

## 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), 500 mg and 1000 mg

Initial U.S. Approval: 1995

#### WARNING: LACTIC ACIDOSIS

See full prescribing information for complete boxed warning

- Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. (5.1)
- Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. (5.1)
- If acidosis is suspected, discontinue GLUMETZA and hospitalize the patient immediately. (5.1)

#### RECENT MAJOR CHANGES

Dosing and Administration: Inclusion of the 1000 mg tablet (3) 12/2007

#### 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. (1.1)

#### DOSAGE AND ADMINISTRATION

- Administer once daily with the evening meal. (2)
- Individualize the dose based on effectiveness and tolerability, while not exceeding the maximum recommended daily dose of 2000 mg. (2)
- If naïve to metformin treatment, initiate with 500 mg daily. (2)
- Swallow whole. Never split, crush or chew. (2)

#### DOSAGE FORMS AND STRENGTHS

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

#### CONTRAINDICATIONS

- Renal impairment (4)

- Metabolic acidosis, including diabetic ketoacidosis (4)
- Hypersensitivity to metformin hydrochloride (4)

#### WARNINGS AND PRECAUTIONS

- Lactic acidosis: Warn against excessive alcohol intake. GLUMETZA is not recommended in hepatic impairment and is contraindicated in renal impairment. Ensure normal renal function before initiating and at least annually thereafter. (5.1)
- Temporarily discontinue in patients undergoing radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures necessitating restricted intake of food and fluids. (5.2)
- Vitamin B12 deficiency: Metformin may lower vitamin B12 levels. Monitor hematologic parameters annually. (5.6)
- Macrovascular outcomes: No conclusive evidence of macrovascular risk reduction with GLUMETZA or any other antidiabetic drug. (5.8)

#### 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 Depomed, Inc. at 1-866-458-6389 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- Cationic drugs: May reduce metformin elimination. Use with caution in patients who are taking cationic medications eliminated by renal tubular secretion. (7.1)

#### 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: Caution should be used when prescribing GLUMETZA to elderly patients because reduced renal functions are associated with increasing age. (8.5)

See 17 for PATIENT COUNSELING INFORMATION, and FDA approved Patient Information

Revised: 04/2011

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1 **FULL PRESCRIBING INFORMATION**

**WARNING: Lactic Acidosis**

**Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure.**

**The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.**

**Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.**

**If acidosis is suspected, GLUMETZA (metformin hydrochloride extended-release tablets), should be discontinued and the patient hospitalized immediately. (See WARNINGS and PRECAUTIONS (5.1))**

2 **1. INDICATIONS AND USAGE**

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

5 *Important Limitations of Use*

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

8 **2. DOSAGE AND ADMINISTRATION**

9 **2.1 Recommended Dosing**

10 GLUMETZA should be taken once daily with the evening meal. The dosage of GLUMETZA must  
11 be individualized on the basis of both effectiveness and tolerability, while not exceeding the  
12 maximum recommended daily dose of 2000 mg. The starting dose of GLUMETZA in patients who  
13 are not currently taking metformin is 500 mg once daily, with the evening meal. The dose can be  
14 uptitrated in 500 mg increments no sooner than every 1-2 weeks if a higher dose of GLUMETZA is  
15 needed and there are no gastrointestinal adverse reactions.

16 If GLUMETZA is considered appropriate for a patient already receiving immediate-release  
17 metformin, the patient can be switched to GLUMETZA once daily at the same total daily dose, up to  
18 2000 mg once daily.

19 GLUMETZA tablets must be swallowed whole and never split, crushed or chewed. Occasionally, the  
20 inactive ingredients of GLUMETZA 500 mg may be eliminated in the feces as a soft, hydrated mass,  
21 while the 1000 mg may leave an insoluble shell that may resemble the original tablet. If a dose of  
22 GLUMETZA is missed, patients should be cautioned against taking two doses of 2000 mg the same  
23 day. Resume dosing as according to prescribing recommendations. (See **PATIENT COUNSELING**  
24 **INFORMATION (17)**)

25 *Patients treated with an insulin secretagogue or insulin*

26 Co-administration of GLUMETZA with an insulin secretagogue (e.g., sulfonylurea) or insulin may  
27 require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

### 28 3. DOSAGE FORMS AND STRENGTHS

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

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

### 33 4. CONTRAINDICATIONS

34 GLUMETZA is contraindicated in patients with:

- 35 • Renal impairment (e.g., serum creatinine levels  $\geq 1.5$  mg/dL for men,  $\geq 1.4$  mg/dL for women  
36 or abnormal creatinine clearance), which may also result from conditions such as  
37 cardiovascular collapse (shock), acute myocardial infarction, and septicemia. (See  
38 **WARNINGS AND PRECAUTIONS (5)**)
- 39 • Known hypersensitivity to metformin hydrochloride.
- 40 • Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis  
41 should be treated with insulin.

