METFORMIN HYDROCHLORIDE- metformin hydrochloride tablets tablet, film coated, extended release

EPIC PHARMA, LLC

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.

Initial U.S. Approval: 1995

WARNING: LACTIC ACIDOSIS

See full prescribing information for complete boxed warning.

INDICATIONS AND USAGE

Metformin hydrochloride extended-release tablets are 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 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

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 (2.2)
  - Initiation is not recommended in patients with eGFR between 30 to 45 mL/minute/1.73 m^2 (2.2)
  - Assess risk/benefit of continuing if eGFR falls below 45 mL/minute/1.73 m^2 (2.2)
  - Discontinue if eGFR falls below 30 mL/minute/1.73 m^2 (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 1,000 mg (3)

CONTRAINDICATIONS

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2) (4, 5.1)
- Hypersensitivity to metformin (4)
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. (4)

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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 Epic Pharma, LLC at 1-888-374-2791 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: 3/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

Post-marketing 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 2,000 mg once daily with the evening meal.
- If glycemic control is not achieved with metformin hydrochloride extended-release tablets 2,000

mg once daily, consider a trial of metformin hydrochloride extended-release tablets 1,000 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 2,000 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 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/min/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/min/1.73 m^2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin hydrochloride extended-release tablets if renal function is stable.

3 DOSAGE FORMS AND STRENGTHS

Metformin hydrochloride extended-release tablets are available as:

- *Extended-release tablets:* 500 mg white-colored, unscored tablets imprinted with 0019 500 on one side.
- *Extended-release tablets:* 1,000 mg white-colored, unscored tablets imprinted with 0018 1000 on one side.

4 CONTRAINDICATIONS

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metforminassociated 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 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/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 m^2 *[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 m^2.
  - 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 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)]. 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 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 also discussed elsewhere in the labeling:

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

6.1 Clinical Studies Experience

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

In placebo-controlled trials, 781 patients were administered metformin HCl extended-release tablets. Adverse reactions reported in greater than 5% of the patients treated with metformin HCl 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 HCl Extended-Release Tablets Occurring >5% and More Common than Placebo in Patients with Type 2 Diabetes Mellitus

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

Diarrhea led to the discontinuation of metformin HCl 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 HCl 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_{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. 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 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 a HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly-controlled diabetes mellitus in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, 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 post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Metformin HCl 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 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)]*.

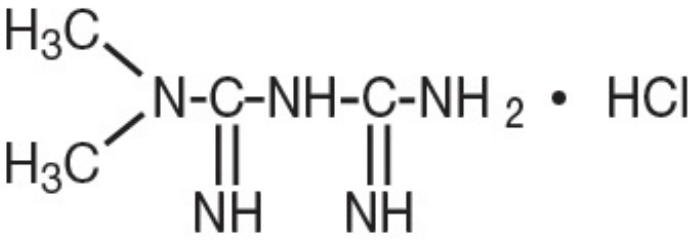
10 OVERDOSAGE

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/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 contain the biguanidine antihyperglycemic agent, metformin, in the form of monohydrochloride salt. The chemical name of metformin HCl is N, N-dimethylimidodicarbonimidic diamide hydrochloride with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63. Its structural formula is:



Metformin HCl is a white or almost white crystals powder that 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 HCl is 6.68.

Metformin hydrochloride extended-release tablets deliver 500 mg or 1,000 mg of metformin HCl, which is equivalent to 389.93 mg or 779.86 mg metformin, respectively. In addition to the active ingredient metformin HCl, each tablet contains the following inactive ingredients: Povidone, Sodium Lauryl Sulfate, Magnesium Stearate, Cellulose Acetate, Polyethylene Glycol (PEG 400, PEG 8000), Triacetin, Hypromellose, Titanium Dioxide, Polysorbate 80, Ferrosoferric Oxide, Shellac.

Metformin Meets USP Dissolution Test 5.

