PRODUCT MONOGRAPH

[Pr]APO-METFORMIN ER

Metformin Hydrochloride Extended-Release Tablets

Apotex Standard

500 mg and 1000 mg

Oral Antihyperglycemic Agent

APOTEX INC.
150 Signet Drive
Toronto Ontario
M9L 1T9

Date of Revision:
March 03, 2023

Submission Control No: 264106

Table of Contents

PrAPO-METFORMIN ER

Metformin Hydrochloride Extended- Release Tablets
Apotex Standard
500 mg and 1000 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1: Summary Product Information

Route of Administration	Dosage Form/Strength	All Nonmedicinal Ingredients
Oral	Extended- release Tablets 500 mg and 1000 mg	**500 mg:** colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, titanium dioxide. **1000 mg:** carbomer homopolymer Type A, carbomer homopolymer Type B, dibutyl sebacate, ethyl cellulose, hydroxypropyl methylcellulose, magnesium stearate.

INDICATIONS AND CLINICAL USE

APO-METFORMIN ER (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.

APO-METFORMIN ER may be used as monotherapy, or concomitantly with a sulfonylurea. APO-METFORMIN ER is a once-daily formulation, which must be taken with food to ensure optimum delivery of metformin to the systemic circulation. Clinical data demonstrates that administration of metformin hydrochloride in the fed state significantly increases the systemic delivery of metformin when compared to the fasted state. Metformin can be of value in the treatment of obese diabetic patients.

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. Metformin treatment should not be initiated in patients greater than 80 years of age, unless measurement of creatinine clearance demonstrates that 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 WARNINGS AND PRECAUTIONS)**.

Pediatrics
The safety and efficacy of metformin hydrochloride in pediatric patients has not been established and no dosage regimen can be recommended in these patients.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.
- Unstable and/or Type 1 (insulin-dependent) diabetes mellitus.
- 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.
- 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 mcmol/L (males), ≥ 124 mcmol/L (females) or abnormal creatinine clearance) 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, metformin hydrochloride should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.
- 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 stressful conditions, such as severe infections, trauma or surgery and the recovery phase thereafter.
- In patients suffering from severe dehydration.
- During pregnancy.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Lactic acidosis is a rare, but serious, metabolic complication that may occur during treatment with APO-METFORMIN ER (see Endocrine and Metabolism, Lactic Acidosis section below).

Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking APO-METFORMIN ER, since alcohol intake potentiates the effect of metformin on lactate metabolism (see Endocrine and Metabolism, Lactic Acidosis section below).

General

Use of APO-METFORMIN ER 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 APO-METFORMIN ER is 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.

Endocrine and Metabolism

Lactic Acidosis

Lactic Acidosis is a rare, but serious, metabolic complication that may occur during treatment with APO-METFORMIN ER. 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, decreased 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) with approximately half of those cases being fatal. 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 APO-METFORMIN ER, and by use of the minimum effective dose of APO-METFORMIN ER. In addition, APO-METFORMIN ER 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, APO-METFORMIN ER should generally be avoided in

patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake when taking APO-METFORMIN ER, 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 APO-METFORMIN ER, the drug should be discontinued immediately. Because metformin hydrochloride is dialysable, prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Hepatic/Biliary/Pancreatic

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

Peri-operative Considerations

Metformin 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.

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. Patients with serum creatinine levels above the upper limit of normal for their age should not receive metformin. 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 regularly and generally should not be titrated to the maximum dose. Before initiation of metformin therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and APO-METFORMIN ER discontinued if evidence of renal impairment is present **(see Boxed Warning on Lactic Acidosis)**.

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.

Sexual Function/Reproduction

There are no adequate and well-controlled studies in pregnant women. Reproduction studies have been conducted in rats at doses up to and including 900 mg/kg/day (approximately 33-fold and 26-fold higher than humans) and have revealed no evidence of harm to the fetus due to metformin. The

NOAEL in rabbits was > 90 mg/kg/day, however, there were no toxicokinetic studies performed in rabbits and a relative exposure could not be determined **(See PART II: SCIENTIFIC INFORMATION, TOXICOLOGY).**

Carcinogenesis, Mutagenesis

A long-term carcinogenicity study was performed in rats (dosing duration of 104 weeks) at metformin doses up to and including 450 mg/kg/day for male rats and 1200 mg/kg/day for female rats. These doses are approximately two and five times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. 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. A carcinogenicity study was also performed in Tg.AC transgenic mice (dosing duration of 26 weeks) at doses up to 2000 mg/kg/day applied dermally. No evidence of carcinogenicity was observed in male or female mice. There was no evidence of mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium* and *E. coli*), and gene mutation test (mouse lymphoma cells). Results of the *in vivo* mouse micronucleus test were also negative. 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 PART II: SCIENTIFIC INFORMATION, TOXICOLOGY).**

