HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FORTAMET safely and effectively. See full prescribing information for FORTAMET.

FORTAMET® (metformin hydrochloride) extended-release tablets, for oral use
Initial U.S. Approval: 1995

WARNING: LACTIC ACIDOSIS

See full prescribing information for complete boxed warning.

- **Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. (5.1)**
- **Risk factors include renal impairment, concomitant use of certain drugs, age >65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin- associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information. (5.1)**
- **If lactic acidosis is suspected, discontinue FORTAMET and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

INDICATIONS AND USAGE

FORTAMET is a biguanide indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

DOSAGE AND ADMINISTRATION

- Swallow FORTAMET tablets whole and never crush, cut or chew (2.1)
- Starting dose: 500 mg orally once daily with the evening meal (2.1)
- Increase the dose in increments of 500 mg weekly, up to a maximum of 2,000 mg once daily with the evening meal (2.1)
- Patients receiving metformin hydrochloride (HCl) tablets may be switched to FORTAMET once daily at the same total daily dose, up to 2,000 mg once daily (2.1)

Renal Impairment:

- Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR) (2.2)
  - Do not use in patients with eGFR below 30 mL/minute/1.73 m^2 (2.2)
  - Initiation is not recommended in patients with eGFR between 30 to 45 mL/minute/1.73 m^2 (2.2)
  - Assess risk/benefit of continuing if eGFR falls below 45 mL/minute/1.73 m^2 (2.2)
  - Discontinue if eGFR falls below 30 mL/minute/1.73 m^2 (2.2)

Discontinuation for Iodinated Contrast Imaging Procedures:

- FORTAMET may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures (2.3)

DOSAGE FORMS AND STRENGTHS

Extended-Release Tablets: 500 mg and 1,000 mg (3)

CONTRAINDICATIONS

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2) (4, 5.1)
- Hypersensitivity to metformin (4)
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. (4)

WARNINGS AND PRECAUTIONS

- *Lactic Acidosis:* See boxed warning. (5.1)
- *Vitamin B_{12} Deficiency:* Metformin may lower vitamin B_{12} levels. Measure hematological parameters annually and vitamin B_{12} at 2 to 3 year intervals and manage any abnormalities. (5.2)
- *Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues:* Increased risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue. Lower dose of insulin or insulin secretagogue may be required. (5.3)

ADVERSE REACTIONS

Common adverse reactions are diarrhea, nausea/vomiting, abdominal pain, constipation, abdomen distention, dyspepsia/heartburn, flatulence, dizziness, headache, upper respiratory infection, taste disturbance. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals USA, Inc. at 1-888-838-2872 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring (7)
- Drugs that reduce metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimetidine) may increase the accumulation of metformin. Consider the benefits and risks of concomitant use (7)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake (7)

USE IN SPECIFIC POPULATIONS

- Females and Males of Reproductive Potential: Advise premenopausal females of the potential for an unintended pregnancy. (8.3)
- Geriatric Use: Assess renal function more frequently. (8.5)
- Hepatic Impairment: Avoid use in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin- associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin- associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL [*see Warnings and Precautions (5.1)*].

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g. carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided [*see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.1)*].

If metformin-associated lactic acidosis is suspected, immediately discontinue FORTAMET and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended [*see Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

FORTAMET is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosage and Administration

- Swallow FORTAMET whole and never crush, cut or chew.
- The recommended starting dose of FORTAMET is 500 mg orally once daily with the evening meal.
- Increase the dose in increments of 500 mg weekly on the basis of glycemic control and tolerability, up to a maximum of 2,000 mg once daily with the evening meal.
- If glycemic control is not achieved with FORTAMET 2,000 mg once daily, consider a trial of FORTAMET 1,000 mg twice daily.
- Patients receiving metformin hydrochloride (HCl) may be switched to FORTAMET once daily at the same total daily dose, up to 2,000 mg once daily.

2.2 Recommendations for Use in Renal Impairment

- Assess renal function prior to initiation of FORTAMET and periodically thereafter.
- FORTAMET is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2.
- Initiation of FORTAMET in patients with an eGFR between 30 to 45 mL/minute/1.73 m^2 is not recommended.
- In patients taking FORTAMET whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit risk of continuing therapy.
- Discontinue FORTAMET if the patient's eGFR later falls below 30 mL/minute/1.73 m^2 [*see Contraindications (4) and Warnings and Precautions (5.1)*].

