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----------
- Starting dose: 500 mg orally once daily with the evening meal (2.1)
- Increase the dose in increments of 500 mg every 1 to 2 weeks, up to a maximum of 2,000 mg once daily with the evening meal. (2.1)
- Patients receiving metformin hydrochloride (HCl) tablets may be switched to Metformin Hydrochloride Extended-Release Tablets once daily at the same total daily dose, up to 2,000 mg once daily. (2.1)
- Swallow Metformin Hydrochloride Extended-Release Tablets whole and never crush, cut or chew. (2.1)

Renal Impairment:
- Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR). (2.2)
  - Do not use in patients with eGFR below 30 mL/minute/1.73 m^2.
  - Initiation is not recommended in patients with eGFR between 30 to 45 mL/minute/1.73 m^2.
  - Assess risk/benefit of continuing Metformin Hydrochloride Extended-Release Tablets if eGFR falls below 45 mL/minute/1.73 m^2.
  - Discontinue if eGFR falls below 30 mL/minute/1.73 m^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----------
Metformin Hydrochloride Extended-Release Tablets: 500 mg and 1,000 mg (3)

----------CONTRAINDICATIONS----------
- Severe renal impairment: (eGFR below 30 mL/minute/1.73 m^2) (4, 5.1)
- Known hypersensitivity to metformin (4)
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma (4)

----------WARNINGS AND PRECAUTIONS----------
- *Lactic Acidosis:* See boxed warning. (5.1)
- *Vitamin B_{12} Deficiency:* Metformin may lower vitamin B_{12} levels. Monitor hematological parameters annually and vitamin B_{12} at 2 to 3 year intervals and manage any abnormalities. (5.2)
- *Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues:* Increased risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue. Lower dose of insulin or insulin secretagogue may be required. (5.3)

----------ADVERSE REACTIONS----------
Adverse reactions occurring >5% in Metformin Hydrochloride Extended-Release Tablets clinical trials: hypoglycemia, diarrhea, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Oceanside Pharmaceuticals at 1-800-221-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

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

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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

- 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 every 1 to 2 weeks on the basis of glycemic control and tolerability, up to a maximum of 2,000 mg once daily with the evening meal.
- Patients receiving metformin hydrochloride (HCl) may be switched to Metformin Hydrochloride Extended-Release Tablets once daily at the same total daily dose, up to 2,000 mg once daily.
- Swallow Metformin Hydrochloride Extended-Release Tablets whole and never crush, cut or chew.
- If a dose of Metformin Hydrochloride Extended-Release Tablets is missed, instruct patients not to take two doses the same day and to resume their usual dose of Metformin Hydrochloride Extended-Release Tablets with the next schedule dose.

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 m^2.
- Initiation of Metformin Hydrochloride Extended-Release Tablets in patients with an eGFR between 30 to 45 mL/minute/1.73 m^2 is not recommended.
- In patients taking Metformin Hydrochloride Extended-Release Tablets whose eGFR later falls below 45 mL/minute/1.73 m^2, 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 m^2 *[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/minute/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart Metformin Hydrochloride Extended-Release Tablets if renal function is stable *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Metformin Hydrochloride Extended-Release Tablets are available as:

- *Extended-release tablets:* 500 mg white, film-coated, oval-shaped tablets with "M500" on one side.
- *Extended-release tablets:* 1,000 mg white, film-coated, oval-shaped tablets with "M1000" on one side.

4 CONTRAINDICATIONS

Metformin Hydrochloride Extended-Release Tablets are contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/minute/1.73 m^2) *[see Warnings and Precautions (5.1)]*.
- Known hypersensitivity to metformin.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis.

Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate/pyruvate ratio; metformin plasma levels 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 Tablets-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin. Metformin HCl is dialyzable, with a clearance of up to 170 mL/minute under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur, instruct them to discontinue 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) and 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/minute/1.73 m^2 *[see Contraindications (4)]*.
  - Initiation of Metformin Hydrochloride Extended-Release Tablets is not recommended in patients with eGFR between 30 to 45 mL/minute/1.73 m^2.
  - Obtain an eGFR at least annually in all patients taking Metformin Hydrochloride Extended-Release Tablets. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
  - In patients taking Metformin Hydrochloride Extended-Release Tablets whose eGFR later falls below 45 mL/minute/1.73 m^2, 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)]*. Therefore, consider more frequent monitoring of patients.
- *Age 65 or Greater:* The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients *[see Use in Specific Populations (8.5)]*.
- *Radiological Studies with Contrast:* Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop 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/minute/1.73 m^2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart 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 also cause prerenal azotemia. When such events occur, discontinue Metformin Hydrochloride Extended-Release Tablets.
- *Excessive Alcohol Intake:* Alcohol potentiates the effect of metformin on lactate metabolism, and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving 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 B_{12} Deficiency

In clinical trials of 29-week duration with metformin HCl tablets, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. Measure hematologic parameters on an annual basis and vitamin B_{12} at 2 to 3 year intervals in patients on 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 discussed in more detail in other sections of the labeling:

- Lactic Acidosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Vitamin B_{12} Deficiency *[see Warnings and Precautions (5.2)]*
- Hypoglycemia *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials 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 clinical trials conducted in the U.S., over 1,000 patients with type 2 diabetes mellitus have been treated with Metformin Hydrochloride Extended-Release Tablets 1,500 to 2,000 mg/day in active-controlled and placebo-controlled studies with the 500 mg dosage form.

In the add-on to sulfonylurea study, patients receiving background glyburide therapy were randomized to receive either Metformin Hydrochloride Extended-Release Tablets or one of three different regimens of Metformin Hydrochloride Extended-Release Tablets or placebo. In total, 431 patients received Metformin Hydrochloride Extended-Release Tablets and glyburide and 144 patients received placebo and glyburide. Adverse reactions reported in greater than 5% of patients treated with Metformin Hydrochloride Extended-Release Tablets that were more common in the combined Metformin Hydrochloride Extended-Release Tablets and glyburide group than in the placebo and glyburide group are shown in Table 1. In 0.7% of patients treated with Metformin Hydrochloride Extended-Release Tablets and glyburide, diarrhea was responsible for discontinuation of study medication compared to no patients in the placebo and glyburide group.

Table 1: Adverse Reactions Reported by >5%* of Patients for the Combined Metformin Hydrochloride Extended-Release Tablets Groups Versus Placebo Group

Adverse Reaction	Metformin Hydrochloride Extended-Release Tablets + Glyburide (n=431)	Placebo + Glyburide (n=144)
Hypoglycemia	14%	5%
Diarrhea	13%	6%
Nausea	7%	4%

*Adverse reactions that were more common in the Metformin Hydrochloride Extended-Release Tablets-treated than in the placebo-treated patients.

Laboratory Tests

Vitamin B_{12} Concentrations
In clinical trials of 29-week duration with metformin HCl tablets, a decrease to subnormal levels of previously normal serum vitamin B_{12} 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 Hydrochloride Extended-Release Tablets. 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

Carbonic Anhydrase Inhibitors	
Clinical Impact:	Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with Metformin Hydrochloride Extended-Release Tablets may increase the risk for lactic acidosis.
Intervention:	Consider more frequent monitoring of these patients.
Examples:	Topiramate, zonisamide, acetazolamide or dichlorphenamide.
Drugs that Reduce Metformin Hydrochloride Extended-Release Tablets Clearance	
Clinical Impact:	Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [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)]*.
Intervention:	Consider the benefits and risks of concomitant use with Metformin Hydrochloride Extended-Release Tablets.
Examples:	Ranolazine, vandetanib, dolutegravir, and cimetidine.
Alcohol	
Clinical Impact:	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
Intervention:	Warn patients against excessive alcohol intake while receiving Metformin Hydrochloride Extended-Release Tablets.
Insulin Secretagogues or Insulin	
Clinical Impact:	Coadministration of Metformin Hydrochloride Extended-Release Tablets with an insulin secretagogue (e.g., sulfonylurea) or insulin may increase the risk of hypoglycemia.
Intervention:	Patients receiving an insulin secretagogue or insulin may require lower doses of the insulin secretagogue or insulin.
Drugs Affecting Glycemic Control	
Clinical Impact:	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control.
Intervention:	When such drugs are administered to a patient receiving 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.
Examples:	Thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Limited data with Metformin 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 3 and 1 times, respectively, a 2,000 mg clinical dose, based on body surface area *[see Data]*.
The estimated background risk of major birth defects is 6–10% in women with pregestational diabetes mellitus with an HbA1c >7 and has been reported to be as high as 20–25% 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 2–4% and 15–20%, respectively.

METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS
500 mg and 1000 mg
9619003 20002705 Rev. 08/2019

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PATIENT INFORMATION
Metformin Hydrochloride
Extended-Release Tablets, for oral use

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 buildup of lactic acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.
Stop taking Metformin Hydrochloride Extended-Release Tablets and call your doctor right away if you get any of the following symptoms of lactic acidosis:

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

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.
- 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 or other procedure for which you need to restrict the amount of food and liquid you eat and drink.
- have congestive heart failure.
- have a heart attack, severe infection, or stroke.
- are 65 years of age or older.

Tell your doctor if you have any of the problems in the list above.
Tell your doctor that you are taking Metformin Hydrochloride Extended-Release Tablets before you have surgery or x-ray tests. Your doctor 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.

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 doctor about all of 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.
- 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 can harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are 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 Hydrochloride Extended-Release Tablets can pass into your breast milk. Talk with your doctor about the best way to feed your baby while you take Metformin Hydrochloride Extended-Release Tablets.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Know the medicines you take. Keep a list of them to show your doctor and pharmacist. Talk to your doctor before you start any new medicine.
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 doctor tells you.
- Metformin Hydrochloride Extended-Release Tablets should be taken 1 time each day with your evening meal 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 Metformin Hydrochloride Extended-Release Tablets. This is normal and will not affect the way Metformin Hydrochloride Extended-Release Tablets work.
- When your body is under some type of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these problems.
- Your doctor should do blood tests to check how well your kidneys are working before and during your treatment with Metformin Hydrochloride Extended-Release Tablets.
- Your doctor 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 doctor 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 doctor tells you to.
- Stay on your prescribed diet and exercise program while taking Metformin Hydrochloride Extended-Release Tablets.
- If you miss a dose of Metformin Hydrochloride Extended-Release Tablets, take your next dose at the normal schedule. Do not take 2 doses of Metformin Hydrochloride Extended-Release Tablets on the same day.
- If you take too much Metformin Hydrochloride Extended-Release Tablets, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking 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 can cause serious side effects, including:

- See **"What is the most important information I should know about Metformin Hydrochloride Extended-Release Tablets?".**
- **Low vitamin B_{12} (vitamin B_{12} deficiency).** Using Metformin Hydrochloride Extended-Release Tablets may cause a decrease in the amount of vitamin B_{12} in your blood, especially if you have had low vitamin B_{12} levels before. Your doctor may do blood tests to check your vitamin B_{12} levels.
- **Low blood sugar (hypoglycemia). Low blood sugar is a serious, but common, side effect of Metformin Hydrochloride Extended-Release Tablets.** If you take Metformin Hydrochloride Extended-Release Tablets with another medicine that can cause low blood sugar, such as sulfonylureas or insulin, you have a higher risk of getting low blood sugar. 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

The most common side effects of Metformin Hydrochloride Extended-Release Tablets include:

- diarrhea
- nausea

These are not all of 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 68°F to 77°F (20°C to 25°C).

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 you have. It may harm them. You can ask your pharmacist or doctor 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 Ingredient: metformin hydrochloride
Inactive Ingredient: 500 mg tablet: coloring, hypromellose, magnesium stearate, microcrystalline cellulose and polyethylene oxide. 1,000 mg tablet: colloidal silicon dioxide, polyvinyl alcohol, crospovidone, glyceryl behenate, polyacrylate dispersion, hypromellose, talc, polyethylene glycol, eudragit, titanium dioxide, simethicone emulsion, polysorbate and coloring.

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This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 08/2019

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 HCl was not teratogenic or embryolethal when administered to rats prior to pregnancy through the period of organogenesis at doses up to 900 mg/kg, or when administered to rabbits during the period of organogenesis at doses up to 90 mg/kg.