Special Populations

Pregnant Women

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. Most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

The metformin hydrochloride nonclinical toxicology program included a complete battery of reproductive toxicity studies (fertility and early embryonic development, embryofetal development, and pre- and postnatal development). 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. A perinatal/postnatal toxicity study in rats demonstrated few findings, except that there was an increased latency in the passive avoidance test for F1 males in the 300 and 600 mg/kg/day groups and a decrease in body weight and feed consumption for F1 females during the precohabitation period in the 300 and 600 mg/kg/day groups. Therefore, the viability and growth NOAEL for this study was 150 mg/kg/day. Mating performance of F1 rats and caesarean-sectioning and litter parameters were unaffected at the highest dose of 600 mg/kg/day.

Based on the results of these studies, it was concluded that metformin produced no biologically significant, reproductive toxicity effects.

Nursing Women

It is not known whether metformin hydrochloride is excreted in human milk, however, studies in lactating rats have shown that metformin is excreted into milk and reaches levels comparable to those in plasma. Caution should be exercised in nursing mothers, and a decision should be made whether to discontinue nursing, or to discontinue treatment with APO-METFORMIN ER, taking into account the importance of the drug to the mother.

Pediatrics: (< 18 years of age)

The safety and efficacy in pediatric patients have not been established and no dosage regimen can presently be recommended in these patients.

Geriatrics: (> 80 years of age)

Metformin treatment should not be initiated in patients greater than 80 years of age, unless measurement of creatinine clearance demonstrates that renal function is not significantly reduced. 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 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions)**.

Vitamin B_{12} levels

Impairment of vitamin B_{12} and folic acid absorption has been reported in some patients treated with metformin. Therefore, measurements of serum vitamin B_{12} and folic acid are advisable in patients on long-term treatment with APO-METFORMIN ER.

Monitoring and Laboratory Tests

Periodic monitoring of fasting blood glucose and glycosylated hemoglobin levels may be useful in the long-term management of patients with type 2 diabetes. During initial dose titration, fasting glucose can be used to determine the therapeutic dose response.

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. While megaloblastic anemia has rarely been seen with metformin hydrochloride therapy, if this is suspected, vitamin B_{12} deficiency should be excluded.

Particular attention should be paid to short range and long-range complications which are peculiar to diabetes. Periodic cardiovascular, ophthalmic, hematological, hepatic and renal assessments are advisable **(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.

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

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Gastrointestinal symptoms (GI) (diarrhea, nausea, vomiting) 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.

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 metformin hydrochloride 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 metformin hydrochloride extended-release tablets 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	Metformin hydrochloride extended-release tablets 1500 mg QD N=176 (%)	Metformin hydrochloride extended-release tablets 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 NOS	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 NOS	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 metformin hydrochloride extended-release tablets 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 metformin hydrochloride extended-release tablets to metformin immediate-release tablets, all four treatment regimens (metformin hydrochloride extended-release tablets 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 metformin hydrochloride extended-release tablets 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 metformin hydrochloride extended-release tablets or placebo. In total, 431 patients received metformin hydrochloride extended-release tablets + SU and 144 patients placebo + SU. Adverse events reported in greater than 5% of patients treated with metformin hydrochloride extended-release tablets, that were more common in the combined metformin hydrochloride extended-release tablets + SU group, than in the placebo + SU group, are shown in Table 3.

In 0.7% of patients treated with metformin hydrochloride extended-release tablets + 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 Metformin Hydrochloride Extended-Release Tablets Group Versus Placebo Group

Adverse Event (MedDRA Preferred Term)	**Metformin hydrochloride extended-release tablets + SU (n = 431)**	**Placebo + SU (n = 144)**
Hypoglycemia NOS	13.7%	4.9%
Diarrhea	12.5%	5.6%
Nausea	6.7%	4.2%

*** AE's that were more common in the metformin hydrochloride extended-release tablets-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 metformin hydrochloride extended-release tablets group and these events occurred more commonly in the metformin hydrochloride extended-release tablets- treated than in the placebo-treated patients:

Ear and labyrinth disorders: ear pain

Gastrointestinal disorders: vomiting NOS, dyspepsia, flatulence, abdominal pain upper, abdominal distension, abdominal pain NOS, toothache, loose stools

General disorders and administration site conditions: asthenia, chest pain

Immune system disorders: seasonal allergy

Infections and infestations: gastroenteritis viral NOS, tooth abscess, tonsillitis, fungal infection NOS

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 NOS

Uncommon Clinical Trial Adverse Drug Reactions (< 1%)

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

Blood Disorders: thrombocytopenia, neutropenia

Eye disorders: vision blurred

Gastrointestinal disorders: flatulence, gastric NOS, gastrointestinal upset, loose stools, vomiting NOS.