2.3 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue FORTAMET at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients

who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart FORTAMET if renal function is stable.

3 DOSAGE FORMS AND STRENGTHS

FORTAMET is available as:

- *Extended-release tablets*: 500 mg white-colored, unscored tablets imprinted with Andrx logo and 574 on one side.
- *Extended-release tablets*: 1,000 mg white-colored, unscored tablets imprinted with Andrx logo and 575 on one side.

4 CONTRAINDICATIONS

FORTAMET is contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2) [*see Warnings and Precautions (5.1)*].
- Hypersensitivity to metformin.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin- associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio; metformin plasma levels were generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of FORTAMET. In FORTAMET treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin HCl is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and, if these symptoms occur, instruct them to discontinue FORTAMET and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

- *Renal impairment*—The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment.

  The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include [*see Dosage and Administration (2.2), Clinical Pharmacology (12.3)*]:

  - Before initiating FORTAMET, obtain an estimated glomerular filtration rate (eGFR).
  - FORTAMET is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 [see *Contraindications (4)*].
  - Initiation of FORTAMET is not recommended in patients with eGFR between 30 to 45 mL/min/1.73 m^2.

- Obtain an eGFR at least annually in all patients taking FORTAMET. In patients at risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
- In patients taking FORTAMET whose eGFR falls below 45 mL/min/1.73 m^2, assess the benefit and risk of continuing therapy.

- *Drug interactions* — The concomitant use of FORTAMET with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance, or increase metformin accumulation *[see Drug Interactions (7)]*. Consider more frequent monitoring of patients.
- *Age 65 or greater* — The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.
- *Radiologic studies with contrast* — Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop FORTAMET at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart FORTAMET if renal function is stable.
- *Surgery and other procedures* — Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension, and renal impairment. FORTAMET should be temporarily discontinued while patients have restricted food and fluid intake.
- *Hypoxic states* — Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may cause prerenal azotemia. When such an event occurs, discontinue FORTAMET.
- *Excessive alcohol intake* — Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving FORTAMET.
- *Hepatic impairment* — Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of FORTAMET in patients with clinical or laboratory evidence of hepatic disease.

5.2 Vitamin B_{12} Deficiency

In clinical trials of 29-week duration with metformin HCl tablets, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. Measure hematologic parameters on an annual basis and vitamin B_{12} at 2 to 3 year intervals in patients on FORTAMET and manage any abnormalities [*see Adverse Reactions (6.1)*].

5.3 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. FORTAMET may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with FORTAMET [*see Drug Interactions (7)*].

5.4 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with FORTAMET.

6 ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere in the labeling:

- Lactic Acidosis [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Vitamin B_{12} Deficiency [*see Warnings and Precautions (5.2)*]
- Hypoglycemia [*see Warnings and Precautions (5.3)*]

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In placebo-controlled trials, 781 patients were administered metformin HCl extended-release tablets. Adverse reactions reported in greater than 5% of the patients treated with metformin HCl extended-release tablets and that were more common than in placebo-treated patients are listed in Table 1.

Table 1: Adverse Reactions from Clinical Trials of Metformin HCl Extended-Release Tablets Occurring >5% and More Common than Placebo in Patients with Type 2 Diabetes Mellitus

Adverse Reaction	Metformin HCl Extended-Release Tablets (n=781)	Placebo (n=195)
Diarrhea	10%	3%
Nausea/Vomiting	7%	2%

Diarrhea led to the discontinuation of metformin HCl extended-release tablets in 0.6% of patients. Additionally, the following adverse reactions were reported in 1.0% to 5.0% of patients treated with metformin HCl extended-release tablets and were more commonly reported than in placebo-treated patients: abdominal pain, constipation, abdomen distention, dyspepsia/heartburn, flatulence, dizziness, headache, upper respiratory infection, taste disturbance.