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

Clinical studies of Metformin Hydrochloride Extended-Release Tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. 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 Dosage and Administration (2.2) and 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/minute/1.73 m^2. *[see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3).]*

8.7 Hepatic Impairment

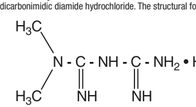
Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Metformin Hydrochloride Extended-Release Tablets are not recommended in patients with hepatic impairment. *[see Warnings and Precautions (5.1).]*

10 OVERDOSAGE

Overdose of metformin HCl has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin 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/minute 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 contain the biguanide antihyperglycemic agent metformin in the form of monohydrochloride salt. The chemical name of metformin hydrochloride is N,N-dimethylimidodicarbonimidic diamide hydrochloride. The structural formula is as shown:



Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

Metformin Hydrochloride Extended-Release Tablets contain 500 mg or 1,000 mg of metformin hydrochloride, which is equivalent to 389.93 mg or 779.86 mg metformin, respectively. Each 500 mg tablet contains coloring, hypromellose, magnesium stearate, microcrystalline cellulose and polyethylene oxide. Each 1,000 mg tablet contains colloidal silicon dioxide, polyvinyl alcohol, crospovidone, glyceryl behenate, polyacrylate dispersion, hypromellose, talc, polyethylene glycol, eudragit, titanium dioxide, simethicone emulsion, polysorbate and coloring.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

Absorption

Following a single oral dose of 1,000 mg (2x500 mg tablets) Metformin Hydrochloride Extended-Release Tablets after a meal, the time to reach maximum plasma metformin concentration (T_{max}) is achieved at approximately 7-8 hours. In both single- and multiple-dose studies in healthy subjects, once daily 1,000 mg (2x500 mg tablets) dosing provides equivalent systemic exposure, as measured by area under the curve (AUC), and up to 35% higher C_{max}, of metformin relative to the immediate-release given as 500 mg twice daily. At usual clinical doses and dosing schedules of metformin, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 mcg/mL. In a two-way, single-dose, crossover study in healthy volunteers, the 1,000 mg tablet was found to be similar to two 500 mg tablets under fed conditions based on equivalent C_{max} and AUCs for the two formulations.

Single oral doses of Metformin Hydrochloride Extended-Release Tablets from 500 mg to 2,500 mg resulted in less than proportional increase in both AUC and C_{max}.

Effect of food: Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from Metformin Hydrochloride Extended-Release Tablets by about 38% and 73%, respectively, relative to fasting. Both meals prolonged metformin T_{max} by approximately 3 hours but C_{max} was not affected.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg metformin HCl 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 healthy subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans), nor biliary excretion.

Excretion

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

Special Populations

Renal Impairment

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

Hepatic Impairment

No pharmacokinetic studies of Metformin Hydrochloride Extended-Release Tablets have been conducted in subjects 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 HCl in healthy elderly subjects suggest that total plasma clearance of metformin is decreased by 35%, the half-life is prolonged by 64% and C_{max} is increased by 76%, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function. *[see Dosage and Administration (2) and Warnings and Precautions (5.1).]*

Gender

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

Race

A trend towards 10% higher metformin C_{max} and AUC values for metformin are obtained in Asian subjects when compared to Caucasian, Hispanic and Black subjects. The differences between the Asian and Caucasian groups are unlikely to be clinically important. In controlled clinical studies of metformin HCl in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51) and Hispanics (n=24).

Pediatrics

There are no available pharmacokinetic data with Metformin Hydrochloride Extended-Release Tablets in pediatric patients.

Drug Interactions

Specific pharmacokinetic drug interaction studies with Metformin Hydrochloride Extended-Release Tablets have not been performed except for one with glyburide. However, such studies have been performed on metformin HCl tablets.

Table 3: Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug[1]	Dose of Metformin HCl[1]	Geometric Mean Ratio (ratio with/ without coadministered drug) No Effect=1.00	
			AUC[2]	C_{max}
No dosing adjustments required for the following:				
Glyburide	5 mg	500 mg[4]	0.98[3]	0.99[3]
Furosemide	40 mg	850 mg	1.09[3]	1.22[3]
Nifedipine	10 mg	850 mg	1.16	1.21
Propranolol	40 mg	850 mg	0.90	0.94
Ibuprofen	400 mg	850 mg	1.05[3]	1.07[3]
Cationic drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin: *[see Warnings and Precautions (5.1) and Drug Interactions (7)].*				
Cimetidine	400 mg	850 mg	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis: *[see Warnings and Precautions (5.1) and Drug Interactions (7)].*				
Topiramate	100 mg[5]	500 mg[5]	1.25[5]	1.17