General disorders and administration site conditions: adverse drug reaction NOS, asthenia, chest pain, fatigue, lethargy, oedema aggravated, oedema peripheral, rigors.

Infection and Infestations: gastroenteritis viral NOS

Investigations: blood glucose decreased, liver function test abnormal NOS, muscle cramp, white blood cell count increased.

Metabolism and Nutrition Disorders: hyperglycemia NOS

Nervous System Disorders: dizziness, migraine NOS, parasthesia, syncope, tremor

Reproductive System and Breast Disorders: sexual dysfunction NOS

Respiratory Disorders: rhinorrhea, sinus congestion

DRUG INTERACTIONS

Overview

Certain drugs may potentiate the effect of metformin in the treatment of diabetes, particularly sulfonylureas, and the "glitazones" rosiglitazone and pioglitazone. This potentiating effect has expanded the number of combination drug therapies for type II diabetes, and improved HbA_{1c} control. The simultaneous administration of potentiating drugs 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. Metformin also potentiates the effect of insulin.

Metformin hydrochloride and sulfonylurea: With concomitant metformin hydrochloride 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 metformin hydrochloride pharmacokinetics was assessed in a single-dose interaction study in healthy subjects. Co-administration of metformin hydrochloride 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 DOSAGE AND ADMINISTRATION**: **Concomitant APO-METFORMIN ER and Oral Sulphonylurea Therapy)**. In a clinical trial of patients with type 2 diabetes and prior treatment with glyburide, metformin hydrochloride plus glyburide combined therapy yielded a significant decrease from baseline to endpoint in mean HbA_{1c}, relative to SU treatment alone (see Clinical Pharmacology, Clinical Studies). With concomitant metformin hydrochloride 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 metformin hydrochloride 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 APO-METFORMIN ER, 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.

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.

Drug-Food Interactions

APO-METFORMIN ER extended-release tablets have been formulated to be dosed with food. APO-METFORMIN ER 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, metformin hydrochloride 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.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking APO-METFORMIN ER, since alcohol intake potentiates the effect of metformin hydrochloride on lactate metabolism. **(See CONTRAINDICATIONS)**

DOSAGE AND ADMINISTRATION

Dosing Considerations

APO-METFORMIN ER tablets must be taken with food to ensure optimum delivery of the metformin dose to the systemic circulation. (Please refer to Drug and Food interaction and Action and Clinical Pharmacology, Pharmacokinetics). In adult type 2 diabetic patients, individual determination of the minimum APO-METFORMIN ER dose that will adequately lower blood glucose should be made. There is no fixed metformin hydrochloride dosage regimen for the management of hyperglycemic patients.

In patients in whom the maximum recommended dose fails to lower the blood glucose adequately, the drug should be discontinued. In some diabetic subjects, short-term administration of the drug may be sufficient during periods of transient loss of blood sugar control.

Recommended Dose and Dose Adjustment

APO-METFORMIN ER therapy should usually be initiated at 1000 mg once-daily, taken with the evening meal. APO-METFORMIN ER 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. 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 APO-METFORMIN ER, and to identify the minimum effective dose for the patients. 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.

Transfer From Other Antidiabetic Therapy

When transferring patients from standard oral hypoglycemic agents, other than chlorpropamide, to APO-METFORMIN ER, no transition period generally is necessary. Patients treated with immediate release metformin have been switched to metformin hydrochloride extended-release tablets once daily without incident (**PART II: SCIENTIFIC INFORMATION, CLINICAL TRIALS**). Following switching, from the IR formulation to metformin hydrochloride extended-release tablets, 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 APO-METFORMIN ER and Oral Sulfonylurea Therapy in Adult Patients

If patients have not responded to four weeks of the maximum dose of APO-METFORMIN ER monotherapy, consideration should be given to gradual addition of oral sulfonylurea while continuing APO-METFORMIN ER 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 metformin hydrochloride 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 **(PART II: SCIENTIFIC INFORMATION, CLINICAL TRIALS).** The minimum effective dose of each drug should be identified. With concomitant APO-METFORMIN ER and sulfonylurea therapy, there is risk of hypoglycemia. Appropriate precautions should be taken. (See Package Insert of the respective sulfonylurea). If patients have not satisfactorily responded to one to three months of concomitant therapy with the maximum dose of APO-METFORMIN ER and the maximum dose of an oral sulfonylurea, consider therapeutic alternatives including switching to insulin.

Missed Dose

If a dose of APO-METFORMIN ER 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.

Administration

APO-METFORMIN ER extended-release tablets must be taken with food, and should be taken whole, with a glass of water. Do not break or crush tablets.