### 42 5. WARNINGS AND PRECAUTIONS

#### 43 5.1 Lactic Acidosis

44 **Lactic acidosis is a serious, metabolic complication that can occur due to metformin**  
45 **accumulation during treatment with GLUMETZA and is fatal in approximately 50% of cases.**  
46 **Lactic acidosis may also occur in association with a number of pathophysiologic conditions,**  
47 **including diabetes mellitus, and whenever there is significant tissue hypoperfusion and**  
48 **hypoxemia. Lactic acidosis is characterized by elevated blood lactate concentrations ( $>5$**   
49 **mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an**  
50 **increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis,**  
51 **metformin plasma levels  $>5$   $\mu\text{g/mL}$  are generally found. The reported incidence of lactic**  
52 **acidosis in patients receiving metformin hydrochloride is approximately 0.03 cases/1000 patient-**  
53 **years, with approximately 0.015 fatal cases/1000 patient-years. In more than 20,000 patient-**  
54 **years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported**  
55 **cases have occurred primarily in diabetic patients with significant renal impairment, including**  
56 **both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple**  
57 **concomitant medical/surgical problems and multiple concomitant medications. Patients with**  
58 **congestive heart failure requiring pharmacologic management, particularly when accompanied**  
59 **by hypoperfusion and hypoxemia due to unstable or acute failure, are at increased risk of lactic**  
60 **acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the**  
61 **patient’s age. The risk of lactic acidosis may, therefore, be significantly decreased by regular**  
62 **monitoring of renal function in patients taking GLUMETZA. In particular, treatment of the**  
63 **elderly should be accompanied by careful monitoring of renal function. GLUMETZA treatment**  
64 **should not be initiated in any patient unless measurement of creatinine clearance demonstrates**  
65 **that renal function is not reduced. In addition, GLUMETZA should be promptly withheld in**  
66 **the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because**

67 **impaired hepatic function may significantly limit the ability to clear lactate, GLUMETZA**  
68 **should generally be avoided in patients with clinical or laboratory evidence of hepatic**  
69 **impairment. Patients should be cautioned against excessive alcohol intake when taking**  
70 **GLUMETZA, because alcohol potentiates the effects of metformin on lactate metabolism. In**  
71 **addition, GLUMETZA should be temporarily discontinued prior to any intravascular**  
72 **radiocontrast study and for any surgical procedure necessitating restricted intake of food or**  
73 **fluids. Use of topiramate, a carbonic anhydrase inhibitor, in epilepsy and migraine prophylaxis**  
74 **may frequently cause dose-dependent metabolic acidosis (In controlled trials, 32% and 67% for**  
75 **adjunctive treatment in adults and pediatric patents, respectively, and 15 to 25% for**  
76 **monotherapy of epilepsy, with decrease in serum bicarbonate to less than 20 mEq/L; 3% and**  
77 **11% for adjunctive treatment in adults and pediatric patents, respectively, and 1 to 7% for**  
78 **monotherapy of epilepsy, with decrease in serum bicarbonate to less than 17 mEq/L) and may**  
79 **exacerbate the risk of metformin-induced lactic acidosis. (See 7.1 Drug Interactions and 12.5**  
80 **Clinical Pharmacology) The onset of lactic acidosis often is subtle, and accompanied only by**  
81 **nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence,**  
82 **and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and**  
83 **resistant bradyarrhythmias with more marked acidosis.**

84 **Patients should be educated to promptly report these symptoms should they occur. If present,**  
85 **GLUMETZA should be withdrawn until lactic acidosis is ruled out. Serum electrolytes, ketones,**  
86 **blood glucose, blood pH, lactate levels, and blood metformin levels may be useful. Once a**  
87 **patient is stabilized on any dose level of GLUMETZA, gastrointestinal symptoms, which are**  
88 **common during initiation of therapy, are unlikely to recur. Later occurrence of gastrointestinal**  
89 **symptoms could be due to lactic acidosis or other serious disease. Levels of fasting venous**  
90 **plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking**  
91 **GLUMETZA do not necessarily indicate impending lactic acidosis and may be explainable by**  
92 **other mechanisms, such as poorly-controlled diabetes or obesity, vigorous physical activity, or**  
93 **technical problems in sample handling. Lactic acidosis should be suspected in any diabetic**  
94 **patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).**  
95 **Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient**  
96 **with lactic acidosis who is taking GLUMETZA, the drug should be discontinued immediately**  
97 **and general supportive measures promptly instituted. Because metformin hydrochloride is**  
98 **dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt**  
99 **hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.**  
100 **Such management often results in prompt reversal of symptoms and recovery. (See**  
101 **CONTRAINDICATIONS (4))**

## 102 **5.2 Monitoring of Renal Function**

103 Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic  
104 acidosis increases with the degree of renal impairment. Therefore GLUMETZA is contraindicated in  
105 patients with renal impairment.

106 Before initiation of GLUMETZA and at least annually thereafter, renal function should be assessed  
107 and verified as normal. In patients in whom development of renal dysfunction is anticipated (e.g.,  
108 elderly), renal function should be assessed more frequently and GLUMETZA discontinued if  
109 evidence of renal impairment is present. Metformin treatment should not be initiated in patients  $\geq 80$   
110 years of age unless measurement of creatinine clearance demonstrates that renal function is not  
111 reduced, as these patients are more susceptible to developing lactic acidosis.

