HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS safely and effectively. See full prescribing information for METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS.
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 metformin hydrochloride extended-release tablets and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)

INDICATIONS AND USAGE
Metformin hydrochloride extended-release tablets are a biguanide indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

DOSAGE AND ADMINISTRATION

- Swallow metformin hydrochloride extended-release tablets whole and never crush, cut or chew (2.1)
- Starting dose: 500 mg orally once daily with the evening meal (2.1)
- Increase the dose in increments of 500 mg weekly, up to a maximum of 2000 mg once daily with the evening meal (2.1)
- Patients receiving metformin hydrochloride (HCl) tablets may be switched to metformin hydrochloride extended-release tablets once daily at the same total daily dose, up to 2000 mg once daily (2.1)

Renal Impairment:
- Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR) (2.2)
  - Do not use in patients with eGFR below 30 mL/minute/1.73 m² (2.2)
  - Initiation is not recommended in patients with eGFR between 30 to 45 mL/minute/1.73 m² (2.2)
  - Assess risk/benefit of continuing if eGFR falls below 45 mL/minute/1.73 m² (2.2)
  - Discontinue if eGFR falls below 30 mL/minute/1.73 m² (2.2)

Discontinuation for Iodinated Contrast Imaging Procedures:
- Metformin hydrochloride extended-release tablets may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures (2.3)

DOSAGE FORMS AND STRENGTHS
Extended-Release Tablets: 500 mg and 1000 mg (3)

CONTRAINDICATIONS
- Severe renal impairment (eGFR below 30 mL/min/1.73 m²) (4, 5.1)
- Hypersensitivity to metformin (4)
WARNINGS AND PRECAUTIONS

- Lactic Acidosis: See boxed warning (5.1)
- Vitamin B₁₂ Deficiency: Metformin may lower vitamin B₁₂ levels. Measure hematological parameters annually and vitamin B₁₂ at 2 to 3 year intervals and manage any abnormalities (5.2)
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Increased risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue. Lower dose of insulin or insulin secretagogue may be required (5.3)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2018
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FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

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

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

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

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

1 INDICATIONS AND USAGE

Metformin hydrochloride extended-release tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosage and Administration

- Swallow metformin hydrochloride extended-release tablets whole and never crush, cut or chew.
- The recommended starting dose of metformin hydrochloride extended-release tablets is 500 mg orally once daily with the evening meal.
- Increase the dose in increments of 500 mg weekly on the basis of glycemic control and tolerability, up to a maximum of 2000 mg once daily with the evening meal.
- If glycemic control is not achieved with metformin hydrochloride extended-release tablets 2000 mg once daily, consider a trial of metformin hydrochloride extended-release tablets 1000 mg twice daily.
- Patients receiving metformin hydrochloride (HCl) may be switched to metformin hydrochloride extended-release tablets once daily at the same total daily dose, up to 2000 mg once daily.

2.2 Recommendations for Use in Renal Impairment

- Assess renal function prior to initiation of metformin hydrochloride extended-release tablets and periodically thereafter.
- Metformin hydrochloride extended-release tablets are contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m²
- Initiation of metformin hydrochloride extended-release tablets in patients with an eGFR between 30 to 45 mL/minute/1.73 m² is not recommended.
- In patients taking metformin hydrochloride extended-release tablets whose eGFR later falls below 45 mL/min/1.73 m², assess the benefit risk of continuing therapy.
- Discontinue metformin hydrochloride extended-release tablets if the patient’s eGFR later falls below 30 mL/minute/1.73 m² [see Contraindications (4) and Warnings and Precautions (5.1)].

2.3 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue metformin hydrochloride extended-release tablets 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 m²; 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 metformin hydrochloride extended-release tablets if renal function is stable.

3 DOSAGE FORMS AND STRENGTHS

Metformin Hydrochloride Extended-Release Tablets, USP are available containing 500 mg or 1000 mg of metformin hydrochloride, USP.

- The 500 mg tablets are pink, film-coated, round, unscored tablets imprinted with M over MN2 in black ink on one side of the tablet and blank on the other side.
- The 1000 mg tablets are pink, film-coated, round, unscored tablets imprinted with M over MN1 in black ink on one side of the tablet and blank on the other side.

