Riomet ER™

(METFORMIN HCL) EXTENDED-RELEASE ORAL SUSPENSION 500 mg/5 mL

Prior Authorization Checklist

Please review this checklist prior to submitting a prior authorization (PA) form to the health plan, as incomplete submissions can lead to delays in processing.

- ☑ Include the patient's name, policy number, and date of birth
- ☑ Provide the healthcare provider's contact information and ID number
- ☑ Confirm the patient's diagnosis (include ICD-10-CM code)
- ☑ Detail the current severity of the patient's condition, including any comorbidities or intolerance to other medications
- ☑ Include the dosage for Riomet ER™
- ☑ List all previous medications, if applicable
- ☑ Document if the patient has satisfied any step-therapy requirements
- ☑ Include a rationale for prescribing Riomet ER™ for the patient

Some health plans may require additional clinical and/or medication history. Be as comprehensive as possible with this information.

Be sure to include ALL information requested by the health plan. Incomplete PA submissions can delay patients' access to treatment

Please see accompanying Full Prescribing Information, including BOXED WARNING.

SUN PHARMA

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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

RIOMET ER™ (metformin hydrochloride for extended-release oral suspension)

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 RIOMET ER and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

----------INDICATIONS AND USAGE----------

RIOMET ER is a biguanide indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus. (1)

----------DOSAGE AND ADMINISTRATION----------

Adult Dosage:

- Starting dose: 500 mg (5 mL) orally once daily, with the evening meal (2.1)
- Increase the dose in increments of 500 mg (5 mL) weekly, up to a maximum dose of 2,000 mg (20 mL) once daily, with the evening meal (2.1)
- Patients receiving metformin hydrochloride (HCl) immediate-release treatment may be switched to RIOMET ER once daily at the same total daily dose, up to 2,000 mg (20 mL) once daily (2.1)

Pediatric Dosage:

- Starting dose: 500 mg (5 mL) orally once daily, with the evening meal (2.2)
- Increase dosage in increments of 500 mg (5 mL) weekly up to a maximum of 2,000 mg (20 mL) once daily, with the evening meal (2.2)

Renal Impairment:

- Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR) (2.3)
  - Do not use in patients with eGFR below 30 mL/minute/1.73 m^2 (2.3)
  - Initiation is not recommended in patients with eGFR between 30 to 45 mL/minute/1.73 m^2 (2.3)
  - Assess risk/benefit of continuing RIOMET ER if eGFR falls below 45 mL/minute/1.73 m^2 (2.3)
  - Discontinue if eGFR falls below 30 mL/minute/1.73 m^2 (2.3)

Discontinuation for Iodinated Contrast Imaging Procedures:

- RIOMET ER may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures (2.4)

Reconstitution Instructions for the Pharmacist:

- See Full Prescribing Information for instructions (2.5).

----------DOSAGE FORMS AND STRENGTHS ----------

For extended-release oral suspension: 47.31 grams of metformin HCl for reconstitution in 473 mL bottle pack. The reconstituted suspension is 500 mg/5 mL (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----------

The most common adverse reactions (> 5.0%) are diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-818-4555 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)
- Warn patients against excessive alcohol intake while receiving RIOMET ER and not to consume alcohol or medications containing alcohol concurrently with RIOMET ER (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: 08/2019

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 (2.3), Contraindications (4), Warnings and Precautions (5.1)]*.**
- **If metformin-associated lactic acidosis is suspected, immediately discontinue RIOMET ER and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended *[see Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