Laboratory Tests

Vitamin B_{12} Concentrations

In clinical trials of 29-week duration with metformin HCl tablets, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of metformin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cholestatic, hepatocellular, and mixed hepatocellular liver injury have been reported with postmarketing use of metformin.

7 DRUG INTERACTIONS

Table 2 presents clinically significant drug interactions with FORTAMET.

Table 2: Clinically Significant Drug Interactions with FORTAMET

Carbonic Anhydrase Inhibitors	
Clinical Impact:	Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with FORTAMET may increase the risk for lactic acidosis.
Intervention:	Consider more frequent monitoring of these patients.
Examples:	Topiramate, zonisamide, acetazolamide or dichlorphenamide.
Drugs that Reduce FORTAMET Clearance	

Clinical Impact:	Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors) could increase systemic exposure to metformin and may increase the risk for lactic acidosis *[see Clinical Pharmacology (12.3)]*.
Intervention:	Consider the benefits and risks of concomitant use with FORTAMET.
Examples:	Ranolazine, vandetanib, dolutegravir, and cimetidine.
Alcohol	
Clinical Impact:	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
Intervention:	Warn patients against excessive alcohol intake while receiving FORTAMET.
Insulin Secretagogues or Insulin	
Clinical Impact:	Coadministration of FORTAMET with an insulin secretagogue (e.g., sulfonylurea) or insulin may increase the risk of hypoglycemia.
Intervention:	Patients receiving an insulin secretagogue or insulin may require lower doses of the insulin secretagogue or insulin.
Drugs Affecting Glycemic Control	
Clinical Impact:	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control.
Intervention:	When such drugs are administered to a patient receiving FORTAMET, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving FORTAMET, observe the patient closely for hypoglycemia.
Examples:	Thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data with FORTAMET in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk *[see Data]*. There are risks to the mother and fetus associated with poorly controlled diabetes mellitus in pregnancy [*see Clinical Considerations*].

No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during the period of organogenesis at doses up to 2- and 5- times, respectively, a 2550 mg clinical dose, based on body surface area *[see Data]*.

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes mellitus with an HbA1C >7 and has been reported to be as high as 20 to 25% in women with a HbA1C >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk
Poorly-controlled diabetes mellitus in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes mellitus increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human Data

Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Metformin HCl did not adversely affect development outcomes when administered to pregnant rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 5 times a 2550 mg clinical dose based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

8.2 Lactation

Risk Summary

Limited published studies report that metformin is present in human milk [*see Data*]. However, there is insufficient information to determine the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FORTAMET and any potential adverse effects on the breastfed child from FORTAMET or from the underlying maternal condition.

Data

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

8.3 Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with FORTAMET may result in ovulation in some anovulatory women.

8.4 Pediatric Use

Safety and effectiveness of FORTAMET in pediatric patients have not been established.

8.5 Geriatric Use

Controlled clinical studies of FORTAMET did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients [*see Warnings and Precautions (5.1)*].

8.6 Renal Impairment

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. FORTAMET is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2 [*see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

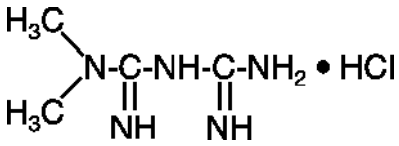
Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. FORTAMET is not recommended in patients with hepatic impairment [*see Warnings and Precautions (5.1)*].

10 OVERDOSAGE

Overdose of metformin HCl has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases [*see Warnings and Precautions (5.1)*]. Metformin is dialyzable with a 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.

11 DESCRIPTION

FORTAMET extended-release tablets contain the biguanidine antihyperglycemic agent, metformin, in the form of monohydrochloride salt. The chemical name of metformin HCl is N, N-dimethylimidodicarbonimidic diamide hydrochloride with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63. Its structural formula is:



Metformin HCl is a white to off-white crystalline powder that is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin HCl is 6.68.