OVERDOSAGE

Overdose with metformin hydrochloride 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. Immediate contact with a physician should be made, to determine if treatment should be stopped and proper supportive therapy 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 Warnings and Precautions). 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.

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

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

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.

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 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 tissue.

Pharmacokinetics

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

Absorption

Following a single oral dose of 1000 mg metformin hydrochloride extended-release tablet 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 metformin hydrochloride 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 metformin hydrochloride 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, metformin hydrochloride 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.

Excretion
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 metformin hydrochloride tablets is approximately 8 hours. Results from a dose proportionality study involving once daily oral doses of metformin hydrochloride 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 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 metformin hydrochloride 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 WARNINGS AND PRECAUTIONS, Special Populations)**.

Gender
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
There were no definitive conclusions on the differences between the races with respect to the pharmacokinetics of metformin hydrochloride 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 metformin hydrochloride 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.

STORAGE AND STABILITY

Store at 15°C to 30°C in tight, light resistant containers. Protect from moisture.

Keep out of reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-METFORMIN ER tablets (metformin hydrochloride extended-release tablets) are available in 500 mg and 1000 mg strengths.

Each APO-METFORMIN ER 500 mg extended-release tablet contains: colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, titanium dioxide.

APO-METFORMIN ER 500 mg tablets are white to off-white, oval, biconvex, coated tablets. Engraved “APO-ER” on one side, “MET500” on the other side.

APO-METFORMIN ER 500 mg are available in bottles of 100 and 500, with desiccant.

Each APO-METFORMIN ER 1000 mg extended-release tablet contains: carbomer homopolymer Type A, carbomer homopolymer Type B, dibutyl sebacate, ethyl cellulose, hydroxypropyl methylcellulose, magnesium stearate.

APO-METFORMIN ER 1000 mg tablets are white to off-white, oval, beveled edge, biconvex coated tablets. Engraved “M1G” on one side, “APO” on the other side.

APO-METFORMIN ER 1000 mg are available in bottles of 100s and 500s with desiccant.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

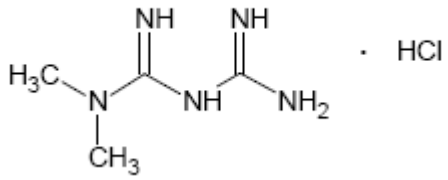
Proper Name: metformin hydrochloride

Chemical Name: 1,1-dimethylbiguanide monohydrochloride

Molecular Formula and: $C_4H_{11}N_5 \cdot HCl$

Molecular Mass: 165.62 g/mol

Structural formula:



Physiochemical Properties:

Description:	Metformin hydrochloride is a white or almost white powder
Solubility:	Freely soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in acetone and in methylene chloride.
pKa:	The pK_{a1} and pK_{a2} of metformin is 2.8 and 11.5 respectively.
pH:	The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

Metformin hydrochloride extended-release tablets are modified release dosage forms that contain 500 mg or 1000 mg of metformin hydrochloride.

CLINICAL TRIALS

Comparative Bioavailability Studies

A blinded, randomized, two-treatment, two-period, single oral dose (1 x 500 mg), crossover comparative bioavailability study of APO-METFORMIN ER extended-release tablets 500 mg (Apotex Inc.) and GLUMETZA® extended-release tablets 500 mg (Biovail Pharmaceuticals Canada),

was conducted in healthy adult male and female subjects under fasting conditions. Comparative bioavailability data from 23 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Metformin (1 x 500 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	3683.65 3826.13 (28)	4067.23 4261.33 (30)	90.6	83.6 – 98.1
AUC_I (ng·h/mL)	3792.85 4024.98 (27)	4249.89 4394.63 (30)	89.2	81.7 – 97.5
C_{max} (ng/mL)	581.85 599.94 (27)	635.47 655.58 (26)	91.6	83.9 – 99.9
T_{max}[3] (h)	3.20 (23)	3.31 (22)		
$T_{½}$[3] (h)	13.05 (78)	10.66 (61)		

[1] APO-METFORMIN ER (metformin hydrochloride) extended-release tablets, 500 mg (Apotex Inc.)
[2] GLUMETZA® (metformin hydrochloride) extended-release tablets, 500 mg (Biovail Pharmaceuticals Canada)
[3] Expressed as the arithmetic mean (CV %) only

A blinded, randomized, two-treatment, two-period, single oral dose (1 x 500 mg), crossover comparative bioavailability study of APO-METFORMIN ER extended-release tablets 500 mg (Apotex Inc.) and GLUMETZA® extended-release tablets 500 mg (Biovail Pharmaceuticals Canada), was conducted in healthy adult male and female subjects under fed conditions. Comparative bioavailability data from 33 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Metformin (1 x 500 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval

Metformin (1 x 500 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	6121.12 6238.61 (20)	5691.07 5822.60 (20)	107.6	101.8 – 113.6
AUC_I (ng·h/mL)	6224.38 6342.14 (20)	5829.34 5944.87 (21)	106.8	101.2 – 112.7
C_{max} (ng/mL)	559.62 567.72 (17)	568.49 577.18 (17)	98.4	94.6 – 102.5
T_{max}[3] (h)	5.10 (24)	5.28 (23)		
$T_{½}$[3] (h)	9.37 (47)	9.88 (60)		

[1] APO-METFORMIN ER (metformin hydrochloride) extended-release tablets, 500 mg (Apotex Inc.)
[2] GLUMETZA® (metformin hydrochloride) extended-release tablets, 500 mg (Biovail Pharmaceuticals Canada)
[3] Expressed as the arithmetic mean (CV %) only

A blinded, randomized, two-treatment, two-period, single oral dose (1 x 1000 mg), crossover comparative bioavailability study of APO-METFORMIN ER extended-release tablets 1000 mg (Apotex Inc.) and GLUMETZA® extended-release tablets 1000 mg (Valeant Canada LP), was conducted in healthy adult male subjects under fasted conditions. Comparative bioavailability data from 28 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Metformin (1 x 1000 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	6153.80 6425.82 (30)	6642.41 7002.65 (32)	92.6	82.7 − 103.8
AUC_I (ng·h/mL)	6305.69 6568.31 (30)	6845.81 7313.12 (32)	92.1	81.3 – 104.4
C_{max} (ng/mL)	807.94 866.07(37)	867.11 922.35(36)	93.2	81.2 – 107.0
T_{max}[3] (h)	3.98 (17)	4.22 (24)		
$T_{½}$[4] (h)	9.43 (61)	11.11 (83)		

[1] APO-METFORMIN ER (metformin hydrochloride) extended-release tablets, 1000 mg (Apotex Inc.)
[2] GLUMETZA® (metformin hydrochloride) extended-release tablets, 1000 mg (Valeant Canada LP)
[3] Expressed as the arithmetic mean (CV %) only

A blinded, randomized, two-treatment, two-period, single oral dose (1 x 1000 mg), crossover comparative bioavailability study of APO-METFORMIN ER extended-release tablets 1000 mg (Apotex Inc.) and GLUMETZA® extended-release tablets 1000 mg (Valeant Canada LP), was conducted in healthy adult male subjects under fed conditions. Comparative bioavailability data from 26 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Metformin (1 x 1000 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	13421.29 13805.90 (23)	13084.59 13366.89 (21)	102.6	97.2 – 108.3
AUC_I (ng·h/mL)	13537.26 13915.74 (23)	13187.13 13468.19 (20)	102.7	97.3 – 108.3
C_{max} (ng/mL)	891.12 923.48 (27)	1093.41 1128.29 (24)	81.5	74.4 – 89.2
T_{max}[3] (h)	7.19 (26)	8.48 (29)		
$T_{½}$[3] (h)	7.45 (36)	7.29 (38)		

[1] APO-METFORMIN ER (metformin hydrochloride) extended-release tablets, 1000 mg (Apotex Inc.)
[2] GLUMETZA® (metformin hydrochloride) extended-release tablets, 1000 mg (Valeant Canada LP)
[3] Expressed as the arithmetic mean (CV %) only

Study Demographics and Trial Design

Four clinical studies were conducted in patients with type 2 diabetes, to establish the safety and efficacy of metformin hydrochloride extended-release tablets, as shown in the following **Table 4**.

Table 4 **Metformin hydrochloride 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-	1500 - 2000 mg/day, orally for 24 weeks	706	54 (24-79)	380 M/ 326 F

controlled, non-inferiority, multicentre				
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

In a multicenter, randomized, double-blind, active-controlled, dose-ranging, parallel group study of metformin hydrochloride 1500 mg once a day, metformin hydrochloride 1500 per day in divided doses (500 mg in the morning and 1000 mg in the evening), and metformin hydrochloride 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 5**). 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 metformin hydrochloride regimens, were at least as effective as metformin IR in all measures of glycemic control. Once daily dosing of metformin hydrochloride was as effective as the commonly prescribed twice daily dosing of the immediate-release product.

