HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

----------RECENT MAJOR CHANGES----------

Boxed Warning	04/2017
Warnings and Precautions (5.1)	04/2017

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

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

Important limitations of use:
Not for treatment of type 1 diabetes or diabetic ketoacidosis. (1)

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

- Starting dose is 500 mg daily with evening meal (2.1)
- Individualize dose based on effectiveness and tolerability, while not exceeding the maximum recommended daily dose of 2000 mg. (2.1)
- 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.
  - Initiation is not recommended in patients with eGFR between 30-45 mL/minute/1.73 m^2.
  - Assess risk/benefit of continuing GLUMETZA if eGFR falls below 45 mL/minute/1.73 m^2.
  - Discontinue if eGFR falls below 30 mL/minute/1.73 m^2.
- GLUMETZA may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures. (2.4)
- Swallow whole. Never split, crush or chew. (2.5)

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

Extended-Release Tablets, 500 mg and 1000 mg (3)

----------CONTRAINDICATIONS----------

- Severe renal impairment: (eGFR below 30 mL/min/1.73 m^2) (4)
- Known hypersensitivity to metformin hydrochloride (4)
- Metabolic acidosis, including diabetic ketoacidosis (4)

----------WARNINGS AND PRECAUTIONS----------

- Lactic acidosis: See boxed warning. (5.1)
- Vitamin B_{12} deficiency: Metformin may lower vitamin B_{12} levels. Monitor hematologic parameters annually. (5.2)
- Macrovascular outcomes: No conclusive evidence of macrovascular risk reduction with GLUMETZA or any other antidiabetic drug. (5.4)

----------ADVERSE REACTIONS----------

The incidence and type of adverse reactions reported by > 5% of patients for the combined GLUMETZA group versus placebo group are hypoglycemia, diarrhea, and nausea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 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. (7.1)
- 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. (7.2)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pediatric Use: Safety and effectiveness in children younger than 18 years of age have not been established. (8.4)
- 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: 04/2017

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 in the full prescribing information *[see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7), and Use in Specific Populations (8.6, 8.7)]*.

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

1 INDICATIONS AND USAGE

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

Important Limitations of Use

GLUMETZA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The starting dose of GLUMETZA in patients who are not currently taking metformin is 500 mg orally, once daily with the evening meal. Increase the dose in 500 mg increments every 1-2 weeks if a higher dose of GLUMETZA is needed and there are no gastrointestinal adverse reactions. The dosage of GLUMETZA must be individualized on the basis of both effectiveness and tolerability, while not exceeding the maximum recommended daily dose of 2000 mg.

2.2 Recommendations for Use in Renal Impairment

Assess renal function prior to initiation of GLUMETZA and periodically thereafter.

GLUMETZA is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2.

Initiation of GLUMETZA in patients with an eGFR between 30–45 mL/minute/1.73 m^2 is not recommended.

In patients taking GLUMETZA whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit risk of continuing therapy.

Discontinue GLUMETZA 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 Switching from Immediate-Release Metformin to Glumetza

If switching from immediate-release metformin to GLUMETZA, initiate GLUMETZA once daily at the same total dose, up to 2000 mg once daily.

2.4 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue GLUMETZA 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 GLUMETZA if renal function is stable *[see Warnings and Precautions (5.1)]*.

2.5 Important Administration Instructions

Administer GLUMETZA orally, once daily with the evening meal. GLUMETZA tablets must be swallowed whole and never split, crushed or chewed. If a dose of GLUMETZA is missed, instruct patients not to take two doses the same day and to resume their usual dose of GLUMETZA with the next schedule dose *[see Patient Counseling Information (17)]*.

3 DOSAGE FORMS AND STRENGTHS

GLUMETZA (metformin hydrochloride extended-release tablets) 500 mg are available as blue, film-coated, oval-shaped tablets debossed with "GMZ" on one side and "500" on the other side.

GLUMETZA (metformin hydrochloride extended-release tablets) 1000 mg are available as white, film-coated, oval-shaped tablets with "M1000" on one side.

4 CONTRAINDICATIONS

GLUMETZA is contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2) *[see Warnings and Precautions (5.1)]*.
- Known hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.