FORTAMET tablets deliver 500 mg or 1,000 mg of metformin HCl, which is equivalent to 389.93 mg or 779.86 mg metformin, respectively. In addition to the active ingredient metformin HCl, each tablet contains the following inactive ingredients: candelilla wax, cellulose acetate, hypromellose, magnesium stearate, polyethylene glycols (PEG 400, PEG 8000), polysorbate 80, povidone, sodium lauryl sulfate, synthetic black iron oxides, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

12.3 Pharmacokinetics

Absorption

In a multiple-dose crossover study, 23 patients with type 2 diabetes mellitus were administered either FORTAMET 2,000 mg once a day (after dinner) or metformin HCl tablets 1,000 mg twice a day (after breakfast and after dinner). After 4 weeks of treatment, steady-state pharmacokinetic parameters, area under the concentration-time curve (AUC), time to peak plasma concentration (T_{max}), and maximum concentration (C_{max}) were evaluated. The appearance of metformin in

plasma from FORTAMET is slower and more prolonged compared to metformin HCl tablets. Results are presented in **Table 3.**

Table 3
FORTAMET vs.
Metformin HCl Tablets
Steady-State Pharmacokinetic Parameters at 4 Weeks

Pharmacokinetic Parameters (mean ± SD)	**FORTAMET 2,000 mg (administered q.d. after dinner)**	**Metformin HCl tablets* 2,000 mg (1,000 mg b.i.d.)**
$AUC_{0\text{-}24hr}$ (ng•hr/mL)	26,811 ± 7055	27,371 ± 5,781
T_{max} (hr)	6 (3-10)	3 (1-8)
C_{max} (ng/mL)	2849 ± 797	1820 ± 370

*Immediate-release metformin HCl tablets

In four single-dose studies and one multiple-dose study, the bioavailability of FORTAMET 2,000 mg given once daily, in the evening, under fed conditions [as measured by AUC] was similar to the same total daily dose administered as metformin HCl tablets 1,000 mg given twice daily. The geometric mean ratios (FORTAMET/ metformin HCL tablets) of $AUC_{0\text{-}24hr}$, $AUC_{0\text{-}72hr}$, and $AUC_{0\text{-}inf}$ for these five studies ranged from 0.96 to 1.08.

In a single-dose, four-period replicate crossover design study, comparing two 500 mg FORTAMET tablets to one 1,000 mg FORTAMET tablet administered in the evening with food to 29 healthy male subjects, two 500 mg FORTAMET tablets were found to be equivalent to one 1,000 mg FORTAMET tablet.

In a study carried out with FORTAMET, there was a dose-associated increase in metformin exposure over 24 hours following oral administration of 1,000, 1,500, 2,000, and 2,500 mg.

In three studies with FORTAMET using different treatment regimens (2,000 mg after dinner; 1,000 mg after breakfast and after dinner; and 2,500 mg after dinner), the pharmacokinetics of metformin as measured by AUC appeared linear following multiple-dose administration.

Effect of food: The extent of metformin absorption (as measured by AUC) from FORTAMET increased by approximately 60% when given with food. When FORTAMET was administered with food, C_{max} was increased by approximately 30% and T_{max} was more prolonged compared with the fasting state (6.1 versus 4.0 hours).

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of metformin HCl tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time.

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.

Elimination

Renal clearance (see Table 4) 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.

Specific Populations

Renal Impairment

In patients with decreased renal function the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased (see Table 4) [*See Dosage and Administration (2.2), Contraindications (4), and Warnings and Precautions (5.1) and Use in Specific Populations (8.6)*].

Hepatic Impairment

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment [*See Warnings and Precautions (5.1) and Use in Specific Populations (8.7)*].

Geriatrics

Limited data from controlled pharmacokinetic studies of metformin HCl tablets 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. It appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see Table 4). [*See Warnings and Precautions (5.1) and Use in Specific Populations (8.5)*].