4 CONTRAINDICATIONS

Metformin hydrochloride extended-release tablets are contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m²) [see Warnings and Precautions (5.1)].
5.1 Lactic Acidosis

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

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

Educate patients and their families about the symptoms of lactic acidosis and, if these symptoms occur, instruct them to discontinue metformin hydrochloride extended-release tablets and report these symptoms to their healthcare provider.

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

- **Renal impairment** — The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient’s renal function include [see Dosage and Administration (2.2), Clinical Pharmacology (12.3)]:
  
  - Before initiating metformin hydrochloride extended-release tablets, obtain an estimated glomerular filtration rate (eGFR).
  - Metformin hydrochloride extended-release tablets are contraindicated in patients with an eGFR less than 30 mL/min/1.73 m² [see Contraindications (4)].
  - Initiation of metformin hydrochloride extended-release tablets is not recommended in patients with eGFR between 30 to 45 mL/min/1.73 m².
  - Obtain an eGFR at least annually in all patients taking metformin hydrochloride extended-release tablets. In patients at risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
  - In patients taking metformin hydrochloride extended-release tablets whose eGFR falls below 45 mL/min/1.73 m², assess the benefit and risk of continuing therapy.

- **Drug interactions** — The concomitant use of metformin hydrochloride extended-release tablets with specific drugs may increase the risk of metformin-associated lactic acidosis: those that
impair renal function, result in significant hemodynamic change, interfere with acid-base balance, or increase metformin accumulation [see Drug Interactions (7)]. Consider more frequent monitoring of patients.

- **Age 65 or greater** — The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.

- **Radiologic studies with contrast** — Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop metformin hydrochloride extended-release tablets 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 m²; 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 metformin hydrochloride extended-release tablets 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. Metformin hydrochloride extended-release tablets should be temporarily discontinued while patients have restricted food and fluid intake.

- **Hypoxic states** — Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may cause prerenal azotemia. When such an event occurs, discontinue metformin hydrochloride extended-release tablets.

- **Excessive alcohol intake** — Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving metformin hydrochloride extended-release tablets.

- **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 metformin hydrochloride extended-release tablets in patients with clinical or laboratory evidence of hepatic disease.

### 5.2 Vitamin B₁₂ Deficiency

In clinical trials of 29-week duration with metformin hydrochloride tablets, a decrease to subnormal levels of previously normal serum vitamin B₁₂ levels was observed in approximately 7% of patients. Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B₁₂ supplementation. Certain individuals (those with inadequate vitamin B₁₂ or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B₁₂ levels. Measure hematologic parameters on an annual basis and vitamin B₁₂ at 2 to 3 year intervals in patients on metformin hydrochloride extended-release tablets and manage any abnormalities [see Adverse Reactions (6.1)].

### 5.3 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

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

### 5.4 Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with metformin hydrochloride extended-release tablets.

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

- Lactic Acidosis [see Boxed Warning and Warnings and Precautions (5.1)]
- Vitamin B<sub>12</sub> Deficiency [see Warnings and Precautions (5.2)]
- Hypoglycemia [see Warnings and Precautions (5.3)]

6.1 Clinical Studies Experience

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

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

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Metformin Hydrochloride Extended-Release Tablets (n = 781)</th>
<th>Placebo (n = 195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>7%</td>
<td>2%</td>
</tr>
</tbody>
</table>

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

Laboratory Tests

Vitamin B<sub>12</sub> Concentrations

In clinical trials of 29-week duration with metformin hydrochloride tablets, a decrease to subnormal levels of previously normal serum vitamin B<sub>12</sub> levels was observed in approximately 7% of patients.

6.2 Postmarketing Experience

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

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

7 DRUG INTERACTIONS
Table 2 presents clinically significant drug interactions with metformin hydrochloride extended-release tablets.