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 2,000 mg once a day (after dinner) or metformin HCl tablets 1,000 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_{max}), and maximum concentration (C_{max}) were evaluated. The appearance of metformin in plasma from metformin hydrochloride extended-release tablets is slower and more prolonged compared to metformin HCl tablets. Results are presented in **Table 3**.

Table 3 Metformin Hydrochloride Extended-Release Tablets vs. Metformin HCl Tablets Steady-State Pharmacokinetic Parameters at 4 Weeks		
Pharmacokinetic Parameters (mean ± SD)	**Metformin Hydrochloride Extended-Release Tablets 2,000 mg (administered q.d. after dinner)**	**Metformin HCl tablets* 2,000 mg (1,000 mg b.i.d.)**
AUC_{0-24hr} (ng•hr/mL)	26,811 ± 7055	27,371 ± 5,781
T_{max} (hr)	6 (3-10)	3 (1-8)
C_{max} (ng/mL)	2849 ± 797	1820 ± 370

*Immediate-release metformin HCl tablets

In four single-dose studies and one multiple-dose study, the bioavailability of metformin hydrochloride extended-release tablets 2,000 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 HCl tablets 1,000 mg given twice daily. The geometric mean ratios (metformin hydrochloride extended-release tablets / metformin HCL tablets) of $AUC0_{-24hr}$, 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 1,000 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 1,000 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 1,000, 1,500, 2,000, and 2,500 mg.

In three studies with metformin hydrochloride extended-release tablets using different treatment regimens (2,000 mg after dinner; 1,000 mg after breakfast and after dinner; and 2,500 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 HCl 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 HCl 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) *[seeWarnings 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 HCl Tablets

Subject Groups: Metformin HCl dose[a] (number of subjects)	**C_{max}[b] (mcg/mL)**	**T_{max}[c] (hrs)**	**Renal Clearance (mL/min)**
Healthy, nondiabetic adults:			
500 mg single dose (24)	1.03 (±0.33)	2.75 (±0.81)	600 (±132)
850 mg single dose (74)[d]	1.60 (±0.38)	2.64 (±0.82)	552 (±139)
850 mg three times daily for 19 doses[e] (9)	2.01 (±0.42)	1.79 (±0.94)	642 (±173)
Adults with type 2 diabetes mellitus:			
850 mg single dose (23)	1.48 (±0.5)	3.32 (±1.08)	491 (±138)
850 mg three times daily for 19 doses[e] (9)	1.90 (±0.62)	2.01 (±1.22)	550 (±160)
Elderly[f], healthy nondiabetic adults:			
850 mg single dose (12)	2.45 (±0.70)	2.71 (±1.05)	412 (±98)
Renal-impaired adults:			
850 mg single dose	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Mild (CLcrg 61 to 90 mL/min) (5)	4.12 (±1.83)	3.75 (±0.50)	108 (±57)
Moderate (CLcr 31 to 60 mL/min) (4)	3.93 (±0.92)	4.01 (±1.10)	130 (±90)
Severe (CLcr 10 to 30 mL/min) (6)			

[a] All doses given fasting except the first 18 doses of the multiple dose studies

[b] Peak plasma concentration

[c] Time to peak plasma concentration

[d] Combined results (average means) of five studies: mean age 32 years (range 23 to 59 years)

[e] Kinetic study done following dose 19, given fasting

[f] Elderly subjects, mean age 71 years (range 65 to 81 years)

[g] CLcr = creatinine clearance normalized to body surface area of 1.73 m^2

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 5: Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	**Dose of Coadministered Drug***	**Dose of Metformin HCl***	**Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00**		
				AUC†	**C_{max}**
No dosing adjustments required for the following:					
Glyburide	5 mg	850 mg	metformin	0.91‡	0.93‡
Furosemide	40 mg	850 mg	metformin	1.09‡	1.22‡
Nifedipine	10 mg	850 mg	metformin	1.16	1.21
Propranolol	40 mg	850 mg	metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	metformin	1.05‡	1.07‡
Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination *[see Warnings and Precautions (5.1) and Drug Interactions (7).]*					
Cimetidine	400 mg	850 mg	metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis *[see Warnings and Precautions (5.1) and Drug Interactions (7).]*					
Topiramate	100 mg§	500 mg§	metformin	1.25§	1.17