Table 4: Select Mean (±S.D.) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of Metformin HCl Tablets

Subject Groups: Metformin HCl dose[a] (number of subjects)	C_{max}[b] (mcg/mL)	T_{max}[c] (hrs)	Renal Clearance (mL/min)
Healthy, nondiabetic adults:			
500 mg single dose (24)	1.03 (±0.33)	2.75 (±0.81)	600 (±132)
850 mg single dose (74)[d]	1.60 (±0.38)	2.64 (±0.82)	552 (±139)
850 mg three times daily for 19 doses[e] (9)	2.01 (±0.42)	1.79 (±0.94)	642 (±173)
Adults with type 2 diabetes mellitus:			
850 mg single dose (23)	1.48 (±0.5)	3.32 (±1.08)	491 (±138)
850 mg three times daily for 19 doses[e] (9)	1.90 (±0.62)	2.01 (±1.22)	550 (±160
Elderly[f], healthy nondiabetic adults:			
850 mg single dose (12)	2.45 (±0.70)	2.71 (±1.05)	412 (±98)
Renal-impaired adults:			
850 mg single dose			
Mild (CLcr[g] 61 to 90 mL/min) (5)	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Moderate (CLcr 31 to 60 mL/min) (4)	4.12 (±1.83)	3.75 (±0.50)	108 (±57)
Severe (CLcr 10 to 30 mL/min) (6)	3.93 (±0.92)	4.01 (±1.10)	130 (±90)

[a] All doses given fasting except the first 18 doses of the multiple dose studies
[b] Peak plasma concentration
[c] Time to peak plasma concentration
[d] Combined results (average means) of five studies: mean age 32 years (range 23 to 59 years)
[e] Kinetic study done following dose 19, given fasting
[f] Elderly subjects, mean age 71 years (range 65 to 81 years)
[g] CLcr = creatinine clearance normalized to body surface area of 1.73 m^2

Pediatrics

There are no available pharmacokinetic data with FORTAMET in pediatric patients.

Gender

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender (males=19, females=16).

Race

No studies of metformin pharmacokinetic parameters according to race have been performed.

Drug Interactions

***In Vivo* Assessment of Drug Interactions**

Table 5: Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC†	C_{max}
No dosing adjustments required for the following:					
Glyburide	5 mg	850 mg	metformin	0.91‡	0.93‡
Furosemide	40 mg	850 mg	metformin	1.09‡	1.22‡
Nifedipine	10 mg	850 mg	metformin	1.16	1.21
Propranolol	40 mg	850 mg	metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	metformin	1.05‡	1.07‡
Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination [*See Warnings and Precautions (5.1) and Drug Interactions (7).*]					
Cimetidine	400 mg	850 mg	metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis [*See Warnings and Precautions (5.1) and Drug Interactions (7).*]					
Topiramate	100 mg§	500 mg§	metformin	1.25§	1.17

* All metformin HCl and coadministered drugs were given as single doses
† AUC = AUC_{inf}
‡ Ratio of arithmetic means
§ At steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC_{0-12h}

Table 6: Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (ratio with/without metformin) No Effect = 1.00		
				AUC†	C_{max}
No dosing adjustments required for the following:					
Glyburide	5 mg	850 mg	glyburide	0.78‡	0.63‡
Furosemide	40 mg	850 mg	furosemide	0.87‡	0.69‡
Nifedipine	10 mg	850 mg	nifedipine	1.10§	1.08
Propranolol	40 mg	850 mg	propranolol	1.01§	1.02
Ibuprofen	400 mg	850 mg	ibuprofen	0.97¶	1.01¶
Cimetidine	400 mg	850 mg	cimetidine	0.95§	1.01

* All metformin HCl and coadministered drugs were given as single doses
† AUC = AUC_{inf} unless otherwise noted
‡ Ratio of arithmetic means, p-value of difference <0.05
§ $AUC_{0-24\ hr}$ reported
¶ Ratio of arithmetic means

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1,500 mg/kg/day, respectively. These doses are both approximately 3 times the maximum recommended human daily dose of 2550 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there

was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of metforminin the following *in vitro* tests: Ames test (S. typhimurium), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 2 times the maximum recommended human daily dose of 2550 mg based on body surface area comparisons.

14 CLINICAL STUDIES

A 24-week, double-blind, placebo-controlled study of metformin HCl extended-release tablets, taken once daily with the evening meal, was conducted in patients with type 2 diabetes mellitus who had failed to achieve glycemic control with diet and exercise. Patients entering the study had a mean baseline HbA_{1c} of 8.0% and a mean baseline FPG of 176 mg/dL. The treatment dose was increased to 1,500 mg once daily if at Week 12 HbA_{1c} was ≥7.0% but <8.0% (patients with HbA_{1c} ≥8.0% were discontinued from the study). At the final visit (24-week), mean HbA_{1c} had increased 0.2% from baseline in placebo patients and decreased 0.6% with metformin HCl extended-release tablets.