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, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate/pyruvate ratio; metformin plasma levels 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 GLUMETZA. In GLUMETZA-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/minute 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 GLUMETZA 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) and Clinical Pharmacology (12.3)]:*

- Before initiating GLUMETZA, obtain an estimated glomerular filtration rate (eGFR).
- GLUMETZA is contraindicated in patients with an eGFR less than 30 mL/minute/1.73 m^2 *[see Contraindications (4)]*.
- Initiation of GLUMETZA is not recommended in patients with eGFR between 30–45 mL/minute/1.73 m^2.
- Obtain an eGFR at least annually in all patients taking GLUMETZA. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
- In patients taking GLUMETZA whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit and risk of continuing therapy.

Drug Interactions: The concomitant use of GLUMETZA 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)]*. Therefore, 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 *[see Use in Specific Populations (8.5)]*.

Radiological 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 GLUMETZA 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 GLUMETZA 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. GLUMETZA 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 also cause prerenal azotemia. When such events occur, discontinue GLUMETZA.

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism, and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving GLUMETZA.

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 GLUMETZA in patients with clinical or laboratory evidence of hepatic disease.

5.2 Vitamin B_{12} Levels

In controlled, 29-week clinical trials of immediate-release metformin, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of GLUMETZA or Vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on GLUMETZA, and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate Vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B_{12} levels. In these patients, routine serum Vitamin B_{12} measurements at two- to three-year intervals may be useful.

5.3 Hypoglycemia

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs.

5.4 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with GLUMETZA or any other oral antidiabetic drug.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Lactic acidosis *[see Warnings and Precautions (5.1)]*
- Vitamin B_{12} Levels *[see Warnings and Precautions (5.2)]*
- Hypoglycemia *[see Warnings and Precautions (5.3)]*

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 clinical practice. In clinical trials conducted in the U.S., over 1000 patients with type 2 diabetes mellitus have been treated with GLUMETZA 1500 to 2000 mg/day in active-controlled and placebo-controlled studies with the 500 mg dosage form.

In the 24-week monotherapy trial comparing GLUMETZA to immediate-release metformin, serious adverse reactions were reported in 3.6% (19/528) of the GLUMETZA-treated patients compared to 2.9% (5/174) of the patients treated with immediate-release metformin. In the add-on to sulfonylurea study, patients receiving background glyburide therapy were randomized to receive add-on treatment of either one of three different regimens of GLUMETZA or placebo. In total, 431 patients received GLUMETZA and glyburide and 144 patients received placebo and glyburide. A serious adverse reaction was reported in 2.1% (9/431) of the GLUMETZA and glyburide-treated patients compared to 1.4% (2/144) of the placebo and glyburide-treated patients. When the data from the monotherapy and add-on to sulfonylurea clinical trials were combined, the most frequently (incidence ≥0.5 %) reported serious adverse reactions classified by system organ class were gastrointestinal disorders (1.0% of GLUMETZA-treated patients compared to 0% of patients not treated with GLUMETZA) and cardiac disorders (0.4% of GLUMETZA-treated patients compared to 0.5% of patients not treated with GLUMETZA). Only 2 serious adverse reactions (unstable angina [n=2] and pancreatitis [n=2]) were reported in more than one GLUMETZA-treated patient.

Adverse reactions reported in greater than 5% of patients treated with GLUMETZA that were more common in the combined GLUMETZA and glyburide group than in the placebo and glyburide group are shown in Table 1.

In 0.7% of patients treated with GLUMETZA and glyburide, diarrhea was responsible for discontinuation of study medication compared to no patients in the placebo and glyburide group.

Table 1: Treatment-Emergent Adverse Reactions Reported by >5%* of Patients for the Combined GLUMETZA Groups Versus Placebo Group

Adverse Reaction	GLUMETZA + Glyburide (n=431)	Placebo + Glyburide (n=144)
Hypoglycemia	13.7%	4.9%
Diarrhea	12.5%	5.6%
Nausea	6.7%	4.2%

*ARs that were more common in the GLUMETZA-treated than in the placebo-treated patients.

Laboratory Tests

Vitamin B_{12} Concentrations

Metformin may lower serum vitamin B_{12} concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on GLUMETZA, and any apparent abnormalities should be appropriately investigated and managed. *[See Warnings and Precautions (5.2).]*

6.2 Postmarketing Experience

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

Cholestatic, hepatocellular, and mixed hepatocellular liver injury.

7 DRUG INTERACTIONS

7.1 Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with GLUMETZA may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.

7.2 Drugs that Reduce Metformin Clearance

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 such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis *[see Clinical Pharmacology (12.3)]*. Consider the benefits and risks of concomitant use.

7.3 Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving GLUMETZA.