Table 5 Mean±SE Changes from Baseline to Final Visit in HbA_{1c}, Fasting Plasma Glucose and Body Weight for the Metformin hydrochloride extended-release tablets and Metformin IR Treatment Groups (24-Week Study)

Parameter	Metformin hydrochloride extended-release tablets			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 metformin hydrochloride extended-release tablets 2000 mg/day treatment during a 24-week open-label trial in order to evaluate the long-term safety and duration of effectiveness of metformin hydrochloride extended-release tablets. This resulted in the exposure of 158 patients to continuous treatment with metformin hydrochloride extended-release tablets 1500-2000 mg/day (56 on 2000 mg/day) for a cumulative period of 48 weeks. Metformin hydrochloride extended-release tablets 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); metformin hydrochloride extended-release tablets 1500 mg once a day + glyburide, metformin hydrochloride extended-release tablets 2000 mg once a day + glyburide, or metformin hydrochloride extended-release tablets 1000 mg twice a day + glyburide. A 3-week metformin hydrochloride extended-release tablets 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 metformin hydrochloride extended-release tablets + 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 metformin hydrochloride extended-release tablets +glyburide groups were comparable.

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

Parameter	Combined Metformin hydrochloride / 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 Alone	-0.60 ± 0.43	N/A	
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.

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.

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.

An overview of the nonclinical toxicology program conducted with metformin hydrochloride is presented in **Table 7** below.

Table 7 Summary of Findings of Definitive Toxicology Studies

Study Type/Name	# of Animals	Doses	NOAEL	Species/ Strain	Route of Admin.	Findings
Chronic Toxicity Testing						
26-week study in rats	160	150, 450, 900 mg/kg/day	150 mg/kg/day	Rats / Sprague-Dawley	Oral / Gavage	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.
39-week study in dogs	32	20, 40, 60, 80 mg/kg/day	80 mg/kg/day	Dogs / Beagle	Oral / Capsule	Treatment-related effects in food consumption seen in females only at 80 mg/kg/day.
Carcinogenicity Testing						
26-week carcinogenicity study in transgenic mice	150	500, 1000, 2000 mg/kg/day	-	Mice / Tg.AC	Dermal	No findings. No papillomas at treatment sites.
104-week carcinogenicity study in rats	400	males: 150, 300, 450 mg/kg/day females: 150, 450, 900, 1200 mg/kg/day	450 mg/kg/day	Rats / Sprague-Dawley	Oral / Gavage	Parathyroid hyperplasia in males at all doses, and not noted for females. Non-neoplastic findings seen in females and not with males. No tumorigenicity. Increase in female kidney weights at 900 and 1200 mg/kg/day.
Genotoxicity Testing						
AMES Assay	N/A	100, 333, 1000, 5000 mcg/plate	-	Salmonella / E.coli	N/A	Negative

Study Type/Name	# of Animals	Doses	NOAEL	Species/ Strain	Route of Admin.	Findings
In vitro cytogenetics– mouse lymphoma assay	N/A	1000, 2000, 3000, 4000, 5000 mcg/plate	-	Mice / Lymphoma cells	N/A	Negative
In vivo cytogenetics–mouse micronucleus assay	70	500, 1000, 2000 mg/kg	-	ICR mice	Oral / Gavage	Negative
Reproductive Toxicity Testing						
Segment I/II toxicity study in rats (Fertility & developmental toxicity)	200	150, 450, 900 mg/kg/day	900 mg/kg/day	Rats / Sprague-Dawley; 100 males & 100 females	Oral / Gavage	Decrease in male reproductive organ weights at 900 mg/kg/day.
Segment III toxicity study in rats (Pre- and postnatal toxicity)	100	150, 300, 600 mg/kg/day	150 mg/kg/day	Rats / Sprague-Dawley; Mated females	Oral / Gavage	Decrease in F1 female body weight and feed consumption at 300 and 600 mg/kg/day.
Segment II toxicity study in rabbits (Developmental toxicity in rabbits)	80	30, 60, 90 mg/kg/day	> 90 mg/kg/day	Rabbits / New Zealand white Time Pregnant females	Oral / Stomach tube	No effects on gross external, soft tissue, or skeletal malformation.
Bridging Study with Final Dosage Form						
Bridging study in dogs	70	250, 500, 1000 mg/day	250 mg/day	Beagle dogs	Oral	Severe weight loss and clinical signs at doses 500 mg/day and higher.

REFERENCES

1. Aljabri K, Kosak SE, Thompson DM. Addition of Pioglitazone or bedtime insulin to maximal doses of sulfonylurea and metformin in type 2 diabetes patients with poor glucose control: a prospective, randomized trial. American Journal of Medicine. 2004 Feb 15;116(4): 276-278

2. Altuntas Y, Ozen B, Ozturk B. Sengul A, Ucak S, Ersoy O, Karul S. Comparison of additional metformin or NPH insulin to mealtime insulin lispro therapy with mealtime human insulin in secondary OAD failure. Diabetes, Obesity and Metabolism 2003; 5:371-378

3. Dailey GE, Noor MA, Park JS, Bruce S, Fiedorek FT. Glycemic control with glyburide/metformin tablets in combination with rosiglitazone in patients with type 2 diabetes: a randomized, double-blind trial. Am J Med. 2004 Feb 15;116(4):223-9.