1 All metformin HCl and coadministered drugs were given as single doses.
2 AUC=$AUC_{0-\infty}$
3 Ratio of arithmetic means
4 Metformin Hydrochloride Extended-Release Tablets 500 mg
5 At steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC=AUC_{0-12h}

Table 4: Effect of Metformin on Coadministered Drug Systemic Exposure

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies have been performed in Sprague Dawley rats at doses of 150, 300, and 450 mg/kg/day in males and 150, 450, 900, and 1,200 mg/kg/day in females. These doses are approximately 2, 4, and 8 times in males, and 3, 7, 12, and 16 times in females of the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female rats. A carcinogenicity study was also performed in Tg.AC transgenic mice at doses up to 2,000 mg applied dermally. No evidence of carcinogenicity was observed in male or female mice.

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

14 CLINICAL STUDIES

In a multicenter, randomized, double-blind, active-controlled, dose-ranging, parallel group study conducted in patients type 2 diabetes mellitus, Metformin Hydrochloride Extended-Release Tablets 1,500 mg once daily, Metformin Hydrochloride Extended-Release Tablets 1,500 per day in divided doses (500 mg in the morning and 1,000 mg in the evening), and Metformin Hydrochloride Extended-Release Tablets 2,000 mg once daily were compared to immediate-release metformin HCl tablets 1,500 mg per day in divided doses (500 mg in the morning and 1,000 mg in the evening). This study included patients (n=338) who were newly diagnosed with diabetes, patients treated only with diet and exercise, patients treated with a single antidiabetic medication (sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, or meglitinides), and patients (n=368) receiving metformin HCl tablets up to 1,500 mg/day plus a sulfonylurea at a dose equal to or less than one-half the maximum dose. Patients who were enrolled on monotherapy or combination antidiabetic therapy underwent a 6-week washout. Patients randomized to Metformin Hydrochloride Extended-Release Tablets began titration from 1,000 mg/day up to their assigned treatment dose over 3 weeks. Patients randomized to immediate-release metformin initiated 500 mg twice daily for 1 week followed by 500 mg with breakfast and 1,000 mg with dinner for the second week. The 3-week treatment period was followed by an additional 21-week period at the randomized dose. The results are presented in Table 5.

Table 5: Mean Changes from Baseline in HbA1c and Fasting Plasma Glucose at Week 24 Comparing Metformin Hydrochloride Extended-Release Tablets versus Metformin HCl Tablets* in Patients with Type 2 Diabetes Mellitus

	Metformin Hydrochloride Extended-Release Tablets			Metformin HCl Tablets* 1,500 mg in Divided Doses (n=174)
	1,500 mg Once Daily (n=178)	1,500 mg in Divided Doses (n=182)	2,000 mg Once Daily (n=172)	
HbA1c (%), N	169	175	159	170
Baseline	8.2	8.5	8.3	8.7
Mean Change at Final Visit	-0.7	-0.7	-1.1	-0.7
Mean Difference from Metformin HCl Tablets* (98.4% CI)	0 (-0.3, 0.3)	0 (-0.3, 0.3)	-0.4 (-0.7, -0.1)	N/A
Fasting Plasma Glucose (mg/dL), N	175	179	170	172
Baseline	190	192.3	184	197
Mean Change at Final Visit	-39	-32	-42	-32
Mean Difference from Metformin HCl Tablets* (95% CI)	-6 (-15, 2)	0 (-8, 9)	-10 (-19, -1)	N/A

*Immediate-release metformin HCl tablets

Mean baseline body weight was 88.2 kg, 90.5 kg, 87.7 kg and 88.7 kg in the Metformin Hydrochloride Extended-Release Tablets 1,500 mg once daily, Metformin Hydrochloride Extended-Release Tablets 1,500 mg in divided doses, Metformin Hydrochloride Extended-Release Tablets 2,000 mg once daily and metformin HCl tablets 1,500 mg in divided doses arms, respectively. Mean change in body weight from baseline to week 24 was -0.9 kg, -0.7 kg, -1.1 kg, and -0.9 kg in the Metformin Hydrochloride Extended-Release Tablets 1,500 mg once daily, Metformin Hydrochloride Extended-Release Tablets 1,500 mg in divided doses, Metformin Hydrochloride Extended-Release Tablets 2,000 mg once daily and metformin HCl tablets 1,500 mg in divided doses arms, respectively.