RIOMET ER is indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosage

- Measure the RIOMET ER dose of suspension in RIOMET ER specific dosing cup supplied.
- The reconstituted suspension is 500 mg/5 mL *[see Dosage and Administration (2.5)]*.
- The recommended starting dose of RIOMET ER is 500 mg (5 mL) orally once daily with the evening meal.
- Increase the dose in increments of 500 mg (5 mL) weekly on the basis of glycemic control and tolerability, up to a maximum dose of 2,000 mg (20 mL) once daily with the evening meal.
- If glycemic control is not achieved with RIOMET ER 2,000 mg (20 mL) once daily, consider a trial of RIOMET ER 1,000 mg (10 mL) twice daily. If higher doses are required, switch to metformin hydrochloride (HCl) immediate-release at total daily doses up to 2,550 mg (25.5 mL) administered in divided daily doses, as described above.
- Patients receiving metformin HCl immediate-release treatment may be switched to RIOMET ER once daily at the same total daily dose, up to 2,000 mg (20 mL) once daily.

2.2 Pediatric Dosage

- Measure the RIOMET ER dose of suspension in the RIOMET ER specific dosing cup supplied.
- The reconstituted suspension is 500 mg/5 mL *[see Dosage and Administration (2.5)]*.
- The recommended starting dose of RIOMET ER for pediatric patients 10 years of age and older is 500 mg (5 mL) orally once daily, with the evening meal.
- Increase dosage in increments of 500 mg (5 mL) weekly on the basis of glycemic control

and tolerability, up to a maximum of 2,000 mg (20 mL) once daily with the evening meal.

2.3 Recommendations for Use in Renal Impairment

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

2.4 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue RIOMET ER 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 RIOMET ER if renal function is stable.

2.5 Reconstitution Instructions for the Pharmacist

RIOMET ER is supplied as a powder for oral suspension which must be reconstituted with the accompanying diluent prior to dispensing. Both the powder and diluent contain metformin HCl.

Please read these instructions completely before you begin.

Round Bottle Pack

Step-A Remove the bottle containing Drug Pellets and Drug Diluent bottle along with RIOMET ER dosing cup from the box. Do not use if: The expiration date has passed. The bottle appears damaged or defective.

Step-B Remove the child-resistant cap (push down and turn) from the bottle containing Drug Pellets and Drug Diluent bottle, and retain.

Step-C Pour the contents of bottle containing Drug Pellets in to the Drug Diluent bottle and discard the empty Pellet bottle **(See Figure 1)**.

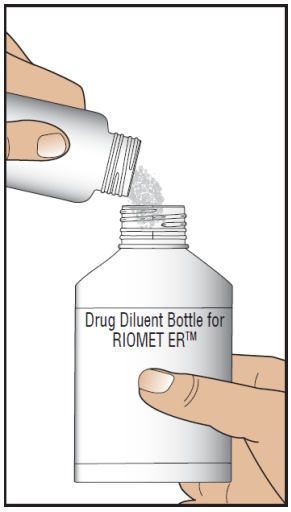


Figure 1

Step-D Close the Drug Diluent bottle with child-resistant cap.
Step-E Shake the Drug Diluent bottle continuously in an up and down direction for at least 2 full minutes. This is important for the product to mix evenly. The reconstituted suspension is 500 mg/5 mL.

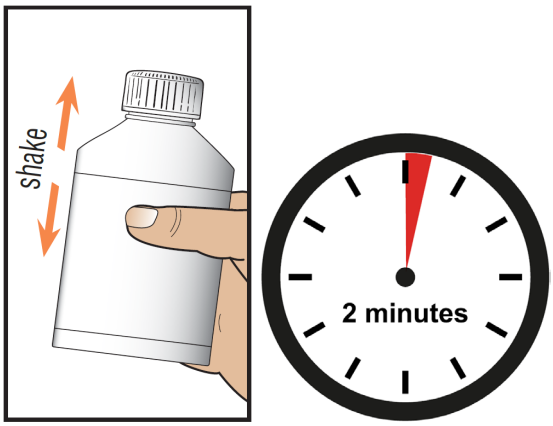


Figure 2

Store reconstituted suspension in the original bottle between 20°C to 25°C (68°F to 77°F). Do not repackage.