4. Dunn C, Peters D. Metformin: A review of its pharmacological properties and therapeutic use in non- insulin-dependent diabetes mellitus. Drugs. 1995; 49(5):721-749.

5. Fujita H, Narita T, Yoshioka N, Hosoba M, Ito S. A case of megaloblastic anemia due to vitamin B12 deficiency precipitated in a totally gastrectomized type II diabetic patient following the introduction of metformin therapy. Endocr J 2003;50:483-484

6. Giannarelli R, Aragona M, Coppelli A, Del Prato S. Reducing insulin resistance with metformin: the evidence today. Diabetes Metab. 2003, 29, 6S28 - 6S35.

7. Gregorio F, Ambrosi F, Manfrini F, Velussi M, Carle F, Testa R et al. Poorly controlled elderly Type 2 diabetic patients: the effects of increasing sulphonylurea dosages or adding metformin. 1999 British Diabetic Association. Diabetic Medicine, 16, 1016-1024.

8. Kirpichnikov D, McFarlene S, Sowers JR. Metformin: An Update. 2002. Annals of Internal Medicine. Volume 137, Number 1, E-25-E33.
9. Leverve XM, Guigas B, Detaille D, Batandier C, Koceir EA, Chauvin C, et al. Mitochondrial metabolism and type-2 diabetes: a specific target of metformin. Diabetes Metab. 2003, 29, 6S88- 6S94.

10. Malone JK, Beattie SD, Campaigne BN, Johnson PA, Howard AS, Milicevic Z. Therapy after single oral agent failure: adding a second oral agent or an insulin mixture. Diabetes Research and Clinical Practice. 2003 Dec; 62(3): 187-195

11. Nagasaka S, Aiso Y, Yoshizawa K, Ishibashi S. Comparison of pioglitazone and metformin efficacy using homeostasis model assessment.Diabet Med. 2004 Feb;21(2):136-41

12. Papoushek C. The “glitazones”: rosiglitazone and pioglitazone. J Obstetrics and Gynecology Canada. 2003; 25:853-857.

13. Poulsen MK, Henriksen JE, Hother-Nielsen O, Beck-Nielsen H. The combined effect of triple therapy with rosiglitazone, metformin, and insulin as part in type 2 diabetic patients. Diabetes Care. 2003 Dec; 26(12):3273-9.

14. Scarpello JHB. Improving survival with metformin: the evidence base today. Diabetes Metab 2003, 29, 6S36-6S43.

15. Setter SM, Iltz JL, Thams J, Campbell RK. Metformin hydrochloride in the treatment of type 2 diabetes mellitus: a clinical review with a focus on dual therapy. Clin. Ther 2003; 25: 2991-3026.

16. Slama G. The potential of metformin for diabetes prevention. Diabetes Metab 2003, 29, 6S104 - 6S111.

17. Standl E. Metformin: drug of choice for the prevention of type 2 diabetes and cardiovascular complications in high-risk subjects. Diabetes Metab. 2003, 29, 6S121-6S122.

18. Vague P. Is metformin more than an oral hypoglycaemic agent? Diabetes Metab. 2003, 29, 6S5-6S7.

19. Wiernsperger and C. J. Bailey. The Antihyperglycaemic Effect of Metformin: Therapeutic and Cellular Mechanisms. 1999 Drugs; 58 Suppl. 1 1:31-39

20. UK Prospective Diabetes Study (UKPDS) Group. Effects of intensive blood -glucose control with metformin on complications in overweight patients with type 2 diabetes. Lancet 1998; 352: 854-865.

21. Product Monograph - GLUMETZA® and GLUMETZA® (SB) (Metformin Hydrochloride Extended-Release Tablets, Mfr. Std.) 500 mg and 1000 mg. Bausch Health, Canada Inc., Date of Revision: October 19, 2021, Control Number 243050.

PART III: CONSUMER INFORMATION

[Pr]APO-METFORMIN ER
Metformin hydrochloride extended-release tablets

This leaflet is part III of a three-part "Product Monograph" published when APO-METFORMIN ER was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-METFORMIN ER. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
APO-METFORMIN ER tablets are used in addition to diet and exercise, to improve blood sugar levels in adults with type 2 diabetes. People with type 2 diabetes are not able to make enough insulin and they do not respond normally to the insulin that their bodies make.

What it does:
APO-METFORMIN ER (metformin hydrochloride) extended-release tablets work to control your blood sugar by:

- helping insulin, naturally produced by your body, be more effective.
- decreasing the amount of sugar your liver makes.
- decreasing the amount of sugar your intestines absorb.