7.4 Insulin Secretagogues or Insulin

Coadministration of GLUMETZA with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

7.5 Drugs Affecting Glycemic Control

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered to a patient receiving GLUMETZA, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving GLUMETZA, the patient should be observed closely for hypoglycemia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, which represent 3 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparison for rats and rabbits, respectively. However, because animal reproduction studies are not always predictive of human response, Metformin HCl should not be used during pregnancy unless clearly needed.

8.2 Labor and Delivery

The safety and effectiveness of GLUMETZA used during labor and delivery has not been evaluated in human studies.

8.3 Nursing Mothers

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Thus, the potential for hypoglycemia in nursing infants after Metformin HCl Oral Solution may exist.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. GLUMETZA is not recommended in pediatric patients below the age of 18 years.

8.5 Geriatric Use

Clinical studies of GLUMETZA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and 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) and Dosage and Administration (2.2).]*

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. GLUMETZA 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. GLUMETZA is not recommended in patients with hepatic impairment. *[See Warnings and Precautions (5.1).]*

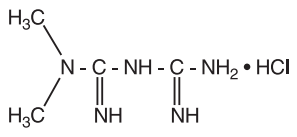
10 OVERDOSAGE

No cases of overdose were reported during GLUMETZA clinical trials. It would be expected that adverse reactions of a more intense character including epigastric discomfort, nausea, and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen. Should those symptoms persist, lactic acidosis should be excluded.

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. *[See Warnings and Precautions (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

GLUMETZA (metformin hydrochloride extended-release tablet) is an oral antihyperglycemic medication used in the management of type 2 diabetes. Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. The structural formula of metformin hydrochloride (metformin HCl) is as shown:



Metformin HCl is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63. Metformin HCl 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 hydrochloride is 6.68. GLUMETZA tablets are modified-release dosage forms that contain 500 mg or 1000 mg of metformin HCl. Each 500 mg tablet contains coloring, hypromellose, magnesium stearate, microcrystalline cellulose and polyethylene oxide. Each 1000 mg tablet contains colloidal silicon dioxide, polyvinyl alcohol, crospovidone, glyceryl behenate, polyacrylate dispersion, hypromellose, talc, polyethylene glycol, eudragit, titanium dioxide, simethicone emulsion, polysorbate and coloring. GLUMETZA 500 mg and 1000 mg tablets are formulated to gradually release metformin to the upper gastrointestinal (GI) tract.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Metformin is a biguanide that improves glucose tolerance in patients with type 2 diabetes, 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. Metformin does not produce hypoglycemia in patients with type 2 diabetes or in healthy subjects except in special circumstances, *[see Warnings and Precautions (5)]* and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may actually decrease.

EPO 9519001 Rev. 04/2017 LI001802

GLUMETZA®
(metformin hydrochloride extended-release tablets)
500 mg

PATIENT INFORMATION

GLUMETZA (Gloo-met-za) (metformin hydrochloride extended-release tablets)

Read the patient information that comes with GLUMETZA before you start taking this medicine and each time you refill your prescription. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment. Ask your doctor or pharmacist if you do not understand some of this information or if you want to know more about this medicine.

What is the most important information I should know about GLUMETZA?

Serious side effects can happen in people taking GLUMETZA, including:

lactic acidosis. Metformin, one of the medicines in GLUMETZA can cause a rare but serious condition called lactic acidosis (a buildup of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

Call your doctor right away if you have any of the following symptoms, which could be signs of lactic acidosis:

- you feel cold in your hands or feet
- you feel dizzy or lightheaded
- you have a slow or irregular heartbeat
- you feel very weak or tired
- you have unusual (not normal) muscle pain
- you have trouble breathing
- you feel sleepy or drowsy
- you have stomach pains, nausea or vomiting

Most people who have had lactic acidosis with metformin have other things that, combined with the metformin, led to the lactic acidosis. Tell your doctor if you have any of the following, because you have a higher chance for getting lactic acidosis with GLUMETZA if you:

- have severe kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye
- have liver problems
- drink alcohol very often, or drink a lot of alcohol in 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 surgery
- have a heart attack, severe infection, or stroke

The best way to keep from having a problem with lactic acidosis from metformin is to tell your doctor if you have any of the problems in the list above. Your doctor may decide to stop your GLUMETZA for a while if you have any of these things.

GLUMETZA can have other serious side effects. See "What are the possible side effects of GLUMETZA?"

What is GLUMETZA?