* All metformin HCl and coadministered drugs were given as single doses

† AUC = AUC_{inf}

‡ Ratio of arithmetic means

§ At steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours;

AUC = AUC_{0-12h}

Table 6: Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	**Dose of Coadministered**	**Dose of Metformin**	**Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00**

Drug	Drug*	HCl*	No Effect = 1.00		
				AUC†	C_{max}
No dosing adjustments required for the following:					
Glyburide	5 mg	850 mg	Glyburide	0.78‡	0.63‡
Furosemide	40 mg	850 mg	Furosemide	0.87‡	0.69‡
Nifedipine	10 mg	850 mg	Nifedipine	1.10§	1.08
Propranolol	40 mg	850 mg	Propranolol	1.01§	1.02
Ibuprofen	400 mg	850 mg	Ibuprofen	0.97¶	1.01¶
Cimetidine	400 mg	850 mg	Cimetidine	0.95§	1.01

* All metformin HCl and coadministered drugs were given as single doses

† AUC = AUC_{inf} unless otherwise noted

‡ Ratio of arithmetic means, p-value of difference <0.05

§ $AUC_{0\text{-}24\ hr}$ reported

¶ Ratio of arithmetic means

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1,500 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 HCl 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_{1c} of 8.0% and a mean baseline FPG of 176 mg/dL. The treatment dose was increased to 1,500 mg once daily if at Week 12 HbA_{1c} was 7.0% but <8.0% (patients with HbA_{1c} 8.0% were discontinued from the study). At the final visit (24-week), mean HbA1c had increased 0.2% from baseline in placebo patients and decreased 0.6% with metformin HCl extended-release tablets.

A 16-week, double-blind, placebo-controlled, dose-response study of metformin HCl 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 7: Mean Changes from Baseline* in HbA1c and Fasting Plasma Glucose at Week 16 Comparing Metformin HCl Extended-Release Tablets vs Placebo in Patients with Type 2

Diabetes Mellitus

	Metformin HCl Extended-Release Tablets					Placebo
	500 mg Once Daily	1,000 mg Once Daily	1,500 mg Once Daily	2,000 mg Once Daily	1,000 mg Twice Daily	
Hemoglobin A_{1c} (%)						
Baseline	**(n=115)** 8.2	**(n=115)** 8.4	**(n=111)** 8.3	**(n=125)** 8.4	**(n=112)** 8.4	**(n=111)** 8.4
Change at FINAL VISIT	–0.4	–0.6	–0.9	–0.8	–1.1	0.1
p-value[a]	<0.001	<0.001	<0.001	<0.001	<0.001	–
FPG (mg/dL)						
Baseline	**(n=126)** 182.7	**(n=118)** 183.7	**(n=120)** 178.9	**(n=132)** 181.0	**(n=122)** 181.6	**(n=113)** 179.6
Change at FINAL VISIT	–15.2	–19.3	–28.5	–29.9	–33.6	7.6
p-value[a]	<0.001	<0.001	<0.001	<0.001	<0.001	–

[a] All comparisons versus Placebo

Mean baseline body weight was 193 lbs, 192 lbs, 188 lbs, 196 lbs, 193 lbs and 194 lbs in the metformin HCl extended-release tablets 500 mg, 1,000 mg, 1,500 mg, and 2,000 mg once daily, 1,000 mg twice daily and placebo arms, respectively. Mean change in body weight from baseline to week 16 was -1.3 lbs, -1.3 lbs, -0.7 lbs, -1.5 lbs, -2.2 lbs and -1.8 lbs, respectively.