112 *Use of concomitant medications that may affect renal function or metformin disposition* —  
113 Concomitant medication(s) that may affect renal function or result in significant hemodynamic  
114 change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated  
115 by renal tubular secretion (see **DRUG INTERACTIONS (7)**), should be used with caution.

116 Radiological studies and surgical procedures:

117 Radiologic studies involving the use of intravascular iodinated contrast materials (for example,  
118 intravenous urogram, intravenous cholangiography, angiography, and computed tomography) can  
119 lead to acute alteration of renal function and have been associated with lactic acidosis in patients  
120 receiving metformin. Therefore, in patients in whom any such study is planned, GLUMETZA should  
121 be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours  
122 subsequent to the procedure and reinstated only after renal function has been re-evaluated and found  
123 to be normal.

124 GLUMETZA therapy should be temporarily suspended for any surgical procedure (except minor  
125 procedures not associated with restricted intake of food and fluids) and should not be restarted until  
126 the patient's oral intake has resumed and renal function has been evaluated as normal.

### 127 **5.3 Hypoxic States**

128 Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial  
129 infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis  
130 and may also cause prerenal azotemia. When such events occur in patients on GLUMETZA therapy,  
131 the drug should be promptly discontinued.

### 132 **5.4 Alcohol Intake**

133 Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore,  
134 should be warned against excessive alcohol intake while receiving GLUMETZA.

### 135 **5.5 Impaired Hepatic Function**

136 Because impaired hepatic function has been associated with some cases of lactic acidosis  
137 GLUMETZA should generally be avoided in patients with clinical or laboratory evidence of hepatic  
138 disease.

### 139 **5.6 Vitamin B12 Levels**

140 In controlled, 29-week clinical trials of immediate release metformin, a decrease to subnormal levels  
141 of previously normal serum Vitamin B12 levels, without clinical manifestations, was observed in  
142 approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from  
143 the B12-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be  
144 rapidly reversible with discontinuation of GLUMETZA or Vitamin B12 supplementation.  
145 Measurement of hematologic parameters on an annual basis is advised in patients on GLUMETZA  
146 and any apparent abnormalities should be appropriately investigated and managed. Certain individuals  
147 (those with inadequate Vitamin B12 or calcium intake or absorption) appear to be predisposed to  
148 developing subnormal Vitamin B12 levels. In these patients, routine serum Vitamin B12  
149 measurements at two- to three-year intervals may be useful.

### 150 **5.7 Hypoglycemia**

151 Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use,  
152 but could occur when caloric intake is deficient, when strenuous exercise is not compensated by

153 caloric supplementation, or during concomitant use with other glucose-lowering agents (such as  
154 sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with  
155 adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic  
156 effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-  
157 adrenergic blocking drugs.

## 158 **5.8 Macrovascular Outcomes**

159 There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction  
160 with GLUMETZA or any other oral anti-diabetic drug.

## 161 **6. ADVERSE REACTIONS**

### 162 **6.1 Clinical Trials Experience**

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

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

169 In the 24-week monotherapy trial comparing GLUMETZA to immediate-release metformin, serious  
170 adverse reactions were reported in 3.6% (19/528) of the GLUMETZA-treated patients compared to  
171 2.9% (5/174) of the patients treated with immediate-release metformin. In the add-on to sulfonylurea  
172 study, patients receiving background glyburide therapy were randomized to receive add-on treatment  
173 of either one of three different regimens of GLUMETZA or placebo. In total, 431 patients received  
174 GLUMETZA and glyburide and 144 patients received placebo and glyburide. A serious adverse  
175 reaction was reported in 2.1% (9/431) of the GLUMETZA and glyburide-treated patients compared to  
176 1.4% (2/144) of the placebo and glyburide-treated patients. When the data from the monotherapy and  
177 add-on to sulfonylurea clinical trials were combined, the most frequently (incidence  $\geq 0.5\%$ )  
178 reported serious adverse reactions classified by system organ class were gastrointestinal disorders  
179 (1.0% of GLUMETZA-treated patients compared to 0% of patients not treated with GLUMETZA)  
180 and cardiac disorders (0.4% of GLUMETZA-treated patients compared to 0.5% of patients not treated  
181 with GLUMETZA). Only 2 serious adverse reactions (unstable angina [n=2] and pancreatitis [n=2])  
182 were reported in more than one GLUMETZA-treated patient.

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

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

188

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

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

191 \*AR's that were more common in the GLUMETZA-treated than in the placebo-treated patients.

192

## 193 **6.2 Laboratory Tests**

### 194 **Vitamin B<sub>12</sub> concentrations**

195 Metformin may lower serum vitamin B<sub>12</sub> concentrations. Measurement of hematologic parameters on  
196 an annual basis is advised in patients on GLUMETZA and any apparent abnormalities should be  
197 appropriately investigated and managed. (See **WARNINGS AND PRECAUTIONS (5.6)**)

## 198 **7. DRUG INTERACTIONS**

199 **7.1 Carbonic Anhydrase Inhibitors** — Topiramate or other carbonic anhydrase inhibitors  
200 (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce  
201 non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic  
202 acidosis. Use these drugs with caution in patients treated with metformin, as the risk of lactic acidosis may  
203 increase.

