrochloride in pediatric and adolescent patients have not been established. Therefore, AG-METFORMIN should not be used in this population (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Pediatrics**).

Geriatrics (> 65 years of age): AG-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 **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism**, Lactic Acidosis). In elderly patients, the initial and maintenance dose of AG-METFORMIN should be conservative, and any dose adjustment should be based on careful assessment of renal function. Renal function should be monitored regularly and generally, AG-METFORMIN should not be titrated to the maximum dose (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Geriatrics**).

Renal Impairment: AG-METFORMIN are contraindicated in patients with impaired renal function, unknown renal function, or in patients with serum creatinine levels above the upper limit of the normal range for their age, due to the risk of lactic acidosis (see

CONTRAINDICATIONS).

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

Missed Dose

In case the patient forgets to take AG-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.

OVERDOSAGE

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

Overdose of Metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see **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 **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**).

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

AG-METFORMIN (metformin hydrochloride) are 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.

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.

Pharmacokinetics

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

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

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 **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**).

Excretion: 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.

STORAGE AND STABILITY

Store at room temperature (15°to 30°C) in well closed containers. Dispense in a light resistant container.

DOSAGE FORMS, COMPOSITION AND PACKAGING

The drug Product AG-METFORMIN (Metformin Hydrochloride Tablets USP), 500 mg and 850 mg is available in two variant types, 'Blackberry Flavoured Tablets' and 'Unflavoured Tablets' for each strength.

AG-METFORMIN (Unflavoured Tablets):
AG-METFORMIN 500 mg (Unflavoured Tablet) contains 500 mg metformin hydrochloride. Each tablet also contains as non-medicinal ingredients: magnesium stearate and povidone. Tablet coating is comprised of hydroxyl propyl methylcellulose, titanium dioxide and polyethylene glycol. AG-METFORMIN 500 mg (Unflavoured Tablets) are white to off white, round, biconvex, film coated tablets with "LA15" debossed on one side and plain on the other side. Available in bottles of 90 and 1000 tablets.

AG-METFORMIN 850 mg (Unflavoured Tablet) contains 850 mg metformin hydrochloride. Each tablet also contains as non-medicinal ingredients: magnesium stearate and povidone. Tablet coating is comprised of hydroxyl propyl methylcellulose, titanium dioxide and polyethylene glycol. AG-METFORMIN 850 mg (Unflavoured Tablets) are white to off white, round, biconvex, film coated tablets with "LA08" debossed on one side and plain on the other side. Available in bottles of 90 and 1000 tablets.

AG-METFORMIN (Blackberry Flavoured Tablets):
AG-METFORMIN 500 mg (Blackberry Flavoured Tablet) contains 500 mg metformin hydrochloride. Each tablet also contains as non-medicinal ingredients: magnesium stearate and povidone. Tablet coating is comprised of hydroxyl propyl methylcellulose, titanium dioxide, polyethylene glycol and artificial blackberry flavour. AG-METFORMIN 500 mg (Blackberry Flavoured Tablets) are white to off white, round, biconvex, blackberry flavoured, film coated tablets with "LL" debossed on one side and plain on the other side. Available in bottles of 90 and 1000 tablets.

AG-METFORMIN 850 mg (Blackberry Flavoured Tablet) contains 850 mg metformin hydrochloride. Each tablet also contains as non-medicinal ingredients: magnesium stearate and povidone. Tablet coating is comprised of hydroxyl propyl methylcellulose, titanium dioxide, polyethylene glycol and artificial blackberry flavour. AG-METFORMIN 850 mg (Blackberry Flavoured Tablets) are white to off white, round, biconvex, blackberry flavoured, film coated tablets with "L0" debossed on one side and plain on the other side. Available in bottles of 90 and 1000 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

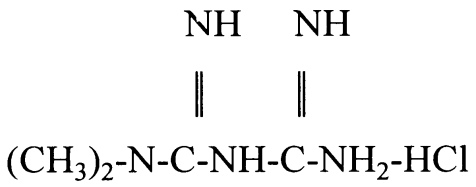
Drug Substance

Proper name: Metformin HCl

Chemical name: N, N-dimethyl biguanide hydrochloride

Molecular formula and molecular mass: 165.6 g/mol

Structural formula:



Physicochemical properties: Metformin HCl is a white crystals.

Metformin HCl is soluble in water and in 96% ethyl alcohol. It is practically insoluble in acetone and in chloroform.

Melting Point: 217-220°C.