- GLUMETZA is a prescription medicine that contains metformin hydrochloride used with diet and exercise to help control high blood sugar in adults with type 2 diabetes.
- GLUMETZA is not for people with type 1 diabetes.
- GLUMETZA is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).

It is not known if GLUMETZA is safe and effective in children younger than 18 years old.

Who should not take GLUMETZA?

Do not take GLUMETZA if you:

- have severe kidney problems
- are allergic to the metformin hydrochloride in GLUMETZA or any of the ingredients in GLUMETZA. See the end of this leaflet for a list of ingredients in GLUMETZA.
- have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in your blood or urine)

What should I tell my doctor before taking GLUMETZA?

Before you take GLUMETZA, tell your doctor if you:

- have type 1 diabetes. GLUMETZA should not be used to treat people with type 1 diabetes.
- have a history or risk for diabetic ketoacidosis (high levels of certain acids, known as ketones, in the blood or urine). GLUMETZA should not be used for the treatment of diabetic ketoacidosis.
- have severe kidney problems
- are going to get an injection of dye or contrast agents for an x-ray procedure, GLUMETZA may need to be stopped for a short time. Talk to your doctor about when you should stop GLUMETZA and when you should start GLUMETZA again. See **"What is the most important information I should know about GLUMETZA?"**
- have liver problems
- have heart problems, including congestive heart failure
- drink alcohol very often, or drink a lot of alcohol in short-term (binge) drinking
- are taking insulin
- have any other medical conditions
- are pregnant or planning to become pregnant. It is not known if GLUMETZA can harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if GLUMETZA passes into your breast milk. Talk with your doctor about the best way to feed your baby while you take GLUMETZA.

Tell your doctor 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 doctor and pharmacist. Talk to your doctor before you start any new medicine.

GLUMETZA may affect the way other medicines work, and other medicines may affect how GLUMETZA works.

How should I take GLUMETZA?

- Take GLUMETZA exactly as your doctor tells you.
- GLUMETZA should be taken 1 time per day with your evening meal.
- Swallow GLUMETZA tablets whole. Do not crush, cut, dissolve, or chew GLUMETZA.
- Tell your doctor if you cannot swallow tablets whole. Your doctor may prescribe a different medicine for you.

- You may sometimes pass a soft mass in your stools (bowel movement) that looks like GLUMETZA tablets. It is normal to see this in your stool.
- When your body is under some type 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 doctor right away if you have any of these problems.
- Your doctor should do blood tests to check how well your kidneys and liver are working before and during your treatment with GLUMETZA.
- Your healthcare provider will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1c.
- Follow your doctor's instructions for treating blood sugar that is too low (hypoglycemia). Talk to your doctor if low blood sugar is a problem for you. See **"What are the possible side effects of GLUMETZA?"**
- Check your blood sugar regularly and as your doctor tells you to.
- Stay on your prescribed diet and exercise program and test your blood sugar regularly while taking GLUMETZA.
- If you miss a dose of GLUMETZA, resume dosing according to schedule.
- If you take too much GLUMETZA, call your doctor, or go to the nearest hospital emergency room right away.

What are the possible side effects of GLUMETZA?

GLUMETZA can cause serious side effects, including:

- See **"What are the most important information I should know about GLUMETZA?"**
- **Low blood sugar (hypoglycemia).** If you take GLUMETZA with another medicine that can cause low blood sugar, such as sulfonylureas or insulin, you have a higher risk of having low blood sugar. Tell your doctor if you take other diabetes medicines. If you have symptoms of low blood sugar, you should check your blood sugar and treat if low, then call your doctor. Symptoms of low blood sugar include:
  - **shaking**
  - **sweating**
  - **rapid heartbeat**
  - **change in vision**
  - **hunger**
  - **headache**
  - **change in mood**

Common side effects of GLUMETZA include:

- hypoglycemia
- diarrhea
- nausea
- upset stomach or stomach pain

Taking GLUMETZA with your evening meal can help lessen the common stomach side effects of metformin that usually happen at the beginning of treatment. If you have unexplained stomach problems, tell your doctor. Stomach problems that start later, during treatment may be a sign of something more serious.

Tell your doctor if these symptoms return, as they may be symptoms of lactic acidosis.

Tell your doctor if you have side effects that bother you or that do not go away.

These are not all of the possible side effects of GLUMETZA. For more information, ask your doctor or pharmacist.

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 GLUMETZA?

- Store GLUMETZA at 68° to 77°F (20° to 25°C).