204 **7.2 Cationic Drugs** — Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide,  
205 quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal  
206 tubular secretion theoretically have the potential for interaction with metformin by competing for  
207 common renal tubular transport systems. Although such interactions remain theoretical (except for  
208 cimetidine), careful patient monitoring and dose adjustment of GLUMETZA and/or the interfering  
209 drug is recommended in patients who are taking cationic medications that are excreted via the  
210 proximal renal tubular secretory system.

211 **7.3 Drugs Affecting Glycemic Control** — Certain drugs tend to produce hyperglycemia and  
212 may lead to loss of glycemic control. These drugs include the thiazides and other diuretics,  
213 corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic  
214 acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered  
215 to a patient receiving GLUMETZA, the patient should be closely observed for loss of blood glucose  
216 control. When such drugs are withdrawn from a patient receiving GLUMETZA, the patient should be  
217 observed closely for hypoglycemia.

218 **8. USE IN SPECIFIC POPULATIONS**

219 **8.1 Pregnancy**

220 **Teratogenic Effects: Pregnancy Category B**

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

226 **8.2 Labor and Delivery**

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

229 **8.3 Nursing Mothers**

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

233 **8.4 Pediatric Use**

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

236 **8.5 Geriatric Use**

237 Clinical studies of GLUMETZA did not include sufficient numbers of subjects aged 65 and over to  
238 determine whether they respond differently from younger subjects. Other reported clinical experience  
239 has not identified differences in responses between the elderly and younger patients. In general, dose  
240 selection for an elderly patient should be cautious, usually starting at the low end of the dosing range,  
241 reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant  
242 disease or other drug therapy and the higher risk of lactic acidosis.

243 (See **WARNINGS AND PRECAUTIONS (5)**)

244 **10. OVERDOSAGE**

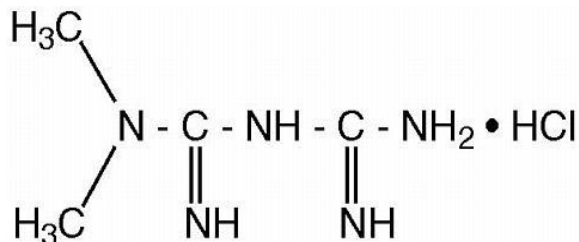
245 No cases of overdose were reported during GLUMETZA clinical trials. It would be expected that  
246 adverse reactions of a more intense character including epigastric discomfort, nausea, and vomiting  
247 followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen.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

249 Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50  
250 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with  
251 metformin hydrochloride has been established. Lactic acidosis has been reported in approximately  
252 32% of metformin overdose cases. (See **WARNINGS AND PRECAUTIONS (5.1)**) Metformin is  
253 dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore,

254 hemodialysis may be useful for removal of accumulated drug from patients in whom metformin  
255 overdosage is suspected.

## 256 11. DESCRIPTION

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



262

263

264 Metformin HCl is a white to off-white crystalline compound with a molecular formula of  
265  $\text{C}_4\text{H}_{11}\text{N}_5 \cdot \text{HCl}$  and a molecular weight of 165.63. Metformin HCl is freely soluble in water and is  
266 practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a  
267 1% aqueous solution of metformin hydrochloride is 6.68. GLUMETZA tablets are modified release  
268 dosage forms that contain 500 mg or 1000 mg of metformin HCl. Each 500 mg tablet contains  
269 coloring, hypromellose, magnesium stearate, microcrystalline cellulose and polyethylene oxide. Each  
270 1000 mg tablet contains colloidal silicon dioxide, polyvinyl alcohol, crospovidone, glyceryl behenate,  
271 polyacrylate dispersion, hypromellose, talc, polyethylene glycol, eudragit, titanium dioxide,  
272 simethicone emulsion, polysorbate and coloring. GLUMETZA 500 mg and 1000 mg tablets are  
273 formulated to gradually release metformin to the upper gastrointestinal (GI) tract.

## 274 12. CLINICAL PHARMACOLOGY

### 275 12.1 Mechanism of Action

276 Metformin is a biguanide that improves glucose tolerance in patients with type 2 diabetes, lowering  
277 both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production,  
278 decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral  
279 glucose uptake and utilization. Metformin does not produce hypoglycemia in patients with type 2  
280 diabetes or in healthy subjects except in special circumstances, (see **WARNINGS AND**  
281 **PRECAUTIONS (5)**) and does not cause hyperinsulinemia. With metformin therapy, insulin  
282 secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may  
283 actually decrease.