A 16-week, double-blind, placebo-controlled, dose-response study of metformin HCl extended-release tablets, taken once daily with the evening meal or twice daily with meals, was conducted in patients with type 2 diabetes mellitus who had failed to achieve glycemic control with diet and exercise. The results are shown in Table 7.

Table 7: Mean Changes from Baseline* in HbA1c and Fasting Plasma Glucose at Week 16 Comparing Metformin HCl Extended-Release Tablets vs Placebo in Patients with Type 2 Diabetes Mellitus

	Metformin HCl Extended-Release Tablets					Placebo
	500 mg Once Daily	1,000 mg Once Daily	1,500 mg Once Daily	2,000 mg Once Daily	1,000 mg Twice Daily	
Hemoglobin A1c (%)	**(n=115)**	**(n=115)**	**(n=111)**	**(n=125)**	**(n=112)**	**(n=111)**
Baseline	8.2	8.4	8.3	8.4	8.4	8.4
Change at FINAL VISIT	–0.4	–0.6	–0.9	–0.8	–1.1	0.1
p-value[a]	<0.001	<0.001	<0.001	<0.001	<0.001	–
FPG (mg/dL)	**(n=126)**	**(n=118)**	**(n=120)**	**(n=132)**	**(n=122)**	**(n=113)**
Baseline	182.7	183.7	178.9	181.0	181.6	179.6
Change at FINAL VISIT	–15.2	–19.3	–28.5	–29.9	–33.6	7.6
p-value[a]	<0.001	<0.001	<0.001	<0.001	<0.001	–

[a] All comparisons versus Placebo

Mean baseline body weight was 193 lbs, 192 lbs, 188 lbs, 196 lbs, 193 lbs and 194 lbs in the metformin HCl extended-release tablets 500 mg, 1,000 mg, 1,500 mg, and 2,000 mg once daily, 1,000 mg twice daily and placebo arms, respectively. Mean change in body weight from baseline to week 16 was -1.3 lbs, -1.3 lbs, -0.7 lbs, -1.5 lbs, -2.2 lbs and -1.8 lbs, respectively.

A 24-week, double-blind, randomized study of metformin HCl extended-release tablets, taken once daily with the evening meal, and metformin HCl tablets, taken twice daily (with breakfast and evening meal), was conducted in patients with type 2 diabetes mellitus who had been treated with metformin HCl tablets 500 mg twice daily for at least 8 weeks prior to study entry. The results are shown in Table 8.

Table 8: Mean Changes from Baseline* in HbA1c and Fasting Plasma Glucose at Week 24 Comparing Metformin HCl Extended-Release vs Metformin HCl in Patients with Type 2 Diabetes Mellitus

	Metformin HCl 500 mg Twice Daily	Metformin HCl Extended-Release	
		1,000 mg Once Daily	1,500 mg Once Daily

Hemoglobin A1c (%)	**(n=67)**	**(n=72)**	**(n=66)**
Baseline	7.06	6.99	7.02
Change at FINAL VISIT (95% CI)	0.14[a] (–0.04, 0.31)	0.27 (0.11, 0.43)	0.13 (–0.02, 0.28)
FPG (mg/dL)	**(n=69)**	**(n=72)**	**(n=70)**
Baseline	127.2	131.0	131.4
Change at FINAL VISIT (95% CI)	14.0 (7.0, 21.0)	11.5 (4.4, 18.6)	7.6 (1.0, 14.2)

†[a] n=68

Mean baseline body weight was 210 lbs, 203 lbs and 193 lbs in the metformin HCl tablets 500 mg twice daily, and metformin HCl extended-release tablets 1,000 mg and 1,500 mg once daily arms, respectively. Mean change in body weight from baseline to week 24 was 0.9 lbs, 1.1 lbs and 0.9 lbs, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

FORTAMET is supplied as:

500 mg	Bottles of 60	NDC 59630-574-60	white-colored, unscored biconvex-shaped, film-coated extended-release tablets imprinted with Andrx logo and 574 on one side
1,000 mg	Bottles of 60	NDC 59630-575-60	white-colored, unscored biconvex-shaped, film-coated extended-release tablets imprinted with Andrx logo and 575 on one side

16.2 Storage

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature] excursions permitted to 15° to 30°C (59° to 86°F). Avoid excessive heat and humidity.