### Table 2: Clinically Significant Drug Interactions with Metformin Hydrochloride Extended-Release Tablets

<table>
<thead>
<tr>
<th>Classification</th>
<th>Clinical Impact</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbonic Anhydrase Inhibitors</strong></td>
<td>Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with metformin hydrochloride extended-release tablets may increase the risk for lactic acidosis.</td>
<td>Consider more frequent monitoring of these patients.</td>
</tr>
<tr>
<td><strong>Examples:</strong></td>
<td>Topiramate, zonisamide, acetazolamide or dichlorphenamide.</td>
<td></td>
</tr>
<tr>
<td><strong>Drugs that Reduce Metformin Clearance</strong></td>
<td>Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2]/multidrug and toxin extrusion [MATE] inhibitors) could increase systemic exposure to metformin and may increase the risk for lactic acidosis [see Clinical Pharmacology (12.3)].</td>
<td>Consider the benefits and risks of concomitant use with metformin hydrochloride extended-release tablets.</td>
</tr>
<tr>
<td><strong>Examples:</strong></td>
<td>Ranolazine, vandetanib, dolutegravir, and cimetidine.</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td>Alcohol is known to potentiate the effect of metformin on lactate metabolism.</td>
<td>Warn patients against excessive alcohol intake while receiving metformin hydrochloride extended-release tablets.</td>
</tr>
<tr>
<td><strong>Insulin Secretagogues or Insulin</strong></td>
<td>Coadministration of metformin hydrochloride extended-release tablets with an insulin secretagogue (e.g., sulfonylurea) or insulin may increase the risk of hypoglycemia.</td>
<td>Patients receiving an insulin secretagogue or insulin may require lower doses of the insulin secretagogue or insulin.</td>
</tr>
<tr>
<td><strong>Drugs Affecting Glycemic Control</strong></td>
<td>Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control.</td>
<td>When such drugs are administered to a patient receiving metformin hydrochloride extended-release tablets, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving metformin hydrochloride extended-release tablets, observe the patient closely for hypoglycemia.</td>
</tr>
<tr>
<td><strong>Examples:</strong></td>
<td>Thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid.</td>
<td></td>
</tr>
</tbody>
</table>

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy
**Risk Summary**

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

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

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

**Clinical Considerations**

*Disease-associated Maternal and/or Embryo/Fetal Risk*

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

**Data**

*Human Data*

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

*Animal Data*

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

**8.2 Lactation**

**Risk Summary**

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

**Data**

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

8.3 Females and Males of Reproductive Potential
Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin hydrochloride extended-release tablets may result in ovulation in some anovulatory women.

8.4 Pediatric Use
Safety and effectiveness of metformin hydrochloride extended-release tablets in pediatric patients have not been established.

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

8.6 Renal Impairment
Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Metformin hydrochloride extended-release tablets are contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m² [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. Metformin hydrochloride extended-release tablets are not recommended in patients with hepatic impairment [see Warnings and Precautions (5.1)].

10 OVERDOSAGE
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 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
Metformin hydrochloride extended-release tablets, USP contain the biguanidine antihyperglycemic agent, metformin, in the form of monohydrochloride salt. The chemical name of metformin hydrochloride is 1,1-Dimethybiguanide monohydrochloride with a molecular formula of C₄H₁₁N₅•HCl and a molecular weight of 165.6. Its structural formula is:
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

Absorption

In a multiple-dose crossover study, 23 patients with type 2 diabetes mellitus were administered either metformin hydrochloride extended-release tablets 2000 mg once a day (after dinner) or metformin hydrochloride tablets 1000 mg twice a day (after breakfast and after dinner). After 4 weeks of treatment, steady-state pharmacokinetic parameters, area under the concentration-time curve (AUC), time to peak plasma concentration ($T_{\text{max}}$), and maximum concentration ($C_{\text{max}}$) were evaluated. The appearance of metformin in plasma from metformin hydrochloride extended-release tablets is slower and more prolonged compared to metformin hydrochloride tablets. Results are presented in Table 3.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters (mean ± SD)</th>
<th>Metformin Hydrochloride Extended-Release Tablets 2000 mg (administered q.d. after dinner)</th>
<th>Metformin Hydrochloride Tablets* 2000 mg (1000 mg b.i.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-24hr} (ng•hr/mL)</td>
<td>26,811 ± 7055</td>
<td>27,371 ± 5781</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>T_{max} (hr)</td>
<td>6 (3-10)</td>
<td>3 (1-8)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>2849 ± 797</td>
<td>1820 ± 370</td>
</tr>
</tbody>
</table>

* Immediate-release metformin hydrochloride tablets

In four single-dose studies and one multiple-dose study, the bioavailability of metformin hydrochloride extended-release tablets 2000 mg given once daily, in the evening, under fed conditions [as measured by AUC] was similar to the same total daily dose administered as metformin hydrochloride tablets 1000 mg given twice daily. The geometric mean ratios (metformin hydrochloride extended-release tablets/metformin hydrochloride tablets) of AUC_{0-24hr}, AUC_{0-72hr}, and AUC_{0-inf} for these five studies ranged from 0.96 to 1.08.