When it should not be used:
Do not use APO-METFORMIN ER if:

- You have a known allergy to metformin or any ingredients found in APO-METFORMIN ER tablets
- You have unstable or Type 1 (insulin dependent) diabetes
- You have acute or chronic metabolic acidosis or diabetic ketoacidosis, with or without coma
- You have a history of lactic acidosis
- You have severe liver dysfunction
- You have cardiovascular collapse or cardiorespiratory insufficiency
- You have kidney disease or impairment
- You drink alcohol
- You are going to have an x-ray procedure with injection. of iodinated contrast materials
- Prior to surgery or during your recovery phase
- You have a severe infection
- You have severe dehydration (have lost a lot of water from your body)
- You are pregnant or planning to become pregnant

What the medicinal ingredient is:

Each tablet contains 500 mg or 1000 mg metformin hydrochloride.

What the important nonmedicinal ingredients are:
APO-METFORMIN ER 500 mg: colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, titanium dioxide.

APO-METFORMIN ER 1000 mg: carbomer homopolymer Type A, carbomer homopolymer Type B, dibutyl sebacate, ethyl cellulose, hydroxypropyl methylcellulose, magnesium stearate

What dosage forms it comes in:
Extended-Release tablets: Each tablet contains 500 mg or 1000 mg metformin hydrochloride.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

APO-METFORMIN ER may rarely be associated with a serious, life-threatening condition called lactic acidosis (see Lactic Acidosis below).

You should not drink a lot of alcohol if you take APO-METFORMIN ER (see section Lactic Acidosis below).

BEFORE you use APO-METFORMIN ER talk to your doctor or pharmacist if you have:

- a history of kidney disease
- are 80 years or older and you have NOT had your kidney function tested
- liver disease
- metabolic acidosis (e.g. diabetic ketoacidosis)
- recent heart attack
- recent stroke
- serious infection
- dehydration
- scheduled surgery
- scheduled x-ray or scanning procedures
- are pregnant, breast-feeding or planning to become pregnant
- vitamin B12 or folic acid deficiency

- drink alcohol

Lactic Acidosis
APO-METFORMIN ER therapy may rarely be associated with a serious, life-threatening condition called lactic acidosis.

Due to potential for lactic acidosis, you should talk to your doctor if you take APO-METFORMIN ER and if you:

- develop or experience a worsening of heart disease and particularly heart failure
- develop a serious medical condition, such as heart attack, severe infection, or a stroke

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 or irregular heartbeat.

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

INTERACTIONS WITH THIS MEDICATION

Always inform your doctor or pharmacist of all prescription over-the-counter, and herbal medicines that you are taking. Medicines which may require additional monitoring of your dose or condition include:

- other diabetes drugs, such as glyburide, insulin, and rosiglitazone
- medications that may increase blood sugar levels such as 'water pills' (diuretics), birth control pills, sympathomimetics (decongestants), thyroid medicines, prednisone (corticosteroid drugs), phenytoin, nicotinic acid, certain drugs which control high blood pressure (eg calcium channel blockers), and isoniazid
- furosemide
- nifedipine
- cationic drugs which may interfere with the elimination of metformin (eg. cimetidine, amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, vancomycin)
- certain 'blood thinners' (coumarin-type anticoagulants)
- alcohol

Interactions with herbal products have not been established

PROPER USE OF THIS MEDICATION

Follow the directions provided by your doctor for using this medicine. Only take this medicine with food, and drink plenty of fluids while taking this medicine. Do not miss any doses. Swallow whole. Do not break or crush tablets.

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

Overdose:

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

If an overdose is suspected, contact your local poison control centre or emergency immediately. 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 a dose of this medication has been missed it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses. If you do not feel well or your home glucose test shows higher levels, contact your physician.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Some common side effects include diarrhea, nausea and stomach upset. If they continue or are bothersome, check with your doctor.

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

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	
Uncommon	Lactic acidosis (a buildup of an acid in the blood) that can cause death or cardiovascular mortality Symptoms include: - very weak or tired - unusual (not normal) muscle pain - trouble breathing - stomach pain with nausea and vomiting, or diarrhea - feel cold, especially in arms and legs - feel dizzy or lightheaded - have a slow or irregular heartbeat		√	√

This is not a complete list of side effects. For any unexpected effects while taking APO-METFORMIN ER, contact your doctor or pharmacist.

HOW TO STORE IT

Store at 15°C to 30°C in tight, light resistant containers. Protect from moisture.

Keep out of reach and sight of children.

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.

MORE INFORMATION

- 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://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.apotex.ca/products., or by calling 1-800-667-4708

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

Last revised: March 03, 2023