CLINICAL TRIALS

Comparative Bioavailability Studies:

A randomized, balanced, blinded, two-treatment, two-period, two-sequence, single-oral dose (1 x 500 mg), two way crossover, comparative bioavailability study was conducted with metformin hydrochloride tablets 500 mg) and GLUCOPHAGE® (metformin hydrochloride) tablets 500 mg (Sanofi-Aventis Canada Inc.) in 22 healthy, adult, human subjects under fasting conditions. The results of the study calculated using data from 22 subjects are summarized below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Metformin (1 x 500 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (hr*ng/mL)	7440.57 7660.29 (23.68)	7471.61 7644.58 (22.70)	99.6	93.1-106.5
AUC_I (hr*ng/mL)	7578.93 7797.47 (23.48)	7610.65 7782.01 (22.40)	99.6	93.2-106.4
C_{max} (ng/mL)	1054.27 1080.59 (22.28)	1074.15 1102.98 (24.25)	98.1	90.6-106.4
T_{max}§ (h)	3.33 (1.00-4.50)	4.00 (1.00-4.50)		
$T_{½}$€ (h)	4.09 (34.50)	3.70 (13.93)		
* AG-METFORMIN (metformin hydrochloride) Tablets 500 mg. † GLUCOPHAGE® (metformin hydrochloride) Tablets 500 mg, Sanofi-Aventis Canada Inc. § Expressed as the median (range) € Expressed as the arithmetic mean (CV %)				

A randomized, balanced, blinded, two-treatment, two-period, two-sequence, single-oral dose (1

x 850 mg), two way crossover, comparative bioavailability study was conducted with AG-METFORMIN (metformin hydrochloride) tablets 850 mg and GLUCOPHAGE® (metformin hydrochloride) tablets 850 mg (Sanofi-Aventis Canada Inc.) in 26 healthy, adult, human subjects under fasting conditions. The results of the study calculated using data from 25 subjects are summarized below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Metformin (1 x 850 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.hr/mL)	10840.73 11048.90 (21.05)	10783.51 10993.27 (20.31)	100.5	97.1 – 104.1
AUC_I (ng.hr/mL)	11006.15 11216.89 (21.01)	10961.51 11173.48 (20.21)	100.4	97.0 – 104.0
Cmax (ng/mL)	1608.12 1633.74 (18.98)	1613.42 1639.65 (16.91)	99.7	95.0– 104.6
T_{max}§ (h)	3.67 (1.00-5.00)	3.67 (2.00-4.50)		
$T_{½}$€ (h)	4.11 (22.22)	4.28 (25.54)		

* AG-METFORMIN (metformin hydrochloride) Tablets 850 mg.
† GLUCOPHAGE® (metformin hydrochloride) Tablets 850 mg, Sanofi-Aventis Canada Inc.
§ Expressed as the median (range)
€ Expressed as the arithmetic mean (CV %)

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

DETAILED PHARMACOLOGY

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

Animal studies with metformin, labelled with ^{14}C have shown that the drug is neither concentrated by liver cells nor is it excreted in the bile; it is concentrated in the intestinal mucosa and salivary glands.

It has been shown that, following a 2 g dose of metformin, the blood level remains under 10 mcg/mL even at the peak, occurring 2 hours after absorption. During the experiments, metformin was shown to be devoid of any notable action in the body, apart from its specific metabolic activity.

In the healthy animal, metformin lowers blood sugar only at a nearly lethal dose. Different animal species are of unequal sensitivity. On the other hand, the animal with experimental diabetes, is sensitive to a much lower dosage, providing some insulin is still secreted.

The antihyperglycemic action of metformin is probably mediated through insulin:
Metformin improves the K co-efficient of glucose assimilation.
Metformin improves the co-efficient of insulin efficiency.

In the obese diabetic with hyperinsulinemia, metformin is reported to normalize insulin output. This normalizing effect is concurrent to that of glycemia.

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. *In vitro*, on muscular tissue isolated in Warburg's apparatus, metformin increases glucose uptake by the muscle. This action follows an aerobic pathway. Even in high concentration, contrary to phenethyl-biguanide, metformin apparently does not block respiration or change carbohydrate metabolism via the anaerobic pathway.

Metformin is eliminated in faeces and urine. It is rapidly excreted by the kidneys in an unchanged form.

Renal clearance is 450 mL/minute; this appears to explain the absence of accumulation.

Metabolites of metformin have not been identified, neither by radio-active nor by chemical methods.

A single Rf spot is always present following radiochromatographic study of urine and always corresponds to that of pure metformin. Administration during 10 consecutive days has not shown any sign of accumulation.