In a single-dose, four-period replicate crossover design study, comparing two 500 mg metformin hydrochloride extended-release tablets to one 1000 mg metformin hydrochloride extended-release tablet administered in the evening with food to 29 healthy male subjects, two 500 mg metformin hydrochloride extended-release tablets were found to be equivalent to one 1000 mg metformin hydrochloride extended-release tablet.

In a study carried out with metformin hydrochloride extended-release tablets, there was a dose-associated increase in metformin exposure over 24 hours following oral administration of 1000, 1500, 2000, and 2500 mg.

In three studies with metformin hydrochloride extended-release tablets using different treatment regimens (2000 mg after dinner; 1000 mg after breakfast and after dinner; and 2500 mg after dinner), the pharmacokinetics of metformin as measured by AUC appeared linear following multiple-dose administration.

**Effect of Food**

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

**Distribution**

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

**Metabolism**

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

**Elimination**

Renal clearance (see Table 4) is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

**Specific Populations**
Renal Impairment

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

Hepatic Impairment

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

Geriatrics

Limited data from controlled pharmacokinetic studies of metformin hydrochloride tablets in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_max is increased, compared to healthy young subjects. It appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see Table 4). [see Warnings and Precautions (5.1) and Use in Specific Populations (8.5)].

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

<table>
<thead>
<tr>
<th>Subject Groups: Metformin Hydrochloride Dose* (number of subjects)</th>
<th>C_max† (mcg/mL)</th>
<th>T_max‡ (hrs)</th>
<th>Renal Clearance (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy, nondiabetic adults: 500 mg single dose (24)</td>
<td>1.03 (±0.33)</td>
<td>2.75 (±0.81)</td>
<td>600 (±132)</td>
</tr>
<tr>
<td>850 mg single dose (74)§</td>
<td>1.60 (±0.38)</td>
<td>2.64 (±0.82)</td>
<td>552 (±139)</td>
</tr>
<tr>
<td>850 mg three times daily for 19 doses¶ (9)</td>
<td>2.01 (±0.42)</td>
<td>1.79 (±0.94)</td>
<td>642 (±173)</td>
</tr>
<tr>
<td>Adults with type 2 diabetes mellitus: 850 mg single dose (23)</td>
<td>1.48 (±0.5)</td>
<td>3.32 (±1.08)</td>
<td>491 (±138)</td>
</tr>
<tr>
<td>850 mg three times daily for 19 doses¶ (9)</td>
<td>1.90 (±0.62)</td>
<td>2.01 (±1.22)</td>
<td>550 (±160)</td>
</tr>
<tr>
<td>Elderly#, healthy nondiabetic adults: 850 mg single dose (12)</td>
<td>2.45 (±0.70)</td>
<td>2.71 (±1.05)</td>
<td>412 (±98)</td>
</tr>
<tr>
<td>Renal-impaired adults: 850 mg single dose</td>
<td>1.86 (±0.52)</td>
<td>3.20 (±0.45)</td>
<td>384 (±122)</td>
</tr>
<tr>
<td>Mild (CLcr P 61 to 90 mL/min) (5)</td>
<td>4.12 (±1.83)</td>
<td>3.75 (±0.50)</td>
<td>108 (±57)</td>
</tr>
<tr>
<td>Moderate (CLcr 31 to 60 mL/min) (4)</td>
<td>3.93 (±0.92)</td>
<td>4.01 (±1.10)</td>
<td>130 (±90)</td>
</tr>
</tbody>
</table>

* All doses given fasting except the first 18 doses of the multiple dose studies
† Peak plasma concentration
‡ Time to peak plasma concentration
§ Combined results (average means) of five studies: mean age 32 years (range 23 to 59 years)
¶ Kinetic study done following dose 19, given fasting
# Elderly subjects, mean age 71 years (range 65 to 81 years)
P CLcr = creatinine clearance normalized to body surface area of 1.73 m²

Pediatrics

There are no available pharmacokinetic data with metformin hydrochloride extended-release tablets in pediatric patients.