3 DOSAGE FORMS AND STRENGTHS

For extended-release oral suspension: 47.31 grams of metformin HCl as white to off-white pellets and white to off-white diluent for reconstitution in 473 mL bottle pack

The reconstituted suspension is 500 mg/5 mL appearing as white to off-white suspension containing white to off-white pellets

4 CONTRAINDICATIONS

RIOMET ER 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 RIOMET ER. In RIOMET ER treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride 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 RIOMET ER 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 (2.1), Clinical Pharmacology (12.3)]*:

  - Before initiating RIOMET ER, obtain an estimated glomerular filtration rate (eGFR).
  - RIOMET ER is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 *[see Contraindications (4)]*.
  - Initiation of RIOMET ER 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 RIOMET ER. In patients at risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
  - In patients taking RIOMET ER 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 RIOMET ER 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. 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 RIOMET ER 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 RIOMET ER 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. RIOMET ER 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 RIOMET ER.

- *Excessive alcohol intake* - Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving RIOMET ER.
- *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 RIOMET ER 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 RIOMET ER 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. RIOMET ER 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 RIOMET ER *[see Drug Interactions (7)]*.

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.

Metformin Immediate-Release

In a U.S. clinical trial of metformin immediate-release tablet in patients with type 2 diabetes mellitus, a total of 141 patients received metformin immediate-release tablet up to 2,550 mg per day. Adverse reactions reported in greater than 5% of metformin immediate-release tablet treated patients and that were more common than in placebo-treated patients, are listed in Table 1.

Table 1: Adverse Reactions from a Clinical Trial of Metformin Occurring >5% and More Common than Placebo in Patients with Type 2 Diabetes Mellitus

	Metformin Immediate-Release Tablet (n = 141)	**Placebo (n = 145)**
Diarrhea	53%	12%
Nausea/Vomiting	26%	8%
Flatulence	12%	6%

	Metformin Immediate-Release Tablet (n = 141)	Placebo (n = 145)
Asthenia	9%	6%
Indigestion	7%	4%
Abdominal Discomfort	6%	5%
Headache	6%	5%

Diarrhea led to discontinuation of metformin immediate-release tablet in 6% of patients. Additionally, the following adverse reactions were reported in ≥ 1% to ≤ 5% of metformin immediate-release tablet treated patients and were more commonly reported with metformin immediate-release tablet than placebo: abnormal stools, hypoglycemia, myalgia, lightheaded, dyspnea, nail disorder, rash, sweating increased, taste disorder, chest discomfort, chills, flu syndrome, flushing, palpitation.

In metformin immediate-release tablet clinical trials of 29 week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels was observed in approximately 7% of patients.

Pediatric Patients
In clinical trials with metformin in pediatric patients with type 2 diabetes mellitus, the profile of adverse reactions was similar to that observed in adults.

Metformin Extended-Release

In placebo-controlled trials, 781 patients were administered metformin extended-release tablet. Adverse reactions reported in greater than 5% of the metformin extended-release tablet patients, and that were more common in metformin extended-release tablet- than placebo-treated patients, are listed in Table 2.

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

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

*Reactions that were more common in metformin hydrochloride extended-release tablet- than placebo-treated patients.

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

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 3 presents clinically significant drug interactions with RIOMET ER.

Table 3: Clinically Significant Drug Interactions with RIOMET ER

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 RIOMET ER may increase the risk for lactic acidosis.
Intervention:	Consider more frequent monitoring of these patients.
Examples:	Topiramate, zonisamide, acetazolamide or dichlorphenamide.
Drugs that Reduce Metformin 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 [OCT_2] / 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 RIOMET ER.
Examples:	Ranolazine, vandetanib, dolutegravir, and cimetidine.
Alcohol and Medications Containing Alcohol	
Clinical Impact:	Alcohol is known to potentiate the effect of metformin on lactate metabolism. Further, consuming alcohol or oral liquid medications containing alcohol (e.g. cough/cold or pain medications) concomitantly with RIOMET ER can accelerate the release and absorption of metformin *[see Clinical Pharmacology (12.3)]*.
Intervention:	Warn patients against excessive alcohol intake while receiving RIOMET ER and not to consume alcohol or medications containing alcohol concurrently with RIOMET ER.
Insulin Secretagogues or Insulin	
Clinical Impact:	Coadministration of RIOMET ER 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 RIOMET ER, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving RIOMET ER, 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 metformin 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 2,550 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, 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 hydrochloride 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 2,550 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 RIOMET ER and any potential adverse effects on the breastfed child from RIOMET ER 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 metformin may result in ovulation in some anovulatory women.