### 284 12.3 Pharmacokinetics

#### 285 Absorption and Bioavailability

286 Following a single oral dose of 1000 mg (2x500 mg tablets) GLUMETZA after a meal, the time to  
287 reach maximum plasma metformin concentration ( $T_{max}$ ) is achieved at approximately 7-8 hours. In  
288 both single and multiple-dose studies in healthy subjects, once daily 1000 mg (2x500 mg tablets)  
289 dosing provides equivalent systemic exposure, as measured by area-under-the-curve (AUC), and up to  
290 35% higher  $C_{max}$ , of metformin relative to the immediate release given as 500 mg twice daily.  
291 GLUMETZA tablets must be administered immediately after a meal to maximize therapeutic benefit.

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

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

### 299 Distribution

300 The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg  
301 immediate release metformin hydrochloride averaged  $654 \pm 358$  L. Metformin is negligibly bound to  
302 plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual  
303 clinical doses and dosing schedules of metformin, steady state plasma concentrations of metformin  
304 are reached within 24-48 hours and are generally  $< 1 \mu\text{g/mL}$ . During controlled clinical trials, which  
305 served as the basis of approval for metformin, maximum metformin plasma levels did not exceed  
306  $5\mu\text{g/mL}$ , even at maximum doses.

### 307 Metabolism

308 Intravenous single-dose studies in healthy subjects demonstrate that metformin is excreted unchanged  
309 in the urine and does not undergo hepatic metabolism (no metabolites have been identified in  
310 humans), nor biliary excretion. Metabolism studies with extended-release metformin tablets have not  
311 been conducted.

### 312 Excretion

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

318 **12.4 Specific Populations**

319 **Renal Impairment:** Following a single dose administration of GLUMETZA 500 mg in patients with  
320 mild and moderate renal failure (based on measured creatinine clearance), the oral and renal clearance  
321 of metformin were decreased by 33% and 50% and 16% and 53%, respectively (see **WARNINGS**  
322 **AND PRECAUTIONS (5)**). Metformin peak and systemic exposure was 27% and 61% greater,  
323 respectively in mild renal impaired and 74% and 2.36-fold greater in moderate renal impaired patients  
324 as compared to healthy subjects. Use of metformin in patients with renal impairment increases the  
325 risk for lactic acidosis. GLUMETZA is contraindicated in patients with renal impairment. (See  
326 **CONTRAINDICATIONS (4)** and **WARNINGS AND PRECAUTIONS (5.2)**)

327 **Hepatic Impairment:** No pharmacokinetic studies of GLUMETZA have been conducted in subjects  
328 with hepatic impairment. Use of metformin in patients with hepatic impairment has been associated  
329 with some cases of lactic acidosis. GLUMETZA is not recommended in patients with hepatic  
330 impairment. (See **WARNINGS AND PRECAUTIONS (5.5)**)

331 **Geriatrics:** Limited data from controlled pharmacokinetic studies of metformin hydrochloride in  
332 healthy elderly subjects suggest that total plasma clearance of metformin is decreased by 35%, the  
333 half-life is prolonged by 64% and  $C_{max}$  is increased by 76%, compared to healthy young subjects.  
334 From these data, it appears that the change in metformin pharmacokinetics with aging is primarily  
335 accounted for by a change in renal function. Metformin treatment should not be initiated in patients of  
336 any age unless measurement of creatinine clearance demonstrates that renal function is normal. (See  
337 **WARNINGS AND PRECAUTIONS (5)** and **DOSAGE AND ADMINISTRATION (2)**)

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

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

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

352

353 **12.5 Drug Interactions**

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

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

Coadministered Drug	Dose of Coadministered Drug <sup>1</sup>	Dose of Metformin <sup>1</sup>	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.00	
			AUC <sup>2</sup>	C <sub>max</sub>
No dosing adjustments required for the following:				
Glyburide	5 mg	500 mg <sup>4</sup>	0.98 <sup>3</sup>	0.99 <sup>3</sup>
Furosemide	40 mg	850 mg	1.09 <sup>3</sup>	1.22 <sup>3</sup>
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 <sup>3</sup>	1.07 <sup>3</sup>
<b>Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination: use with caution. (See WARNINGS AND PRECAUTIONS (5) and DRUG INTERACTIONS (7))</b>				
Cimetidine	400 mg	850 mg	1.40	1.61
<b>Carbonic anhydrase inhibitors may cause metabolic acidosis: use with caution (See WARNINGS AND PRECAUTIONS (5) and DRUG INTERACTIONS (7))</b>				
Topiramate	100 mg <sup>5</sup>	500 mg <sup>5</sup>	1.25 <sup>5</sup>	1.17
1. All metformin and coadministered drugs were given as single doses 2. AUC = AUC <sub>0-∞</sub> 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 <sub>0-12h</sub>				

357

359 **Table 3: Effect of Metformin on Coadministered Drug Systemic Exposure**

Coadministered Drug	Dose of Coadministered Drug <sup>1</sup>	Dose of Metformin <sup>1</sup>	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.00	
			AUC <sup>2</sup>	C <sub>max</sub>
No dosing adjustments required for the following:				
Glyburide	5 mg	500 mg <sup>4</sup>	0.78 <sup>3</sup>	0.63 <sup>3</sup>
Furosemide	40 mg	850 mg	0.87 <sup>3</sup>	0.69 <sup>3</sup>
Nifedipine	10 mg	850 mg	1.10 <sup>4</sup>	1.08
Propranolol	40 mg	850 mg	1.01 <sup>4</sup>	0.94
Ibuprofen	400 mg	850 mg	0.97 <sup>5</sup>	1.01 <sup>5</sup>
Cimetidine	400 mg	850 mg	0.95 <sup>4</sup>	1.01
1. All metformin and coadministered drugs were given as single doses 2. AUC = AUC <sub>0-∞</sub> 3. Ratio of arithmetic means, p-value of difference <0.05 4. AUC <sub>0-24 hr</sub> reported 5. Ratio of arithmetic means				