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

General information about the safe and effective use of GLUMETZA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use GLUMETZA for a condition for which it was not prescribed.

Do not give GLUMETZA to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information summarizes the most important information about GLUMETZA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about GLUMETZA that is written for health professionals.

For more information, go to www.GlumetzaXR.com or call 1-800-508-0024.

What are the ingredients in GLUMETZA?

Active Ingredient: metformin hydrochloride

Inactive Ingredient: 500 mg tablet: coloring, hypromellose, magnesium stearate, microcrystalline cellulose and polyethylene oxide.

1000 mg tablet: colloidal silicon dioxide, polyvinyl alcohol, crospovidone, glyceryl behenate, polyacrylate dispersion, hypromellose, talc, polyethylene glycol, eudragit, titanium dioxide, simethicone emulsion, polysorbate and coloring.

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems.

The main goal of treating diabetes is to lower your blood sugar to a normal level.

High blood sugar can be lowered by diet and exercise, and by certain medicines when necessary.

Talk to your doctor about how to prevent, recognize, and take care of low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and problems you have because of your diabetes.

Manufactured for:

Salix Pharmaceuticals, a division of Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

www.GlumetzaXR.com

For prescription only

U.S. Patent Numbers: 6,488,962; 7,780,987; and 8,323,692

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12.3 Pharmacokinetics

Absorption

Following a single oral dose of 1000 mg (2x500 mg tablets) GLUMETZA after a meal, the time to reach maximum plasma metformin concentration (T_{max}) is achieved at approximately 7-8 hours. In both single- and multiple-dose studies in healthy subjects, once daily 1000 mg (2x500 mg tablets) dosing provides equivalent systemic exposure, as measured by area-under-the-curve (AUC), and up to 35% higher C_{max}, of metformin relative to the immediate release given as 500 mg twice daily. GLUMETZA tablets must be administered immediately after a meal to maximize therapeutic benefit.

Single oral doses of GLUMETZA from 500 mg to 2500 mg resulted in less than proportional increase in both AUC and C_{max}. Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from GLUMETZA tablets by about 38% and 73%, respectively, relative to fasting. Both meals prolonged metformin T_{max} by approximately 3 hours but C_{max} was not affected.

In a two-way, single-dose crossover study in healthy volunteers, the 1000 mg tablet was found to be bioequivalent to two 500 mg tablets under fed conditions based on equivalent C_{max} and AUCs for the two formulations.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg immediate-release metformin hydrochloride averaged 654±358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 mcg/mL. During controlled clinical trials, which served as the basis of approval for metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism

Intravenous single-dose studies in healthy 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. Metabolism studies with extended-release metformin tablets have not been conducted.

Excretion

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special Populations

Renal Impairment: Following a single-dose administration of GLUMETZA 500 mg in subjects with mild and moderate renal impairment, the oral and renal clearance of metformin were decreased by 33% and 50% and 16% and 53%, respectively. Metformin peak and systemic exposure was 27% and 61% greater, respectively in subjects with mild renal impairment and 74% and 2.36-fold greater in subjects with moderate renal impairment as compared to healthy subjects. *[See Dosage and Administration (2.2), Contraindications (4), and Warnings and Precautions (5.1).]*

Hepatic Impairment: No pharmacokinetic studies of GLUMETZA have been conducted in subjects with hepatic impairment. *[See Warnings and Precautions (5.1).]*

Geriatrics: Limited data from controlled pharmacokinetic studies of metformin hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin is decreased by 35%, the half-life is prolonged by 64% and C_{max} is increased by 76%, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function. *[See Warnings and Precautions (5.1) and Dosage and Administration (2).]*

Gender: In the pharmacokinetic studies in healthy volunteers, there were no important differences between male and female subjects with respect to metformin AUC and $t^{1/2}$. However, C_{max} for metformin was 40% higher in female subjects as compared to males. The gender differences for C_{max} are unlikely to be clinically important. Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin hydrochloride tablets was comparable in males and females.

Race: There were no definitive conclusions on the differences between the races with respect to the pharmacokinetics of metformin because of the imbalance in the respective sizes of the racial groups. However, the data suggest a trend towards higher metformin C_{max} and AUC values for metformin are obtained in Asian subjects when compared to Caucasian, Hispanic and Black subjects. The differences between the Asian and Caucasian groups are unlikely to be clinically important. In controlled clinical studies of metformin hydrochloride in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51) and Hispanics (n=24).