8.4 Pediatric Use
The safety and effectiveness of RIOMET ER as an adjunct to diet and exercise to improve glycemic control in pediatric patients 10 years of age and older with type 2 diabetes mellitus have been established. Use of RIOMET ER for this indication is supported by evidence from adequate and well-

controlled studies of metformin HCl immediate-release tablet in adults with additional data from a controlled clinical study using metformin HCl immediate-release tablets in pediatric patients 10 to 16 years old with type 2 diabetes mellitus *[see Clinical Studies (14.1)]*.

Safety and effectiveness of RIOMET ER have not been established in pediatric patients less than 10 years old.

8.5 Geriatric Use

Controlled clinical studies of metformin HCl immediate-release tablet and HCl extended-release tablet 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. RIOMET ER 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 (2.3), Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

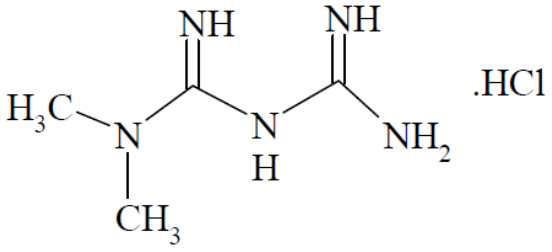
Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. RIOMET ER is not recommended in patients with hepatic impairment *[see Warnings and Precautions (5.1)]*.

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 hydrochloride 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

RIOMET ER (metformin hydrochloride for extended-release oral suspension) is a biguanide. The chemical name of metformin hydrochloride is *N*,*N*-dimethylimidodicarbonimidic diamide hydrochloride. The structural formula is as shown below:



Metformin hydrochloride, USP is a white crystalline powder with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.62. It is freely soluble in water, slightly soluble in

alcohol; practically insoluble in acetone and in methylene chloride. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride, USP is 6.37 to 6.53.

RIOMET ER is available as follows:

- 16 oz. Round Bottle Pack containing white to off-white pellets containing 37.85 g of metformin HCl (equivalent to 29.52 g metformin base) in drug pellets bottle and white to off-white dispersion containing 9.46 g of metformin hydrochloride (equivalent to 7.38 g metformin base) in drug diluent bottle intended for reconstitution.

Following reconstitution, the volume of the oral suspension is 473.12 mL (16 oz.) containing 500 mg/5mL metformin HCl equivalent to 389.95 mg metformin base.

The oral suspension include the following inactive ingredients: carboxymethyl cellulose sodium, colloidal silicon dioxide, dibutyl sebacate, ethyl cellulose, hypromellose, magnesium stearate, methyl paraben, microcrystalline cellulose, propyl paraben, sucralose, strawberry flavor Type FL # 28082 (flavoring ingredients, propylene glycol and glycerin) xanthan gum and xylitol.

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

Following a single oral dose of RIOMET ER 500 mg/5 mL (dose: 750 mg) in healthy adult male subjects (N=52) when taken with high-fat meal, the mean C_{max} and AUC_{0-t} values is 815 ng/mL and 7694 ng•hr/mL, respectively (Table 4). The T_{max} is achieved with a median value of 4.5 hours and a range of 3.5 to 6.5 hours.