Keep tightly closed (protect from moisture). Protect from light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Lactic Acidosis:

Explain the risks of lactic acidosis, its symptoms, and conditions that predispose to its development. Advise patients to discontinue FORTAMET immediately and to promptly notify their healthcare provider if unexplained hyperventilation, myalgias, malaise, unusual somnolence or other nonspecific symptoms occur. Counsel patients against excessive alcohol intake and inform patients about importance of regular testing of renal function while receiving FORTAMET. Instruct patients to inform their doctor that they are taking FORTAMET prior to any surgical or radiological procedure, as temporary discontinuation may be required [*see Warnings and Precautions (5.1)*].

Hypoglycemia:

Inform patients that hypoglycemia may occur when FORTAMET is coadministered with oral sulfonylureas and insulin. Explain to patients receiving concomitant therapy the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development [*see Warnings and Precautions (5.3)*].

Vitamin B_{12} Deficiency:

Inform patients about importance of regular hematological parameters while receiving FORTAMET [*see Warnings and Precautions (5.2)*].

Females of Reproductive Age:

Inform females that treatment with FORTAMET may result in ovulation in some premenopausal anovulatory women which may lead to unintended pregnancy [*see Use in Specific Populations (8.3)*].

Administration Information:

Inform patients that FORTAMET must be swallowed whole and not crushed, cut, or chewed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that may resemble the original tablet.

Manufactured by:
Actavis Laboratories FL, Inc.
Fort Lauderdale, FL 33314 USA

Distributed by:
Shionogi Inc.
Florham Park, NJ 07932

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PATIENT INFORMATION
FORTAMET® (for-TAH-met)
(metformin hydrochloride)
extended-release tablets

What is the most important information I should know about FORTAMET?
FORTAMET can cause serious side effects including:
Lactic Acidosis. Metformin hydrochloride, the medicine in FORTAMET, can cause a rare, but serious side effect called lactic acidosis (a build-up of lactic acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in a hospital.
Stop taking FORTAMET and call your healthcare provider right away if you get any of the following symptoms of lactic acidosis:

- feel very weak and tired
- have unusual (not normal) muscle pain
- have trouble breathing
- have unexplained stomach or intestinal problems with nausea and vomiting, or diarrhea
- have unusual sleepiness or sleep longer than usual
- feel cold, especially in your arms and legs
- feel dizzy or lightheaded
- have a slow or irregular heartbeat

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

- have severe kidney problems. See "**Do not take FORTAMET if you:**"
- have liver problems.
- have congestive heart failure that requires treatment with medicines.
- drink a lot of alcohol (very often or short-term "binge" drinking).
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
- have certain x-ray tests with injectable dyes or contrast agents.
- have surgery.
- have a heart attack, severe infection, or stroke.
- are 65 years of age or older.

Tell your healthcare provider if you have any of the problems in the list above.
Tell your healthcare provider that you are taking FORTAMET before you have surgery or x-ray tests. Your healthcare provider may need to stop FORTAMET for a while if you have surgery or certain x-ray tests).
FORTAMET can have other serious side effects. See "**What are the possible side effects of FORTAMET?**"

What is FORTAMET?

- FORTAMET is a prescription medicine that contains metformin hydrochloride. FORTAMET is used with diet and exercise to help control high blood sugar (hyperglycemia) in adults with type 2 diabetes.
- It is not known if FORTAMET is safe and effective in children under 18 years of age.

Do not take FORTAMET if you:

- have severe kidney problems
- are allergic to metformin HCl or any of the ingredients in FORTAMET. See the end of this Patient Information leaflet for a complete list of ingredients in FORTAMET.
- have a condition called metabolic acidosis including diabetic ketoacidosis (high levels of certain acids called "ketones" in your blood or urine).