Inhibition of glyconeogenesis has been observed in animals following its stimulation by fasting, cortisol, alcohol or other substrates such as alanine lactate or pyruvate. However, such an effect varies according to the type and dosage of the biguanide used, nutritional state of the animal species and design of experimental model.

This inhibition of glyconeogenesis is observed only in the presence of insulin and it does not appear to play an important role in man.

Inhibition of intestinal absorption of sugars, which is not related to a malabsorption phenomenon, has been observed with biguanides under certain experimental conditions in animal and in man. In one study, a 20% retardation of galactose absorption was observed in man receiving metformin. However, such an effect of metformin could not be confirmed in another study in man.

Recent findings appear to indicate that most of the metabolic effects of the biguanides are exerted through a single mechanism, namely inhibition of fatty acid oxidation and of acetyl-CoA generation.

However, inhibition of insulin-stimulated lipogenesis which has also been observed appears to be due to the inhibition of acetyl-CoA carboxylase by the biguanides. Such an effect may explain, at least partly, the weight-reducing effect exerted by these drugs in obese diabetic patients.

TOXICOLOGY

1. Animal Toxicity

Acute Toxicity (LD_{50})

Animal	Subcutaneously	Orally
Mouse	225 mg/kg	3500 mg/kg
Chicken	150 mg/kg	
Rat	300 mg/kg	1000 mg/kg
Rabbit	150 mg/kg	350 mg/kg
Guinea Pig	150 mg/kg	500 mg/kg

Chronic Toxicity

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

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

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

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

1st Group	control
2nd Group	150 mg/kg per os
3rd Group	300 mg/kg per os
4th Group	300 mg/kg per os, dose increased by 100 mg/kg/day every 15 days

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

C) Chronic toxicity studies of 9 months duration were carried through with 16 beagle dogs, although the complete intolerance of this animal species to oral hypoglycemic agents is a well established fact. Trophic and neurologic disorders with cachexia rapidly lead to the dog's death. During the periods of metformin administration, laboratory findings were within normal limits. The levels of enzymes were somewhat elevated, but it is difficult to ascribe a pathological significance to their values, since subjects in the control group were at the same level as treated animals.

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

2. Human Toxicity

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

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases / 1000 patient/years with approximately 0.015 fatal cases / 1000 patients/years).

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

3. Teratology

Teratological studies were carried out in albino rats divided in three groups:
No abnormalities were found, even when high doses were administered. The number of animals was the same in each group.

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

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

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IMPORTANT: READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

PrAG-METFORMIN
Metformin Hydrochloride Tablets, USP
500 mg, 850 mg

This leaflet is part III of a three-part "Product Monograph" published when AG-METFORMIN was approved for sale in Canada and is designed specifically for Consumers. Read this leaflet carefully before you start taking AG-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 AG-METFORMIN

ABOUT THIS MEDICATION

What is AG-METFORMIN used for?
AG-METFORMIN (metformin hydrochloride) are used in addition to proper diet, exercise and weight reduction, to improve blood sugar levels in adults with type 2 diabetes mellitus.

How does AG-METFORMIN work?
People with type 2 diabetes mellitus are not able to make enough insulin or respond normally to the insulin their bodies make. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems including kidney damage, amputations, and blindness. Diabetes is also closely linked to heart disease. The main goal of treating diabetes is to lower your blood sugar to a normal level.

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 your diabetes medicine, continue to exercise and follow the diet advised by your doctor for your diabetes.

No matter what your recommended diabetes management plan is, studies have shown that maintaining good blood sugar control can prevent or delay complications of diabetes, such as blindness.

AG-METFORMIN helps to control your blood sugar.

Although the mode of action of AG-METFORMIN is not fully understood, it is believed to help your body respond better to the insulin it makes naturally by:

- Decreasing the amount of sugar your liver makes, and
- Decreasing the amount of sugar your intestines absorb.

What are the ingredients in AG-METFORMIN?

Medicinal ingredients:
The medicinal ingredient in AG-METFORMIN is metformin hydrochloride.

Nonmedicinal ingredients:
AG-METFORMIN 500 mg and 850 mg (unflavoured tablets) contain the following non-medicinal ingredients: magnesium stearate and povidone. Tablet coating is comprised of hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide.

AG-METFORMIN 500 mg and 850 mg (blackberry flavoured tablets) contain the following non-medicinal ingredients: magnesium stearate and povidone. Tablet coating is comprised of hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide and artificial blackberry flavor.