A 24-week, double-blind, randomized study of metformin HCl extended-release tablets, taken once daily with the evening meal, and metformin HCl tablets, taken twice daily (with breakfast and evening meal), was conducted in patients with type 2 diabetes mellitus who had been treated with metformin HCl 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_{1c} and Fasting Plasma Glucose at Week 24 Comparing Metformin HCl Extended-Release vs Metformin HCl in Patients with Type 2 Diabetes Mellitus

	Metformin HCl 500 mg Twice Daily	Metformin HCl Extended-Release	
		1,000 mg Once Daily	1,500 mg Once Daily
Hemoglobin A_{1c} (%)	**(n=67)** 7.06	**(n=72)** 6.99	**(n=66)** 7.02
Baseline	0.14a	0.27	0.13
Change at FINAL VISIT (95% CI)	(–0.04, 0.31)	(0.11, 0.43)	(–0.02, 0.28)
FPG (mg/dL)	**(n=69)** 127.2	**(n=72)** 131.0	**(n=70)** 131.4
Baseline	14.0	11.5	7.6
Change at FINAL VISIT	(7.0, 21.0)	(4.4, 18.6)	(1.0, 14.2)

(95% CI)			

†a n=68

Mean baseline body weight was 210 lbs, 203 lbs and 193 lbs in the metformin HCl tablets 500 mg twice daily, and metformin HCl extended-release tablets 1,000 mg and 1,500 mg once daily arms, respectively. Mean change in body weight from baseline to week 24 was 0.9 lbs, 1.1 lbs and 0.9 lbs, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Metformin hydrochloride extended-release tablets are supplied as:

500 mg	Bottles of 60	NDC 42806-405-60	white-colored, unscored biconvex-shaped, film-coated extended-release tablets imprinted with 0019 500 on one side.
1,000 mg	Bottles of 60	NDC 42806-406-60	white-colored, unscored biconvex-shaped, film-coated extended-release tablets imprinted with 0018 1000 on one side.

16.2 Storage

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature] excursions permitted to 15° to 30°C (59° to 86°F). Avoid excessive heat and humidity.

Keep tightly closed (protect from moisture). Protect from light.

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.

Manufactured by:

Qingdao BAHEAL Pharmaceutical Co., Ltd.

NO.268 Yingcheng Road, Jimo, Qingdao PR China

Distributed by:

Epic Pharma LLC

Laurelton, NY 11413

Rev. 02/19

Patient Medication Information

PATIENT INFORMATION
Metformin hydrochloride
extended-release tablets

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 usual
- have unusual (not normal) muscle pain
- feel cold, especially in your arms and legs
- have trouble breathing
- feel dizzy or lightheaded
- have unexplained stomach or intestinal problems with nausea and vomiting, or diarrhea
- 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.
- 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 "W**hat are the possible side effects of metformin hydrochloride extended-release tablets?"**

What are metformin hydrochloride extended-release tablets?

- Metformin hydrochloride extended-release tablets are prescription medicine that contain 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 HCl 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.
- 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 hydrochloride extended-release tablets 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.

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 metformin hydrochloride extended-release tablets. This is not harmful and will not affect the way metformin hydrochloride extended-release tablets works.
- 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 much 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?
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 B_{12} (vitamin B_{12} deficiency).** Using metformin hydrochloride extendedrelease 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
- hunger
- dizziness
- drowsiness
- fast heartbeat
- sweating
- weakness
- confusion
- irritability
- shaking or feeling jittery

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

- diarrhea
- stomach-area (abdominal) pain and swelling
- nausea and vomiting
- headache
- gassiness (flatulence)
- taste disturbance (unpleasant metallic taste)
- indigestion

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 68°F to 77°F (20°C to 25°C). 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 it was not prescribed. Do not give metformin hydrochloride extendedrelease tablets to other people, even if they have the same symptoms that you have. It 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: Povidone, Sodium Lauryl Sulfate, Magnesium Stearate, Cellulose Acetate, Polyethylene Glycol (PEG 400, PEG 8000), Triacetin, Hypromellose, Titanium Dioxide, Polysorbate 80, Ferrosoferric Oxide, Shellac.