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

**Race**

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

**Drug Interactions**

*In Vivo Assessment of Drug Interactions*

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose of Coadministered Drug*</th>
<th>Dose of Metformin Hydrochloride*</th>
<th>Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide</td>
<td>5 mg</td>
<td>850 mg</td>
<td>metformin</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40 mg</td>
<td>850 mg</td>
<td>metformin</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10 mg</td>
<td>850 mg</td>
<td>metformin</td>
</tr>
<tr>
<td>Propranolol</td>
<td>40 mg</td>
<td>850 mg</td>
<td>metformin</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400 mg</td>
<td>850 mg</td>
<td>metformin</td>
</tr>
</tbody>
</table>

*Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination [See Warnings and Precautions (5.1) and Drug Interactions (7).]*

Coadministered Drug | Dose of Coadministered Drug | Dose of Metformin Hydrochloride | Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide</td>
<td>5 mg</td>
<td>850 mg</td>
<td>metformin</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40 mg</td>
<td>850 mg</td>
<td>metformin</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10 mg</td>
<td>850 mg</td>
<td>metformin</td>
</tr>
<tr>
<td>Propranolol</td>
<td>40 mg</td>
<td>850 mg</td>
<td>metformin</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400 mg</td>
<td>850 mg</td>
<td>metformin</td>
</tr>
</tbody>
</table>

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

**Table 6: Effect of Metformin on Coadministered Drug Systemic Exposure**

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose of Coadministered Drug*</th>
<th>Dose of Metformin Hydrochloride*</th>
<th>Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide</td>
<td>5 mg</td>
<td>850 mg</td>
<td>glyburide</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40 mg</td>
<td>850 mg</td>
<td>furosemide</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10 mg</td>
<td>850 mg</td>
<td>nifedipine</td>
</tr>
<tr>
<td>Propranolol</td>
<td>40 mg</td>
<td>850 mg</td>
<td>propranolol</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400 mg</td>
<td>850 mg</td>
<td>ibuprofen</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>400 mg</td>
<td>850 mg</td>
<td>cimetidine</td>
</tr>
</tbody>
</table>

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

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 3 times the maximum recommended human daily dose of 2550 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

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

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

14 CLINICAL STUDIES

A 24-week, double-blind, placebo-controlled study of metformin hydrochloride extended-release tablets, taken once daily with the evening meal, was conducted in patients with type 2 diabetes mellitus who had failed to achieve glycemic control with diet and exercise. Patients entering the study had a mean baseline HbA\textsubscript{1c} of 8.0% and a mean baseline FPG of 176 mg/dL. The treatment dose was increased to 1500 mg once daily if at Week 12 HbA\textsubscript{1c} was ≥ 7.0% but < 8.0% (patients with HbA\textsubscript{1c} ≥ 8.0% were discontinued from the study). At the final visit (24-week), mean HbA\textsubscript{1c} had increased 0.2% from baseline in placebo patients and decreased 0.6% with metformin hydrochloride extended-release tablets.

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

<table>
<thead>
<tr>
<th>Metformin Hydrochloride Extended-Release Tablets</th>
<th>500 mg Once Daily</th>
<th>1000 mg Once Daily</th>
<th>1500 mg Once Daily</th>
<th>2000 mg Once Daily</th>
<th>1000 mg Twice Daily</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin A\textsubscript{1c} (%) Baseline</td>
<td>(n = 115)</td>
<td>(n = 115)</td>
<td>(n = 111)</td>
<td>(n = 125)</td>
<td>(n = 112)</td>
<td>(n = 111)</td>
</tr>
<tr>
<td>Change at FINAL VISIT p-value*</td>
<td>8.2</td>
<td>8.4</td>
<td>8.3</td>
<td>8.4</td>
<td>8.4</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>-0.4</td>
<td>-0.6</td>
<td>-0.9</td>
<td>-0.8</td>
<td>-1.1</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>-</td>
</tr>
</tbody>
</table>

| FPG (mg/dL) Baseline                          | (n = 126)         | (n = 118)         | (n = 120)         | (n = 132)         | (n = 122)         | (n = 113) |
|                                               | 182.7             | 183.7             | 178.9             | 181.0             | 181.6             | 179.6    |
| Change at FINAL VISIT                         | -15.2             | -19.3             | -28.5             | -29.9             | -33.6             | -       |

*Ratio of arithmetic means
Mean baseline body weight was 193 lbs, 192 lbs, 188 lbs, 196 lbs, 193 lbs and 194 lbs in the metformin hydrochloride extended-release tablets 500 mg, 1000 mg, 1500 mg, and 2000 mg once daily, 1000 mg twice daily and placebo arms, respectively. Mean change in body weight from baseline to week 16 was -1.3 lbs, -1.3 lbs, -0.7 lbs, -1.5 lbs, -2.2 lbs and -1.8 lbs, respectively.