A double-blind, randomized, placebo-controlled (glyburide add-on) multicenter study enrolled patients with type 2 diabetes mellitus who were newly diagnosed or treated with diet and exercise (n=144), or who were receiving monotherapy with metformin, sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, or meglitinides, or treated with combination therapy consisting of metformin HCl/glyburide at doses up to 1,000 mg metformin + 10 mg glyburide per day (or equivalent doses of glipizide or glimepiride up to half the maximum therapeutic dose) (n=431).

All patients were stabilized on glyburide for a 6-week run-in period, and then randomized to 1 of 4 treatments: placebo + glyburide (glyburide alone); Metformin Hydrochloride Extended-Release Tablets 1,500 mg once a day + glyburide, Metformin Hydrochloride Extended-Release Tablets 2,000 mg once a day + glyburide, or Metformin Hydrochloride Extended-Release Tablets 1,000 mg twice a day + glyburide. A 3-week Metformin Hydrochloride Extended-Release Tablets titration period was followed by a 21-week maintenance treatment period. Use of insulin and oral hypoglycemic agents other than the study drugs were prohibited. The results are presented in Table 6.

Table 6: Mean Changes from Baseline in HbA1c and Fasting Plasma Glucose at Week 24 for the Metformin Hydrochloride Extended-Release Tablets + Glyburide Groups and Placebo+ Glyburide Treatment Group in Patients with Type 2 Diabetes Mellitus

	Metformin Hydrochloride Extended-Release Tablets + Glyburide*			Placebo + Glyburide*
	1,500 mg Once Daily (n=144)	1,000 mg Twice Daily (n=141)	2,000 mg Once Daily (n=146)	(n=144)
HbA1c (%), N	136	136	144	141
Baseline	7.9	7.8	7.7	8.1
Mean Change at Final Visit	-0.7	-0.8	-0.7	-0.1
Mean Difference from Glyburide Alone (95% CI)	-0.8[a] (-1.0, -0.6)	-0.9[a] (-1.1, -0.7)	-0.8[a] (-1.0, -0.6)	N/A
Fasting Plasma Glucose (mg/dL), N	143	141	145	144
Baseline	163	163	159	164
Mean Change at Final Visit	-14	-16	-9	16
Mean Difference from Glyburide Alone (95% CI)	-29.2[a] (-39, -20)	-31.2[a] (-41, -22)	-24.9[a] (-35, -15)	N/A

*Glyburide was administered as 10 mg at breakfast and 5 mg at dinner.
[a] p-value for pairwise comparison <0.001

Mean baseline body weight was 89.4 kg, 103.7 kg, 102.9 kg and 95.6 kg in the Metformin Hydrochloride Extended-Release Tablets 1,500 mg once daily, Metformin Hydrochloride Extended-Release Tablets 1,500 mg in divided doses, Metformin Hydrochloride Extended-Release Tablets 2,000 mg once daily and metformin HCl tablets 1,500 mg in divided doses arms, respectively. Mean change in body weight from baseline to week 24 was 0.3 kg, 0.1 kg, 0 kg, and 0.7 kg in the Metformin Hydrochloride Extended-Release Tablets 1,500 mg once daily, Metformin Hydrochloride Extended-Release Tablets 1,500 mg in divided doses, Metformin Hydrochloride Extended-Release Tablets 2,000 mg once daily and metformin HCl tablets 1,500 mg in divided doses arms, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

Metformin Hydrochloride Extended-Release Tablets are supplied as:

500 mg	Bottles of 100	NDC 68682-021-50	white, film-coated, oval-shaped, extended-release tablets with "M500" on one side.
1,000 mg	Bottles of 90	NDC 68682-018-90	white, film-coated, oval-shaped, extended-release tablets with "M1000" on one side.

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

17 PATIENT COUNSELING INFORMATION

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

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 B_{12} 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.

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