AG-METFORMIN comes in the following dosage forms:

Tablets; 500 mg and 850 mg (unflavoured)
Tablets; 500 mg and 850 mg (blackberry flavoured)

Do not use AG-METFORMIN if:

- You have unstable and/or insulin-dependent (Type I) diabetes mellitus
- You have metabolic acidosis (including diabetic ketoacidosis, with or without coma, history of ketoacidosis with or without coma)
- You have a history of lactic acidosis (too much acid in the blood)
- You drink a lot of alcohol (regularly drink alcohol or sometimes drink a lot of alcohol, binge drinking)
- You have liver or kidney problems (severe liver dysfunction or liver disease, or kidney disease or impairment)
- You are going to have an x-ray procedure with injection of dyes (iodinated contrast materials).
- You are stressed, have a severe infection, or are experiencing trauma
- Before surgery and during your recovery after your surgery
- You suffer from severe dehydration (have lost a lot of water from your body)
- You are hypersensitive (have a high blood pressure) or allergic to metformin hydrochloride or any ingredient in the formulation or component of the container
- You are pregnant or planning to become pregnant
- You are breastfeeding (nursing a child)
- You have cardiovascular collapse (abrupt failure of blood circulation) or a disease that can cause hypoxemia (low oxygen in the blood) such as cardiorespiratory insufficiency

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AG-METFORMIN .Talk about any health conditions or problems you may have.

Lactic Acidosis

AG-METFORMIN may rarely cause a serious, life-threatening condition called lactic acidosis.

You should not take AG-METFORMIN due to greater risk for lactic acidosis if you:
- Have kidney problems or a history of kidney disease
- Are 80 years of age or older and you have NOT had your kidney function tested
- Are seriously dehydrated (have lost a lot of water from your body)
- Have liver disease
- Have metabolic acidosis (e.g. diabetic ketoacidosis)
- Drink a lot of alcohol (regularly drink alcohol or sometimes drink a lot of alcohol, binge drinking)
- Have an x-ray procedure with injection of dyes (contrast agents)
- Before surgery and during the recovery phase thereafter
- Develop a serious medical condition, such as heart attack, severe infection, or a stroke

Due to greater risk for lactic acidosis, you should talk to your doctor if you take AG-METFORMIN and if you:
- Develop or experience a worsening of heart disease and particularly heart failure

Signs and symptoms of lactic acidosis include: discomfort, muscle pain, difficult or fast breathing, extreme tiredness, weakness, upset stomach, stomach pain, feeling cold, low blood pressure or slow heartbeat.

If any of the above side effects occur, consult your doctor immediately.

Other warnings you should know about:
You should tell your doctor if you have any other medical condition including: Vitamin B-12 deficiency or anemia, excessive alcohol use, allergies, or hypothyroidism (low levels of thyroid hormones).

Do not drive or operate machines if you develop hypoglycemia (low blood sugar levels). Do not start or stop any medicine without the approval of your healthcare professional.

INTERACTIONS WITH THIS MEDICATION

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

The following drugs may interact with AG-METFORMIN and require careful monitoring of your dose or condition:
- Other diabetes drugs such as glyburide
- Furosemide (diuretic (water pills)), used for œdema (fluid retention), and high blood pressure)
- Nifedipine (calcium-channel blocker used for high blood pressure; angina; Raynaud's phenomenon)
- Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin)
- Certain "blood thinners" (phenprocoumon or other antivitamin K anticoagulants)
- Diuretics (water pills), especially loop diuretics, that may increase the risk of lactic acidosis (too much acid in the blood) due to their potential to decrease renal function
- Drugs that tend to produce hyperglycemia (high blood sugar) and may lead to a loss of blood

sugar control. Some example of drugs that can increase the blood sugar include:

- Thiazide and other diuretics (water pills)
- Corticosteroids (such as prednisone)
- Phenothiazines (antipsychotic medicine)
- Thyroid hormone replacement drugs e.g. Levothyroxine
- Estrogens or estrogens plus progestogen (female hormones)
- Oral contraceptives
- Phenytoin (medicine used to treat epilepsy)
- Nicotinic Acid (medicine used to prevent and treat niacin deficiency)
- Sympathomimetics
- Calcium channel blocking drugs (such as nifedipine, amlodipine, felodipine, veramapil, diltiazem)
- Isoniazid (medicine used to treat active tuberculosis infections)
- Medicines for asthma such as salbutamol or formoterol (Beta-2-agonists)

- ACE inhibitors (drugs used to treat hypertension (high blood pressure)) may lower blood glucose and the combination with AG-METFORMIN should be carefully monitored.