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

### Table 8: Mean Changes from Baseline* in HbA\textsubscript{1c} and Fasting Plasma Glucose at Week 24 Comparing Metformin Hydrochloride Extended-Release vs Metformin Hydrochloride in Patients with Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th></th>
<th>Metformin Hydrochloride 500 mg Twice Daily</th>
<th>Metformin Hydrochloride Extended-Release 1000 mg Once Daily</th>
<th>Metformin Hydrochloride Extended-Release 1500 mg Once Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemoglobin A\textsubscript{1c} (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>(n = 67) 7.06</td>
<td>(n = 72) 6.99</td>
<td>(n = 66) 7.02</td>
</tr>
<tr>
<td>Change at FINAL VISIT (95% CI)</td>
<td>0.14* (-0.04, 0.31)</td>
<td>0.27 (0.11, 0.43)</td>
<td>0.13 (-0.02, 0.28)</td>
</tr>
<tr>
<td><strong>FPG (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>(n = 69) 127.2</td>
<td>(n = 72) 131.0</td>
<td>(n = 70) 131.4</td>
</tr>
<tr>
<td>Change at FINAL VISIT (95% CI)</td>
<td>14.0 (7.0, 21.0)</td>
<td>11.5 (4.4, 18.6)</td>
<td>7.6 (1.0, 14.2)</td>
</tr>
</tbody>
</table>

Mean baseline body weight was 210 lbs, 203 lbs and 193 lbs in the metformin hydrochloride tablets 500 mg twice daily, and metformin hydrochloride extended-release tablets 1000 mg and 1500 mg once daily arms, respectively. Mean change in body weight from baseline to week 24 was 0.9 lbs, 1.1 lbs and 0.9 lbs, respectively.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 16.1 How Supplied

Metformin Hydrochloride Extended-Release Tablets, USP are available containing 500 mg or 1000 mg of metformin hydrochloride, USP.

The 500 mg tablets are pink, film-coated, round, unscored tablets imprinted with M over MN2 in black ink on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-6002-91  
bottles of 60 tablets

The 1000 mg tablets are pink, film-coated, round, unscored tablets imprinted with M over MN1 in black ink on one side of the tablet and blank on the other side. They are available as follows:
16.2 Storage
Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature.]
Avoid excessive heat and humidity. Protect from light and moisture.
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep tightly closed.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information).

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

Hypoglycemia: Inform patients that hypoglycemia may occur when metformin hydrochloride extended-release tablets are coadministered with oral sulfonylureas and insulin. Explain to patients receiving concomitant therapy the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development [see Warnings and Precautions (5.3)].

Vitamin B₁₂ Deficiency: Inform patients about importance of regular hematological parameters while receiving metformin hydrochloride extended-release tablets [see Warnings and Precautions (5.2)].

Females of Reproductive Age: Inform females that treatment with metformin hydrochloride extended-release tablets may result in ovulation in some premenopausal anovulatory women which may lead to unintended pregnancy [see Use in Specific Populations (8.3)].

Administration Information: Inform patients that metformin hydrochloride extended-release tablets must be swallowed whole and not crushed, cut, or chewed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that may resemble the original tablet.

Patient Information

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

- feel very weak and tired
- have unusual sleepiness or sleep longer than
You have a higher chance of getting lactic acidosis if you:

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

Tell your healthcare provider if you have any of the problems in the list above.

Tell your healthcare provider that you are taking metformin hydrochloride extended-release tablets before you have surgery or x-ray tests. Your healthcare provider may need to stop metformin hydrochloride extended-release tablets for a while if you have surgery or certain x-ray tests). Metformin hydrochloride extended-release tablets can have other serious side effects. See “What are the possible side effects of metformin hydrochloride extended-release tablets?”

What are metformin hydrochloride extended-release tablets?