360 **13. NONCLINICAL TOXICOLOGY**361 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

374 **14. CLINICAL STUDIES**

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

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

381 In a multicenter, randomized, double-blind, active-controlled, dose-ranging, parallel group trial  
382 GLUMETZA 1500 mg once daily, GLUMETZA 1500 per day in divided doses (500 mg in the  
383 morning and 1000 mg in the evening), and GLUMETZA 2000 mg once daily were compared to  
384 immediate-release metformin 1500 mg per day in divided doses (500 mg in the morning and 1000 mg  
385 in the evening). This trial enrolled patients (n = 338) who were newly diagnosed with diabetes,  
386 patients treated only with diet and exercise, patients treated with a single anti-diabetic medication  
387 (sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, or meglinitides ), and patients  
388 (n = 368) receiving metformin up to 1500 mg/day plus a sulfonylurea at a dose equal to or less than  
389 one-half the maximum dose. Patients who were enrolled on monotherapy or combination anti-  
390 diabetic therapy underwent a 6-week washout. Patients randomized to GLUMETZA began titration  
391 from 1000 mg/day up to their assigned treatment dose over 3 weeks. Patients randomized to  
392 immediate-release metformin initiated 500 mg twice daily for 1 week followed by 500 mg with  
393 breakfast and 1000 mg with dinner for the second week. The 3-week treatment period was followed  
394 by an additional 21-week period at the randomized dose. For HbA1c and fasting plasma glucose,  
395 each of the GLUMETZA regimens was at least as effective as immediate-release metformin.  
396 Additionally, once daily dosing of GLUMETZA was as effective as twice daily dosing of the  
397 immediate release metformin formulation.

398

399

400 **Table 4: Mean±SE Changes from Baseline to Final Visit in HbA<sub>1c</sub>, Fasting Plasma Glucose**  
 401 **and Body Weight for the GLUMETZA and Metformin Immediate-Release**  
 402 **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 <sub>1c</sub> (%)				
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 ± 0.1	-0.0 ± 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)	

403

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

407 In a double-blind, randomized, placebo-controlled (glyburide add-on) multicenter trial, patients with  
 408 type 2 diabetes mellitus who were newly diagnosed or treated with diet and exercise (n = 144), or who

409 were receiving monotherapy with metformin, sulfonylureas, alpha-glucosidase inhibitors,  
410 thiazolidinediones, or meglinitides, or treated with combination therapy consisting of  
411 metformin/glyburide at doses up to 1000 mg metformin + 10 mg glyburide per day (or equivalent  
412 doses of glipizide or glimepiride up to half the maximum therapeutic dose) (n = 431) were enrolled.  
413 All patients were stabilized on glyburide for a 6-week run-in period, and then randomized to 1 of 4  
414 treatments: placebo + glyburide (glyburide alone); GLUMETZA 1500 mg once a day + glyburide,  
415 GLUMETZA 2000 mg once a day + glyburide, or GLUMETZA 1000 mg twice a day + glyburide. A  
416 3-week GLUMETZA titration phase was followed by a 21-week maintenance treatment phase. Use  
417 of insulin and oral hypoglycemic agents other than the study drugs were prohibited. The difference in  
418 the change from Baseline in HbA1c levels between the combined GLUMETZA + glyburide groups  
419 and the glyburide only group was statistically significant at week 24 (p<0.001). The changes in  
420 glycemic control across the three GLUMETZA+glyburide groups were comparable.

421

422

423 **Table 5: Mean±SE Changes from Baseline to Final Visit in HbA<sub>1c</sub>, Fasting Plasma Glucose**  
 424 **and Body Weight for the GLUMETZA/Glyburide Groups and Placebo/Glyburide**  
 425 **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 <sub>1c</sub> (%)				
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	

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

427

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

435 A second double-blind, placebo-controlled study (n=51), with 16 weeks of randomized treatment,  
436 demonstrated that in patients with type 2 diabetes controlled on insulin for 8 weeks with an average  
437 HbA<sub>1c</sub> of  $7.46 \pm 0.97\%$ , the addition of metformin maintained similar glycemic control (HbA<sub>1c</sub>  $7.15 \pm$   
438  $0.61$  versus  $6.97 \pm 0.62$  for metformin plus insulin and placebo plus insulin, respectively) with 19%  
439 less insulin versus baseline (reduction of  $23.68 \pm 30.22$  versus an increase of  $0.43 \pm 25.20$  units for  
440 metformin plus insulin and placebo plus insulin, p<0.01). In addition, this study demonstrated that the  
441 combination of metformin plus insulin resulted in reduction in body weight of  $3.11 \pm 4.30$  lbs,  
442 compared to an increase of  $1.30 \pm 6.08$  lbs for placebo plus insulin, p=0.01.