Effect of food: In the same study, the administration of RIOMET ER 500 mg/5 mL following a standardized high-fat, high-calorie breakfast (containing approximately 150 kcal from protein, 250 kcal from carbohydrates and 500 kcal from fat) had minimal effect on the AUC of metformin; however, C_{max} is decreased by approximately 20% when compared to dosing under fasting condition (Table 4). The median T_{max} is delayed by 1 hour under fed condition compared to fasting condition.

The observed elimination half-life ($t_{1/2}$) is similar under both fasting and fed conditions.

Table 4: Pharmacokinetic Parameters for Single 750 mg Dose of RIOMET ER 500 mg/5 mL

	C_{max} (ng/mL) Mean (±SD)	**T_{max} (hr)# Median (Range)**	**AUC_{0-t} (ng•hr/mL) Mean (±SD)**	**$t_{1/2}$ (hr) Mean (±SD)**
Fasting condition (N = 52)	1067.56 ± 377.11	4.50 (3.50 to 6.50)	7472.02 ± 1946.10	4.63 ± 1.97
Fed condition (N = 52)	815.39 ± 180.15	5.50 (3.50 to 10.00)	7694.78 ± 1692.11	4.19 ± 1.03

In vitro alcohol interaction: An *in vitro* dissolution study indicated an accelerated release rate of metformin from the RIOMET ER when tested with 5-40% alcohol content in the medium. The dissolution rate of metformin in the suspension increased with increasing alcohol content.

Distribution
The apparent average volume of distribution (V/F) of metformin following single 750 mg oral doses of RIOMET ER is 596±173 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 5) 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 5) *[See Dosage and Administration (2.3), Contraindications (4), 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 hydrochloride immediate-release tablet 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 5). *[See Warnings and Precautions (5.1) and Use in Specific Populations (8.5)]*.

Table 5: Select Mean (±S.D.) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of Metformin HCl Immediate-Release Tablet

Subject Groups: Metformin HCl Immediate-Release Tablet dose[a] (number of subjects)	Cmax[b] (mcg/mL)	Tmax[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** (CL_{cr}[g] 61 to 90 mL/min) (5)	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Moderate (CL_{cr} 31 to 60 mL/min) (4)	4.12 (±1.83)	3.75 (±0.50)	108 (±57)
Severe (CL_{cr} 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] CL_{cr} = creatinine clearance normalized to body surface area of 1.73 m^2

Pediatrics

Pharmacokinetics study has not been conducted on RIOMET ER in pediatric population. After administration of a single oral metformin hydrochloride 500 mg immediate-release tablet with food, geometric mean metformin C_{max} and AUC differed less than 5% between pediatric type 2 diabetic patients (12 to 16 years of age) and gender- and weight-matched healthy adults (20 to 45 years of age), all with normal renal function.

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 6: Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC†	C_{max}
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 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 7: Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin*	Geometric Mean Ratio (ratio with/without metformin) No Effect = 1.00		
				AUC†	C_{max}
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 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 1500 mg/kg/day, respectively. These doses are both approximately 3 times the maximum recommended human daily dose of 2,550 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 metformin in 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 2,550 mg based on body surface area comparisons.

14 CLINICAL STUDIES

14.1 Metformin HCl Immediate-Release

Adult Clinical Studies

A double-blind, placebo-controlled, multicenter US clinical trial involving obese patients with type 2 diabetes mellitus whose hyperglycemia was not adequately controlled with dietary management alone (baseline fasting plasma glucose [FPG] of approximately 240 mg/dL) was conducted. Patients were treated with metformin HCl immediate-release tablet (up to 2,550 mg/day) or placebo for 29 weeks. The results are presented in Table 8.