Before taking FORTAMET, tell your healthcare provider about all your medical conditions, including if you:

- have a history or risk for diabetic ketoacidosis. See "**Do not take FORTAMET if you:**"
- have kidney problems.
- have liver problems.
- have heart problems, including congestive heart failure.
- are 65 years of age or older.
- drink alcohol very often or drink a lot of alcohol in short-term "binge" drinking.
- are taking insulin or a sulfonylurea medicine.
- are pregnant or plan to become pregnant. It is not known if FORTAMET will harm your unborn baby. If you are pregnant, talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.

- are a woman who has not gone through menopause (premenopausal) who does not have periods regularly or at all. FORTAMET can cause the release of an egg from an ovary in a woman (ovulation). This can increase your chance of getting pregnant.
- are breastfeeding or plan to breastfeed. FORTAMET can pass into your breast milk. Talk with your healthcare provider about the best way to feed your baby while you take FORTAMET.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.
FORTAMET may affect the way other medicines work, and other medicines may affect how FORTAMET works.

How should I take FORTAMET?

- Take FORTAMET exactly as your healthcare provider tells you.
- FORTAMET should be taken with your evening meals to help decrease an upset stomach.
- Swallow FORTAMET whole. Do not crush, cut, or chew the tablets.
- You may sometimes pass a soft mass in your stools (bowel movement) that looks like FORTAMET. This is not harmful and will not affect the way FORTAMET works.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine that you need may change. Tell your healthcare provider right away if you have any of these problems.
- Your healthcare provider should do blood tests to check how well your kidneys are working before and during your treatment with FORTAMET.
- Your healthcare provider will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.
- Low blood sugar (hypoglycemia) can happen more often when FORTAMET is taken with certain other diabetes medicines.
  Talk to your healthcare provider about how to prevent, recognize and manage low blood sugar. See "**What are the possible side effects of FORTAMET?**"
- Check your blood sugar as your healthcare provider tells you to.
- Stay on your prescribed diet and exercise program while taking FORTAMET.
- If you take too much FORTAMET, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking FORTAMET?
Do not drink a lot of alcoholic drinks while taking FORTAMET. This means you should not binge drink for short periods, and you should not drink a lot of alcohol on a regular basis. Alcohol can increase the chance of getting lactic acidosis.

What are the possible side effects of FORTAMET?
FORTAMET may cause serious side effects, including:

- See **"What is the most important information I should know about FORTAMET?"**
- **Low vitamin B_{12} (vitamin B_{12} deficiency).** Using FORTAMET may cause a decrease in the amount of vitamin B_{12} in your blood, especially if you have had low vitamin B_{12} levels before. Your healthcare provider may do blood tests to check your vitamin B_{12} levels.
- **Low blood sugar (hypoglycemia).** If you take FORTAMET with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take FORTAMET. Signs and symptoms of low blood sugar may include:
  - headache
  - drowsiness
  - weakness
  - irritability
  - hunger
  - fast heartbeat
  - confusion
  - shaking or feeling jittery
  - dizziness
  - sweating

Common side effects of FORTAMET include:

- diarrhea
- nausea and vomiting
- gassiness (flatulence)
- indigestion
- stomach-area (abdominal) pain and swelling
- headache
- taste disturbance (unpleasant metallic taste)

These are not all the possible side effects of FORTAMET.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store FORTAMET?

Store FORTAMET at room temperature between 68°F to 77°F (20°C to 25°C). See insert.
Keep bottle tightly closed between each use to protect the FORTAMET tablets from moisture.
Protect from light.

Keep FORTAMET and all medicines out of the reach of children.

General information about the safe and effective use of FORTAMET

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use FORTAMET for a condition for which it was not prescribed. Do not give FORTAMET to other people, even if they have the same symptoms that you have. It may harm them.
You can ask your pharmacist or healthcare provider for information about FORTAMET that is written for health professionals.

What are the ingredients in FORTAMET?

Active ingredients: metformin hydrochloride.
Inactive ingredients: candelilla wax, cellulose acetate, hypromellose, magnesium stearate, polyethylene glycols (PEG 400, PEG 8000), polysorbate 80, povidone, sodium lauryl sulfate, synthetic black iron oxides, titanium dioxide, and triacetin.

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