443 **16. HOW SUPPLIED/STORAGE AND HANDLING**

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

446 GLUMETZA tablets 1000 mg are available as white, film coated, oval-shaped tablets with “M1000”  
447 on one side.

448 They are supplied as follows:

449 <b>Package</b>	<b>Strength</b>	<b>NDC Code</b>
450 Bottles of 100	500 mg	13913-002-13
451 Bottles of 90	1000 mg	13913-003-16

452

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

455 **17. PATIENT COUNSELING INFORMATION**

456 **Information for Patients**

- 457 • Patients should be informed of the potential risks and benefits of GLUMETZA and of  
458 alternative modes of therapy. They should also be informed about the importance of adherence  
459 to dietary instructions, of a regular exercise program, and of regular testing of blood glucose,  
460 and hemoglobin A1c. During periods of stress such as fever, trauma, infection, or surgery,  
461 medication requirements may change and patients should be advised to seek medical advice  
462 promptly.
- 463 • The risks of lactic acidosis, its symptoms, and conditions that predispose to its development,  
464 as noted in the GLUMETZA sections, should be explained to patients. Patients should be  
465 advised to discontinue GLUMETZA immediately and to promptly notify their health  
466 practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other  
467 nonspecific symptoms occur. Once a patient is stabilized on any dose level of GLUMETZA,  
468 gastrointestinal symptoms, which are common during initiation of metformin therapy, are  
469 unlikely to recur. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis  
470 or other serious disease.
- 471 • Patients should be advised to notify their health practitioner or call the Poison Control Center  
472 immediately in case of GLUMETZA overdose.
- 473 • Patients should be informed about the importance of regular testing of renal function and  
474 hematological parameters when receiving treatment with GLUMETZA.
- 475 • Patients should be counseled against excessive alcohol intake, either acute or chronic, while  
476 receiving GLUMETZA.
- 477 • GLUMETZA (metformin hydrochloride extended-release tablets) alone does not usually cause  
478 hypoglycemia, although it may occur when GLUMETZA is used in conjunction with insulin  
479 secretagogues, such as sulfonylureas and insulin.

480 • Patients should be informed that GLUMETZA must be swallowed whole and not crushed or  
481 chewed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft  
482 mass that may resemble the original tablet.

483

484 **PATIENT INFORMATION**

485

486 **GLUMETZA (Gloo-met-za)**

487 **(metformin hydrochloride extended-release tablets)**

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

493

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

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

496 **Lactic Acidosis.** Metformin hydrochloride, the medicine in GLUMETZA can cause a rare, but  
497 serious condition called lactic acidosis (a buildup of an acid in the blood) that can cause death. Lactic  
498 acidosis is a medical emergency and must be treated in the hospital.

499

500 **Stop taking GLUMETZA and call your doctor right away if you get any of the following**  
501 **symptoms of lactic acidosis:**

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

510 **You have a higher chance for getting lactic acidosis with GLUMETZA if you:**

- 511 • have kidney problems. People whose kidneys are not working properly should not take  
512 GLUMETZA.
- 513 • have liver problems
- 514 • have congestive heart failure that requires treatments with medicines
- 515 • drink a lot of alcohol (very often or short-term “binge” drinking)
- 516 • get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a  
517 fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity  
518 or exercise and do not drink enough fluids.
- 519 • have certain x-ray tests with injectable dyes or contrast agent

- 520 • have surgery
- 521 • have a heart attack, severe infection, or stroke

522

### 523 **What is GLUMETZA?**

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

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

530

### 531 **Who should not take GLUMETZA?**

#### 532 **Do not take GLUMETZA if you:**

- 533 • have kidney problems
- 534 • are allergic to the metformin hydrochloride in GLUMETZA or any of the ingredients in  
535 GLUMETZA. See the end of this leaflet for a list of ingredients in GLUMETZA.
- 536 • you are going to get an injection of dye or contrast agents for an x-ray procedure,  
537 GLUMETZA will need to be stopped for a short time. Talk to your doctor about when you  
538 should stop GLUMETZA and when you should start GLUMETZA again. See “What is the  
539 most important information I should know about GLUMETZA?”
- 540 • have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in your  
541 blood or urine).

542

### 543 **What should I tell my doctor before taking GLUMETZA?**

544 Before you take GLUMETZA, tell your doctor if you:

- 545 • have type 1 diabetes. GLUMETZA should not be used to treat people with type 1 diabetes.
- 546 • have a history or risk for diabetic ketoacidosis (high levels of certain acids, known as ketones,  
547 in the blood or urine). GLUMETZA should not be used for the treatment of diabetic  
548 ketoacidosis.
- 549 • have kidney problems
- 550 • have liver problems
- 551 • have heart problems, including congestive heart failure.
- 552 • drink alcohol very often, or drink a lot of alcohol in short-term (binge) drinking
- 553 • are taking insulin
- 554 • have any other medical conditions
- 555 • **are pregnant or planning to become pregnant.** It is not known if GLUMETZA can harm  
556 your unborn baby. If you are pregnant, talk with your doctor about the best way to control  
557 your blood sugar while you are pregnant.