Table 8: Mean Change in Fasting Plasma Glucose and HbA1c at Week 29 Comparing Metformin HCl vs Placebo in Patients with Type 2 Diabetes Mellitus

	Metformin HCl (n = 141)	Placebo (n = 145)	p-Value
FPG (mg/dL)			
Baseline	241.5	237.7	NS*
Change at FINAL VISIT	–53.0	6.3	0.001
Hemoglobin A_{1c} (%)			
Baseline	8.4	8.2	NS*
Change at FINAL VISIT	–1.4	0.4	0.001

* Not statistically significant

Mean baseline body weight was 201 lbs and 206 lbs in the metformin HCl and placebo arms, respectively. Mean change in body weight from baseline to week 29 was -1.4 lbs and -2.4 lbs in the metformin HCl and placebo arms, respectively. A 29-week, double-blind, placebo-controlled study of metformin HCl immediate-release tablet and glyburide, alone and in combination, was conducted in obese patients with type 2 diabetes mellitus who had failed to achieve adequate glycemic control while on maximum doses of glyburide (baseline FPG of approximately 250 mg/dL). Patients randomized to the combination arm started therapy with metformin HCl 500 mg immediate-release tablet and glyburide 20 mg. At the end of each week of the first 4 weeks of the trial, these patients had their dosages of metformin HCl immediate-release tablet increased by 500 mg if they had failed to reach target fasting plasma glucose. After week 4, such dosage adjustments were made monthly, although no patient was allowed to exceed metformin hydrochloride 2,500 mg immediate-release tablet. Patients in the metformin HCl immediate-release tablet only arm

(metformin plus placebo) discontinued glyburide and followed the same titration schedule. Patients in the glyburide arm continued the same dose of glyburide. At the end of the trial, approximately 70% of the patients in the combination group were taking metformin HCl immediate-release tablet 2,000 mg/glyburide 20 mg or metformin HCl immediate-release tablet 2,500 mg/glyburide 20 mg. The results are displayed in Table 9.

Table 9: Mean Change in Fasting Plasma Glucose and HbA1c at Week 29 Comparing Metformin HCl/Glyburide (Comb) vs Glyburide (Glyb) vs Metformin HCl (GLU): in Patients with Type 2 Diabetes Mellitus with Inadequate Glycemic Control on Glyburide

	Comb (n = 213)	Glyb (n = 209)	GLU (n = 210)	p-Values		
				Glyb vs Comb	GLU vs Comb	GLU vs Glyb
Fasting Plasma Glucose (mg/dL)						
Baseline	250.5	247.5	253.9	NS*	NS*	NS*
Change at FINAL VISIT	–63.5	13.7	–0.9	0.001	0.001	0.025
Hemoglobin A_{1c} (%)						
Baseline	8.8	8.5	8.9	NS*	NS*	0.007
Change at FINAL VISIT	–1.7	0.2	–0.4	0.001	0.001	0.001

* Not statistically significant

Mean baseline body weight was 202 lbs, 203 lbs, and 204 lbs in the metformin HCl/glyburide, glyburide, and metformin HCl arms, respectively. Mean change in body weight from baseline to week 29 was 0.9 lbs, -0.7 lbs, and -8.4 lbs in the metformin HCl/glyburide, glyburide, and metformin HCl arms, respectively.

Pediatric Clinical Studies

A double-blind, placebo-controlled study in pediatric patients aged 10 to 16 years with type 2 diabetes mellitus (mean FPG 182.2 mg/dL), treatment with metformin HCl immediate-release tablet (up to 2,000 mg/day) for up to 16 weeks (mean duration of treatment 11 weeks) was conducted. The results are displayed in Table 10.

Table 10: Mean Change in Fasting Plasma Glucose at Week 16 Comparing metformin HCl vs Placebo in Pediatric Patients[a] with Type 2 Diabetes Mellitus

	Metformin HCl	Placebo	p-Value
FPG (mg/dL)	**(n = 37)**	**(n = 36)**	
Baseline	162.4	192.3	
Change at FINAL VISIT	–42.9	21.4	<0.001

[a] Pediatric patients mean age 13.8 years (range 10 to 16 years)

Mean baseline body weight was 205 lbs and 189 lbs in the metformin HCl and placebo arms, respectively. Mean change in body weight from baseline to week 16 was -3.3 lbs and -2.0 lbs in the metformin and placebo arms, respectively.