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

Do not take metformin hydrochloride extended-release tablets if you:

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

Before taking metformin hydrochloride extended-release tablets, tell your healthcare provider about all your medical conditions, including if you:

- have a history or risk for diabetic ketoacidosis. See “Do not take metformin hydrochloride extended-release tablets if you:”
- have kidney problems.
Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

Metformin hydrochloride extended-release tablets may affect the way other medicines work, and other medicines may affect how metformin hydrochloride extended-release tablets work.

How should I take metformin hydrochloride extended-release tablets?

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

What should I avoid while taking metformin hydrochloride extended-release tablets?

- have liver problems.
- have heart problems, including congestive heart failure.
- are 65 years of age or older.
- drink alcohol very often or drink a lot of alcohol in short-term “binge” drinking.
- are taking insulin or a sulfonylurea medicine.
- are pregnant or plan to become pregnant. It is not known if metformin hydrochloride extended-release tablets will harm your unborn baby. If you are pregnant, talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are a woman who has not gone through menopause (premenopausal) who does not have periods regularly or at all. Metformin hydrochloride extended-release tablets can cause the release of an egg from an ovary in a woman (ovulation). This can increase your chance of getting pregnant.
- are breastfeeding or plan to breastfeed. Metformin can pass into your breast milk. Talk with your healthcare provider about the best way to feed your baby while you take metformin hydrochloride extended-release tablets.
Do not drink a lot of alcoholic drinks while taking metformin hydrochloride extended-release tablets. This means you should not binge drink for short periods, and you should not drink a lot of alcohol on a regular basis. Alcohol can increase the chance of getting lactic acidosis.

What are the possible side effects of metformin hydrochloride extended-release tablets?
Metformin hydrochloride extended-release tablets may cause serious side effects, including:

- See “What is the most important information I should know about metformin hydrochloride extended-release tablets?”
- **Low vitamin B₁₂ (vitamin B₁₂ deficiency).** Using metformin hydrochloride extended-release tablets may cause a decrease in the amount of vitamin B₁₂ in your blood, especially if you have had low vitamin B₁₂ levels before. Your healthcare provider may do blood tests to check your vitamin B₁₂ levels.
- **Low blood sugar (hypoglycemia).** If you take metformin hydrochloride extended-release tablets with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take metformin hydrochloride extended-release tablets. Signs and symptoms of low blood sugar may include:
  - headache
  - drowsiness
  - weakness
  - irritability
  - hunger
  - fast heartbeat
  - confusion
  - shaking or feeling jittery
  - dizziness
  - sweating
  - diarrhea
  - nausea and vomiting
  - gassiness (flatulence)
  - indigestion
  - stomach-area (abdominal) pain and swelling
  - headache
  - taste disturbance (unpleasant metallic taste)

Common side effects of metformin hydrochloride extended-release tablets include:

- These are not all the possible side effects of metformin hydrochloride extended-release tablets.
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 metformin hydrochloride extended-release tablets?
Store metformin hydrochloride extended-release tablets at room temperature between 20° to 25°C (68° to 77°F). See insert. Keep bottle tightly closed between each use to protect the metformin hydrochloride extended-release tablets from moisture.
Protect from light.

Keep metformin hydrochloride extended-release tablets and all medicines out of the reach of children.

General information about the safe and effective use of metformin hydrochloride extended-release tablets
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use metformin hydrochloride extended-release tablets for a condition for which they were not prescribed. Do not give metformin hydrochloride extended-release tablets to other people, even if they have the same symptoms that you have. They may harm them.
You can ask your pharmacist or healthcare provider for information about metformin hydrochloride extended-release tablets that is written for health professionals.

What are the ingredients in metformin hydrochloride extended-release tablets?
**Active ingredients:** metformin hydrochloride.

**Inactive ingredients:** cellulose acetate, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, povidone, red iron oxide, sodium lauryl sulfate, talc, titanium dioxide, triacetin, triethyl citrate and yellow iron oxide. In addition, the black imprinting ink contains ammonium hydroxide, black iron oxide, propylene glycol and shellac glaze.

**Manufactured for:** Mylan Pharmaceuticals Inc., Morgantown, WV 26505 U.S.A.

**Manufactured by:** Mylan Laboratories Limited, Hyderabad — 500 096, India

For more information, call Mylan at 1-877-446-3679 (1-877-4-INFO-RX).
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

Each film-coated tablet contains:
Metformin hydrochloride, USP  500 mg

Usual Dosage: See accompanying prescribing information.
Extended-release tablets should not be broken, crushed or chewed.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Protect from light and moisture.
Avoid excess heat and humidity.