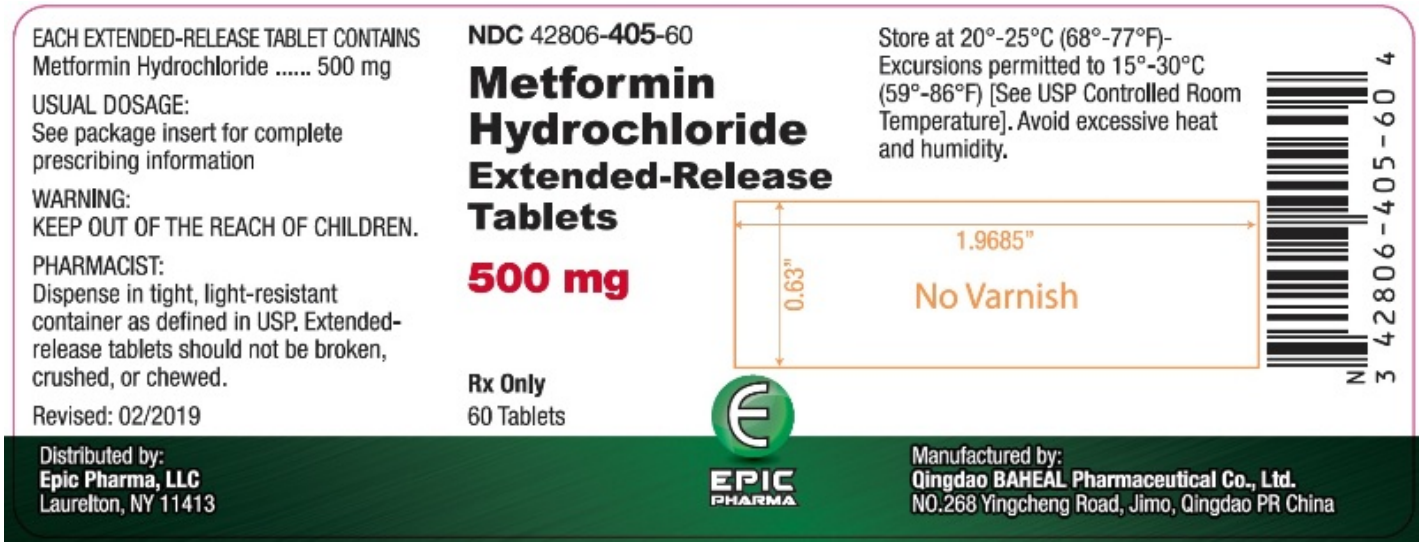
Manufactured by:

Qingdao BAHEAL Pharmaceutical Co., Ltd.