558 • **are breastfeeding or plan to breastfeed.** It is not known if GLUMETZA passes into your  
559 breast milk. Talk with your doctor about the best way to feed your baby while you take  
560 GLUMETZA.

561  
562 **Tell your doctor about all the medicines you take,** including prescription and nonprescription  
563 medicines, vitamins and herbal supplements. Know the medicines you take. Keep a list of them to  
564 show your doctor and pharmacist. Talk to your doctor before you start any new medicine.

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

567

### 568 **How should I take GLUMETZA?**

- 569 • Take GLUMETZA exactly as your doctor tells you.
- 570 • GLUMETZA should be taken 1 time per day with your evening meal.
- 571 • Swallow GLUMETZA tablets whole. Do not crush, cut, dissolve, or chew GLUMETZA.
- 572 • Tell your doctor if you cannot swallow tablets whole. Your doctor may prescribe a different  
573 medicine for you.
- 574 • You may sometimes pass a soft mass in your stools (bowel movement) that looks like  
575 GLUMETZA tablets. It is normal to see this in your stool.
- 576 • When your body is under some type of stress, such as fever, trauma (such as a car accident),  
577 infection, or surgery, the amount of diabetes medicine that you need may change. Tell your  
578 doctor right away if you have any of these problems.
- 579 • Your doctor should do blood tests to check how well your kidneys and liver are working  
580 before and during your treatment with GLUMETZA.
- 581 • Your healthcare provider will check your diabetes with regular blood tests, including your  
582 blood sugar levels and your hemoglobin A1C.
- 583 • Follow your doctor's instructions for treating blood sugar that is too low (hypoglycemia). Talk  
584 to your doctor if low blood sugar is a problem for you. See "**What are the possible side  
585 effects of GLUMETZA?**"
- 586 • Check your blood sugar regularly and as your doctor tells you to.
- 587 • Stay on your prescribed diet and exercise program and test your blood sugar regularly while  
588 taking GLUMETZA.
- 589 • If you miss a dose of GLUMETZA, resume dosing according to schedule.
- 590 • If you take too much GLUMETZA, call your doctor, or go to the nearest hospital emergency  
591 room right away.

592

### 593 **What are the side effects of GLUMETZA?**

#### 594 **GLUMETZA can cause serious side effects, including:**

- 595 • See "**What is the most important information I should know about GLUMETZA?**"
- 596 • **Low blood sugar (hypoglycemia).** If you take GLUMETZA with another medicine that can  
597 cause low blood sugar, such as sulfonylureas or insulin, you have a higher risk of having low  
598 blood sugar. Tell your doctor if you take other diabetes medicines. If you have symptoms of  
599 low blood sugar, you should check your blood sugar and treat if low, then call your doctor.  
600 Symptoms of low blood sugar include:

- 601 ○ shaking
- 602 ○ sweating
- 603 ○ rapid heartbeat
- 604 ○ change in vision
- 605 ○ hunger
- 606 ○ headache
- 607 ○ change in mood
- 608

609 **Common side effects of GLUMETZA include:**

- 610 ● hypoglycemia
- 611 ● diarrhea
- 612 ● nausea
- 613 ● upset stomach or stomach pain

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

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

619  
620 Tell your doctor if you have side effects that bother you or that do not go away.

621  
622 These are not all of the possible side effects of GLUMETZA. For more information, ask your doctor  
623 or pharmacist.

624  
625 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-  
626 FDA-1088.

627  
628 **How should I store GLUMETZA?**

- 629 ● Store GLUMETZA at 59°F to 86°F (15°C to 30°C).

630  
631 **Keep GLUMETZA and all medicines out of the reach of children.**

632  
633 **General information about the safe and effective use of GLUMETZA.**

634 Medicines are sometimes prescribed for purposes other than those listed in a Patient Information  
635 leaflet. Do not use GLUMETZA for a condition for which it was not prescribed. Do not give  
636 GLUMETZA to other people, even if they have the same symptoms you have. It may harm them.

637

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

641 For more information, go to [www.GlumetzaXR.com](http://www.GlumetzaXR.com) or call 1 866 458 6389.

642

643 **What are the ingredients in GLUMETZA?**

644 **Active Ingredient:** metformin hydrochloride

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

647 1000 mg tablet: colloidal silicon dioxide, polyvinyl alcohol, crospovidone, glyceryl behenate,  
648 polyacrylate dispersion, hypromellose, talc, polyethylene glycol, eudragit, titanium dioxide,  
649 simethicone emulsion, polysorbate and coloring.

650

651 **What is type 2 diabetes?**

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

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

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

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

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661 Depomed, Inc.  
662 1360 O'Brien Drive

663 Menlo Park, CA  
664 (866) 458-6389  
665 ©2011 Depomed, Inc.

666 [www.GlumetzaXR.com](http://www.GlumetzaXR.com)

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