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Made in India

Mylan.com

RMX6001D2

Keep this and all medication out
of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89
FERRIC OXIDE RED (UNII: 1K09F3G67S)
SHELLAC (UNII: 46N107B71O)
SODIUM LAUROYL SULFATE (UNII: 368GB514I1)
TALC (UNII: 7SEV7J4R1U)
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)
TRIACETIN (UNII: XHX3C3X673)
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)

### Product Characteristics

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### Packaging

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<th>Marketing End Date</th>
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<tbody>
<tr>
<td>1</td>
<td>NDC:0378-6002-91</td>
<td>60 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product</td>
<td>08/23/2016</td>
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### Marketing Information

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<tr>
<th>Marketing Category</th>
<th>Application Number or Monograph Citation</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
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<tbody>
<tr>
<td>ANDA</td>
<td>ANDA200690</td>
<td>08/23/2016</td>
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### METFORMIN HYDROCHLORIDE

**metformin tablet, film coated, extended release**

### Product Information

<table>
<thead>
<tr>
<th>Product Type</th>
<th>HUMAN PRESCRIPTION DRUG</th>
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<tr>
<td>Route of Administration</td>
<td>ORAL</td>
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### Active Ingredient/Active Moiety

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
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<tbody>
<tr>
<td>METFORMIN HYDROCHLORIDE (UNII: 786Z46389E) (METFORMIN - UNII:9 100L32L2N)</td>
<td>METFORMIN HYDROCHLORIDE</td>
<td>1000 mg</td>
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### Inactive Ingredients

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Strength</th>
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<tbody>
<tr>
<td>AMMONIA (UNII: 5138Q19F1X)</td>
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</tr>
<tr>
<td>FERROSOFERRIC OXIDE (UNII: XM0M87F357)</td>
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</tr>
<tr>
<td>CELLULOSE ACETATE (UNII: 3J2P07GV6)</td>
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<tr>
<td>Active Ingredient</td>
<td>UNII Code</td>
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<tr>
<td>-------------------------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>CELLULOSE ACETATE</td>
<td>3J2P07GVB6</td>
</tr>
<tr>
<td>HYDROXYETHYLCELLULOSE, UNSPECIFIED</td>
<td>3NXW29V3WO</td>
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<tr>
<td>LACTOSE MONOHYDRATE</td>
<td>EWQ57Q15X</td>
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<tr>
<td>MAGNESIUM STEARATE</td>
<td>70097M6310</td>
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<tr>
<td>POLYETHYLENE GLYCOL, UNSPECIFIED</td>
<td>3WJQ0SDW1A</td>
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<tr>
<td>Povidone, UNSPECIFIED</td>
<td>FZ989GH94E</td>
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<tr>
<td>PROPYLENE GLYCOL</td>
<td>6DC9Q167V3</td>
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<tr>
<td>FERRIC OXIDE RED</td>
<td>1K09F3G675</td>
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<tr>
<td>SHELLAC</td>
<td>46N107B71O</td>
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<td>SODIUM LAURYL SULFATE</td>
<td>368GB5141J</td>
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<tr>
<td>Talc</td>
<td>7SEV7J4R1IU</td>
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<tr>
<td>TITANIUM DIOXIDE</td>
<td>15FIX9V2JP</td>
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<tr>
<td>TRIACETIN</td>
<td>XHX3C3X673</td>
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<tr>
<td>TRIETHYL CITRATE</td>
<td>8Z96QXD6UM</td>
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<tr>
<td>FERRIC OXIDE YELLOW</td>
<td>EX438O2MRT</td>
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**Product Characteristics**

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<tr>
<th>Color</th>
<th>Score</th>
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<tr>
<td>PINK</td>
<td>no score</td>
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<tr>
<td>Shape</td>
<td>Size</td>
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<td>ROUND</td>
<td>13mm</td>
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<tr>
<td>Flavor</td>
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**Packaging**

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<th>Item Code</th>
<th>Package Description</th>
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**Labeler** - Mylan Pharmaceuticals Inc. (059295980)

Revised: 11/2018