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.

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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

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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)*].

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- 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

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- 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	

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