Pediatrics: No pharmacokinetic data from studies of GLUMETZA in pediatric subjects are available.

Drug Interactions: Specific pharmacokinetic drug interaction studies with GLUMETZA have not been performed except for one with glyburide. However, such studies have been performed on metformin.

Table 2: Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug[1]	Dose of Metformin[1]	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.00	
			AUC[2]	C_{max}
No dosing adjustments required for the following:				
Glyburide	5 mg	500 mg[4]	0.98[3]	0.99[3]
Furosemide	40 mg	850 mg	1.09[3]	1.22[3]
Nifedipine	10 mg	850 mg	1.16	1.21
Propranolol	40 mg	850 mg	0.90	0.94
Ibuprofen	400 mg	850 mg	1.05[3]	1.07[3]
Drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin: *[see Warnings and Precautions (5) and Drug Interactions (7)].*				
Cimetidine	400 mg	850 mg	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis: *[see Warnings and Precautions (5) and Drug Interactions (7)].*				
Topiramate	100 mg[5]	500 mg[5]	1.25[5]	1.17

[1] All metformin and coadministered drugs were given as single doses.
[2] AUC=$AUC_{0-\infty}$
[3] Ratio of arithmetic means
[4] GLUMETZA (metformin hydrochloride extended-release tablets) 500 mg
[5] At steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC=AUC_{0-12h}

Table 3: Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug[1]	Dose of Metformin[1]	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.00	
			AUC[2]	C_{max}
No dosing adjustments required for the following:				
Glyburide	5 mg	500 mg[4]	0.78[3]	0.63[3]
Furosemide	40 mg	850 mg	0.87[3]	0.69[3]
Nifedipine	10 mg	850 mg	1.10[4]	1.08
Propranolol	40 mg	850 mg	1.01[4]	0.94
Ibuprofen	400 mg	850 mg	0.97[5]	1.01[5]
Cimetidine	400 mg	850 mg	0.95[4]	1.01

[1] All metformin and coadministered drugs were given as single doses.
[2] AUC=$AUC_{0-\infty}$
[3] Ratio of arithmetic means, p-value of difference <0.05
[4] $AUC_{0-24\ hr}$ reported
[5] Ratio of arithmetic means

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies have been performed in Sprague Dawley rats at doses of 150, 300, and 450 mg/kg/day in males and 150, 450, 900, and 1200 mg/kg/day in females. These doses are approximately 2, 4, and 8 times in males, and 3, 7, 12, and 16 times in females of the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female rats. A carcinogenicity study was also performed in Tg.AC transgenic mice at doses up to 2000 mg applied dermally. No evidence of carcinogenicity was observed in male or female mice.

Genotoxicity assessments in the Ames test, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes) and in vivo mouse micronucleus tests were negative. Fertility of male or female rats was not affected by metformin when administered at doses up to 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparisons.

14 CLINICAL STUDIES

GLUMETZA has been studied as monotherapy and in combination with a sulfonylurea and insulin. Other formulations of metformin have been studied with other classes of antihyperglycemic agents, either as immediate- or as extended-release tablets.

Double-Blind, Randomized, Parallel Group Clinical Trial to Compare the Efficacy, Safety, and Tolerability of Metformin ER (M-ER) Tablets and Metformin Immediate-Release (M-IR) Tablets in the Treatment of Type 2 Diabetes Mellitus

In a multicenter, randomized, double-blind, active-controlled, dose-ranging, parallel group trial, GLUMETZA 1500 mg once daily, GLUMETZA 1500 per day in divided doses (500 mg in the morning and 1000 mg in the evening), and GLUMETZA 2000 mg once daily were compared to immediate-release metformin 1500 mg per day in divided doses (500 mg in the morning and 1000 mg in the evening). This trial enrolled patients (n=338) who were newly diagnosed with diabetes, patients treated only with diet and exercise, patients treated with a single antidiabetic medication (sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, or meglitinides), and patients (n=368) receiving metformin up to 1500 mg/day plus a sulfonylurea at a dose equal to or less than one-half the maximum dose. Patients who were enrolled on monotherapy or combination antidiabetic therapy underwent a 6-week washout. Patients randomized to GLUMETZA began titration from 1000 mg/day up to their assigned treatment dose over 3 weeks. Patients randomized to immediate-release metformin initiated 500 mg twice daily for 1 week followed by 500 mg with breakfast and 1000 mg with dinner for the second week. The 3-week treatment period was followed by an additional 21-week period at the randomized dose. For HbA_{1c} and fasting plasma glucose, each of the GLUMETZA regimens was at least as effective as immediate-release metformin. Additionally, once daily dosing of GLUMETZA was as effective as twice daily dosing of the immediate-release metformin formulation.