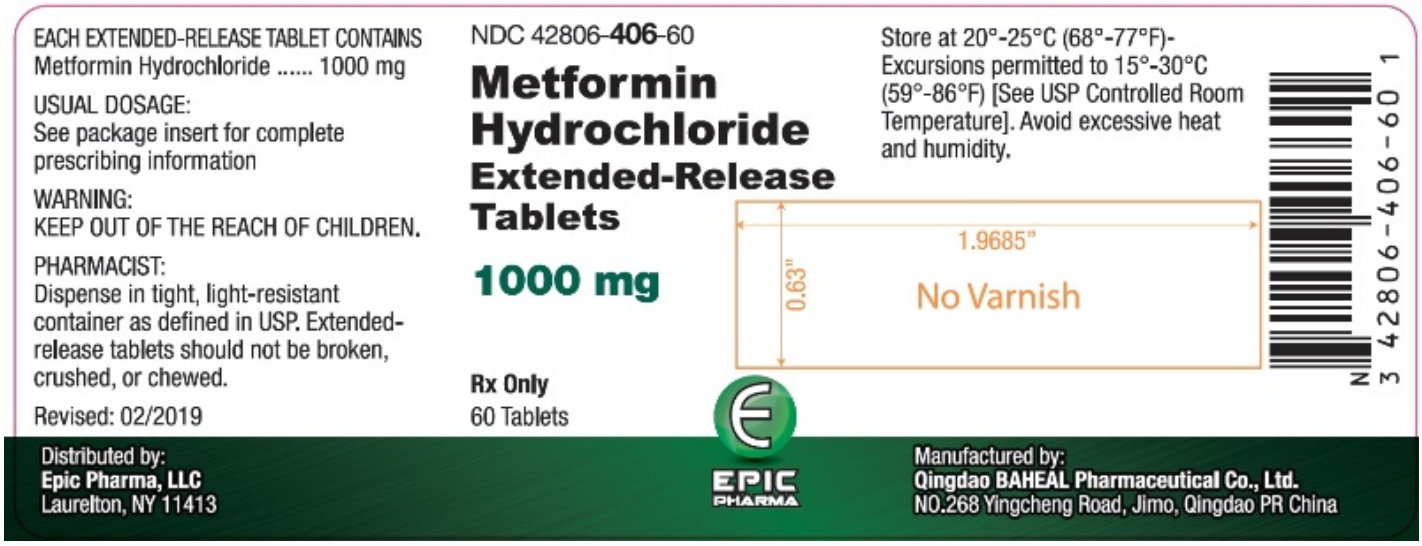
NO.268 Yingcheng Road, Jimo, Qingdao PR China

Distributed by:
Epic Pharma LLC
Laurelton, NY 11413
Rev. 02/19

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL – Metformin 500 mg 60ct



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL – Metformin 1000 mg 60ct



METFORMIN HYDROCHLORIDE

metformin hydrochloride tablets tablet, film coated, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:42806-405
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
METFORMIN HYDROCHLORIDE (UNII: 786Z46389E) (METFORMIN - UNII:9100L32L2N)	METFORMIN HYDROCHLORIDE	500 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ACETONE (UNII: 1364PS73AF)	
CELLULOSE ACETATE (UNII: 3J2P07GVB6)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SHELLAC (UNII: 46N107B71O)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIACETIN (UNII: XHX3C3X673)	

Product Characteristics			
Color	WHITE	**Score**	no score
Shape	ROUND	**Size**	12mm
Flavor		**Imprint Code**	0019;500
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:42806-405-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	01/04/2019	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA209993	01/04/2019	

METFORMIN HYDROCHLORIDE

metformin hydrochloride tablet tablet, film coated, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:42806-406
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
METFORMIN HYDROCHLORIDE (UNII: 786Z46389E) (METFORMIN - UNII:9100L32L2N)	METFORMIN HYDROCHLORIDE	1000 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ACETONE (UNII: 1364PS73AF)	
CELLULOSE ACETATE (UNII: 3J2P07GVB6)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SHELLAC (UNII: 46N107B71O)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIACETIN (UNII: XHX3C3X673)	

Product Characteristics			
Color	WHITE	**Score**	2 pieces
Shape	ROUND	**Size**	13mm
Flavor		**Imprint Code**	;0018;1000;
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:42806-406-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	01/04/2019	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA209993	01/04/2019	

Labeler - EPIC PHARMA, LLC (827915443)

Registrant - Qingdao BAHEAL Pharmaceutical Co., Ltd. (546626586)

Establishment

Name	Address	ID/FEI	Business Operations

Qingdao BAHEAL Pharmaceutical Co., Ltd.		546626586	MANUFACTURE(42806-405, 42806-406)