Before using any drugs or herbal products, consult your healthcare professional.

PROPER USE OF THIS MEDICATION

How to take AG-METFORMIN:
AG-METFORMIN tablets are to be taken orally (by mouth).

Usual dose:
Your doctor will tell you how much medicine to take and when to take it. Follow the directions provided by your doctor for using this medicine. Taking this medicine with food will decrease symptoms such as nausea and vomiting.

Overdose:
In general, an overdose may lead to increased symptoms as described under "**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**" including stomach discomfort, nausea, vomiting, diarrhea, drowsiness, weakness, dizziness, malaise, and headache.

A serious, life-threatening condition called lactic acidosis may also occur (see **WARNINGS and PRECAUTIONS, Lactic Acidosis**).

If you think you have taken too much AG-Metformin, immediately see your doctor, contact your regional Poison Control Centre or go to the nearest hospital emergency department. Do this even if there are no signs of discomfort or poisoning.

Missed Dose:
If you forget to take AG-METFORMIN tablets, do not take a double dose to make up for forgotten individual doses. Take the next dose at the usual time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

What are possible side effects from using AG-METFORMIN?

The side effects described below are not all the possible side effects you may feel when taking AG-METFORMIN. If you experience any side effects not listed here, contact your healthcare professional. Please also see ***Warnings and Precautions.***

Common side effects of AG-METFORMIN include:

- diarrhea
- nausea
- upset stomach
- abdominal bloating
- gas
- loss of appetite

These side effects generally go away after you take the medicine for a while. Taking your medicine with meals can help reduce these side effects. Tell your doctor if the side effects bother you a lot, last for more than a few weeks, come back after they've gone away, or start later in treatment . You may need a lower dose of AG-METFORMIN or need to stop taking the medicine for a short period or for good.

After you are on the same dose of AG-METFORMIN for several days or weeks, if any of these side effects come back, tell your doctor immediately. A late reappearance of stomach symptoms may be due to a serious medical condition (lactic acidosis).

AG-METFORMIN rarely causes hypoglycemia (low blood sugar) by itself. However, hypoglycemia can happen if you do not eat enough, if you drink alcohol, or if you take other medicines to lower blood sugar.

Lactic Acidosis: **In rare cases, AG-METFORMIN can cause a serious side effect called lactic acidosis. This is caused by a buildup of lactic acid in your blood. This build-up can cause serious damage.** Lactic acidosis caused by AG-METFORMIN is rare and has occurred mostly in people whose kidneys were not working normally. Although rare, if lactic acidosis does occur, it can be fatal in up to half of the people who develop it.

It is also important for your liver to be working normally when you take AG-METFORMIN. Your liver helps remove lactic acid from your blood.

Make sure you tell your doctor before you use AG-METFORMIN if you have kidney or liver problems.

Your skin may be more sensitive to sunlight when you take AG-METFORMIN. Protect your skin from the sun.

You should also **stop using AG-METFORMIN and call your doctor right away if you have signs of lactic acidosis. Lactic acidosis is a medical emergency that must be treated in a hospital.**

If your medical condition suddenly changes, stop taking AG-METFORMIN and call your doctor right away. This may be a sign of lactic acidosis or another serious side effect.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM	
Symptom / effect	**Stop taking drug and call your doctor or pharmacist**
UNCOMMON **Feeling very week, tired or uncomfortable**	√
Unusual muscle pain	√
Trouble breathing	√
Unusual or unexpected stomach discomfort	√
Feeling cold	√
Feeling dizzy or lightheaded	√
Suddenly developing a slow or irregular heartbeat	√
RARE **Lactic Acidosis (a build up of lactic acid in the blood) that can cause death or cardiovascular mortality** **Symptoms include**: • 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.	√
Hemolytic anemia (when red blood cells are destroyed faster than bone marrow can replace them): symptoms may include fatigue, pale color, rapid heartbeat, shortness of breath, dark urine, chills, and backache.	√
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.	√
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.	√

This is not a complete list of side effects. For any unexpected effects while taking AG-METFORMIN, contact your healthcare professional. 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.

HOW TO STORE IT

Store at room temperature (15° to 30°C) in well closed containers. Dispense in a light resistant container. 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.

MORE INFORMATION

If you want more information about AG-METFORMIN:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); or by contacting the sponsor, Angita Pharma Inc., at: 450-449-9272.

This leaflet was prepared by
Angita Pharma Inc.
1310 rue Nobel
Boucherville, Québec, Canada
J4B 5H3

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