Table 4: Mean±SE Changes from Baseline to Final Visit in HbA_{1c}, Fasting Plasma Glucose and Body Weight for the GLUMETZA and Metformin Immediate-Release Treatment Groups (First 24-Week Study)

Parameter	GLUMETZA			Metformin Immediate-Release 1500 mg in Divided Doses (n=174)
	1500 mg Once Daily (n=178)	1500 mg in Divided Doses (n=182)	2000 mg Once Daily (n=172)	
HbA_{1c} (%)				
N	169	175	159	170
Baseline	8.2±0.3	8.5±0.2	8.3±0.2	8.7±0.3
Mean Change±SE at Final Visit	-0.7±0.1	-0.7±0.1	-1.1±0.1	-0.7±0.1
Mean Difference±SE from Metformin IR	0±0.1	0±0.1	-0.4±0.1	N/A
98.4% CI for Difference	(-0.3, 0.3)	(-0.3, 0.3)	(-0.7, -0.1)	
Fasting Plasma Glucose (mg/dL)				
N	175	179	170	172
Baseline	190±10	192.3±10	184±10	197±11
Mean Change±SE at Final Visit	-39±4	-32±4	-42±5	-32±5
Mean Difference±SE from Metformin IR	-6±4	0±4	-10±4	N/A
95% CI for Difference	(-15, 2)	(-8, 9)	(-19, -1)	
Body Weight (kg)				
N	176	180	171	173
Baseline	88.2±3.7	90.5±3.7	87.7±3.7	88.7±3.9
Mean Change±SE at Final Visit	-0.9±0.4	-0.7±0.4	-1.1±0.4	-0.9±0.4
Mean Difference±SE from Metformin IR	-0.1±0.4	0.2±0.4	-0.3±0.4	N/A
95% CI for Difference	(-0.9, 0.7)	(-0.6, 0.9)	(-1.0, 0.5)	

A Double-Blind, Randomized, Parallel-Group Study to Compare the Safety, Efficacy, and Tolerability of Metformin Extended-Release (M-ER) Tablets in Combination with a Sulfonylurea (SU) and SU Alone in the Management of Patients with Type 2 Diabetes Mellitus

In a double-blind, randomized, placebo-controlled (glyburide add-on) multicenter trial, patients with type 2 diabetes mellitus who were newly diagnosed or treated with diet and exercise (n=144), or who were receiving monotherapy with metformin, sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, or meglitinides, or treated with combination therapy consisting of metformin/glyburide at doses up to 1000 mg metformin + 10 mg glyburide per day (or equivalent doses of glipizide or glimepiride up to half the maximum therapeutic dose) (n=431) were enrolled. All patients were stabilized on glyburide for a 6-week run-in period, and then randomized to 1 of 4 treatments: placebo + glyburide (glyburide alone); GLUMETZA 1500 mg once a day + glyburide, GLUMETZA 2000 mg once a day + glyburide, or GLUMETZA 1000 mg twice a day + glyburide. A 3-week GLUMETZA titration phase was followed by a 21-week maintenance treatment phase. Use of insulin and oral hypoglycemic agents other than the study drugs were prohibited. The difference in the change from Baseline in HbA_{1c} levels between the combined GLUMETZA + glyburide groups and the glyburide only group was statistically significant at week 24 ($p<0.001$). The changes in glycemic control across the three GLUMETZA + glyburide groups were comparable.

Table 5: Mean±SE Changes from Baseline to Final Visit in HbA_{1c}, Fasting Plasma Glucose and Body Weight for the GLUMETZA/Glyburide Groups and Placebo/Glyburide Treatment Group (Second 24-Week Study)