14.2 Metformin HCl Extended-Release

A 24 week, double-blind, placebo-controlled study of metformin HCl extended-release tablet, taken once daily with the evening meal, was conducted in patients with type 2 diabetes who had failed to achieve glycemic control with diet and exercise. Patients entering the study had a mean baseline HbA1c of 8% 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% but < 8% (patients with HbA_{1c} ≥ 8% 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 tablet.

A 16-week, double-blind, placebo-controlled, dose-response study of metformin HCl extended-release tablet, taken once daily with the evening meal or twice daily with meals, was conducted in patients with type 2 diabetes who had failed to achieve glycemic control with diet and exercise. The results are shown in Table 11.

Table 11: 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 tablet 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 tablet, taken once daily with the evening meal, and metformin HCl immediate-release tablet, taken twice daily (with breakfast and evening meal), was conducted in patients with type 2 diabetes mellitus who had been treated with metformin HCl 500 mg immediate-release tablets twice daily for at least 8 weeks prior to study entry. The results are shown in Table 12.

Table 12: Mean Changes from Baseline* in HbA1c and Fasting Plasma Glucose at Week 24 Comparing Metformin HCl Extended-Release Tablet vs Metformin HCl Immediate-Release Tablet in Patients with Type 2 Diabetes Mellitus

	Metformin HCl Immediate-Release Tablet 500 mg Twice Daily	Metformin HCl Extended-Release Tablet	
		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	0.14[a]	0.27	0.13
(95% CI)	(–0.04, 0.31)	(0.11, 0.43)	(–0.02, 0.28)
FPG (mg/dL)	**(n = 69)**	**(n = 72)**	**(n = 70)**
Baseline	127.2	131.0	131.4
Change at FINAL VISIT	14.0	11.5	7.6
(95% CI)	(7.0, 21.0)	(4.4, 18.6)	(1.0, 14.2)

*[a] n = 68

Mean baseline body weight was 210lbs, 203 lbs and 193 lbs in the metformin HCl immediate-release tablet 500 mg twice daily, and metformin HCl extended-release tablet 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

RIOMET ER (metformin hydrochloride for extended-release oral suspension): 47.31 grams of metformin HCl as white to off-white pellets and white to off-white diluent for reconstitution in 473 mL bottle pack

The reconstituted suspension is 500 mg/5 mL appearing as white to off-white suspension containing white to off-white pellets. It is supplied as following:

Package Configuration	NDC	Description	Supplied as
16 oz (473 mL) Round Bottle Pack	10631-019-17	White to off-white pellets containing 37.85 g of metformin HCl in drug pellets bottle and white to off-white dispersion containing 9.46 g of metformin HCl in drug diluent bottle intended for reconstitution.	Carton contains 1 bottle of drug pellets, 1 bottle of diluent, and one dosing cup.

16.2 Storage

Store between 20°C to 25°C (68°F to 77°F) in the original bottle.

Excursions permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature.]

Do not repackage.

The shelf-life of the constituted oral suspension is 100 days. Any unused portion of the reconstituted suspension must be discarded after 100 days.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Administration:
Instruct patients or caregivers to use the supplied dosing cup to measure the prescribed amount of medication.

Lactic Acidosis:
Explain the risks of lactic acidosis, its symptoms, and conditions that predispose to its development. Advise patients to discontinue RIOMET ER 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 RIOMET ER. Instruct patients to inform their doctor that they are taking RIOMET ER 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 RIOMET ER 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 RIOMET ER *[see Warnings and Precautions (5.2)]*.

Females of Reproductive Age:
Inform females that treatment with RIOMET ER may result in ovulation in some premenopausal anovulatory women which may lead to unintended pregnancy *[see Use in Specific Populations (8.3)]*.

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