Parameter	GLUMETZA + Glyburide*			Placebo/ Glyburide* (n=144)
	1500 mg QD (n=144)	1000 mg BID (n=141)	2000 mg QD (n=146)	
HbA_{1c} (%)				
N	136	136	144	141
Baseline	7.9±0.1	7.8±0.1	7.7±0.1	8.1±0.1
Mean Change±SE at Final Visit	-0.7±0.1	-0.8±0.1	-0.7±0.1	-0.1±0.1
Mean Difference±SE from Glyburide Alone	-0.8±0.1	-0.9±0.1	-0.8±0.1	N/A
95% CI for Difference	(-1.0, -0.6)	(-1.1, -0.7)	(-1.0, -0.6)	
p-Value for Pairwise Comparison	<0.001	<0.001	<0.001	
Fasting Plasma Glucose (mg/dL)				
N	143	141	145	144
Baseline	163±5	163±5	159±5	164±5
Mean Change±SE at Final Visit	-14±4	-16±4	-9±4	16±4
Mean Difference±SE from Glyburide Alone	-29.2±4.9	-31.2±40.9	-24.9±4.9	N/A
95% CI for Difference	(-39, -20)	(-41, -22)	(-35, -15)	
p-Value for Pairwise Comparison	<0.001	<0.001	<0.001	
Body Weight (kg)				
N	143	141	146	144
Baseline	89.4±11.2	103.7±11.2	102.9±11.2	95.6±8.0
Mean Change±SE at Final Visit	0.3±1.1	0.1±1.1	0±1.1	0.7±1.0
Mean Difference±SE from Glyburide Alone	-0.4±0.5	-0.6±0.5	-0.7±0.5	N/A
95% CI for Difference	(-1.5, 0.6)	(-1.7, 0.4)	(-1.8, 0.3)	
p-Value for Pairwise Comparison	0.410	0.230	0.156	

*Glyburide was administered as 10 mg at breakfast and 5 mg at dinner.

A 24-week, double-blind, placebo-controlled trial of immediate-release metformin plus insulin versus insulin plus placebo was conducted in patients with type 2 diabetes who failed to achieve adequate glycemic control on insulin alone. Patients randomized to receive metformin plus insulin achieved a mean reduction in HbA_{1c} of 2.10%, compared to a 1.56% reduction in HbA_{1c} achieved by insulin plus placebo. The improvement in glycemic control was achieved at the final study visit with 16% less insulin, 93.0 U/day vs. 110.6 U/day, metformin plus insulin versus insulin plus placebo, respectively, p=0.04.

A second double-blind, placebo-controlled study (n=51), with 16 weeks of randomized treatment, demonstrated that in patients with type 2 diabetes controlled on insulin for 8 weeks with an average HbA_{1c} of 7.46±0.97%, the addition of metformin maintained similar glycemic control (HbA_{1c} 7.15±0.61 versus 6.97±0.62 for metformin plus insulin and placebo plus insulin, respectively) with 19% less insulin versus baseline (reduction of 23.68±30.22 versus an increase of 0.43±25.20 units for metformin plus insulin and placebo plus insulin, p<0.01). In addition, this study demonstrated that the combination of metformin plus insulin resulted in reduction in body weight of 3.11±4.30 lbs, compared to an increase of 1.30±6.08 lbs for placebo plus insulin, p=0.01.

16 HOW SUPPLIED/STORAGE AND HANDLING

GLUMETZA tablets 500 mg are available as blue, film-coated, oval-shaped tablets debossed with "GMZ" on one side and "500" on the other side.

They are supplied as follows:

NDC Code	Strength	Package
68012-002-13	500 mg	Bottles of 100

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

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

Information for Patients

- Patients should be informed of the potential risks and benefits of GLUMETZA and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, and hemoglobin A1c. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.
- The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the GLUMETZA sections, should be explained to patients. Patients should be advised to discontinue GLUMETZA immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of GLUMETZA, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to recur. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.
- Patients should be advised to notify their health practitioner or call the Poison Control Center immediately in case of GLUMETZA overdose.
- Patients should be informed about the importance of regular testing of renal function and hematological parameters when receiving treatment with GLUMETZA.
- Instruct patients to inform their doctor that they are taking GLUMETZA prior to any surgical or radiological procedure, as temporary discontinuation of GLUMETZA may be required until renal function has been confirmed to be normal *[see Warnings and Precautions (5.1)]*.
- Patients should be counseled against excessive alcohol intake, either acute or chronic, while receiving GLUMETZA.
- GLUMETZA (metformin hydrochloride extended-release tablets) alone does not usually cause hypoglycemia, although it may occur when GLUMETZA is used in conjunction with insulin secretagogues, such as sulfonylureas and insulin.
- Patients should be informed that GLUMETZA must be swallowed whole and not crushed or chewed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that may resemble the original tablet.

Salix

Manufactured for:

Salix Pharmaceuticals, a division of Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

U.S. Patent Numbers: 6,488,962; 7,780,987; and 8,323,692

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