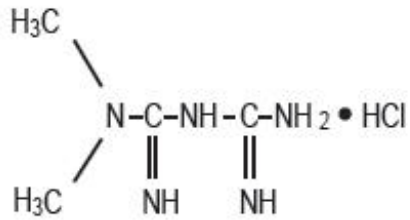
METFORMIN HYDROCHLORIDE- metformin hydrochloride tablet, extended release
Denton Pharma, Inc. DBA Northwind Pharmaceuticals

Metformin Hydrochloride Extended-Release Tablets, USP

Rx only

DESCRIPTION

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



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

Metformin hydrochloride extended-release tablets, USP contain 500 mg or 750 mg of metformin hydrochloride as the active ingredient. In addition, each tablet contains the following inactive ingredients: copovidone, carboxymethylcellulose sodium, hypromellose, microcrystalline cellulose and magnesium stearate.

The USP dissolution test is pending.

CLINICAL PHARMACOLOGY

Mechanism of Action

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see **PRECAUTIONS**) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacokinetics

Absorption and Bioavailability

Following a single oral dose of metformin hydrochloride extended-release tablets, C_{max} is achieved with a median value of 7 hours and a range of 4 to 8 hours. Peak plasma levels are approximately 20%

lower compared to the same dose of metformin hydrochloride tablets, however, the extent of absorption (as measured by AUC) is similar to metformin hydrochloride tablets.

At steady state, the AUC and C_{max} are less than dose proportional for metformin hydrochloride extended-release tablets within the range of 500 to 2,000 mg administered once daily. Peak plasma levels are approximately 0.6, 1.1, 1.4, and 1.8 mcg/mL for 500, 1,000, 1,500, and 2,000 mg once-daily doses, respectively. The extent of metformin absorption (as measured by AUC) from metformin hydrochloride extended-release tablets at a 2,000 mg once-daily dose is similar to the same total daily dose administered as metformin hydrochloride tablets 1,000 mg twice daily. After repeated administration of metformin hydrochloride extended-release tablets, metformin did not accumulate in plasma.

Within-subject variability in C_{max} and AUC of metformin from metformin hydrochloride extended-release tablets is comparable to that with metformin hydrochloride tablets.

Although the extent of metformin absorption (as measured by AUC) from the metformin hydrochloride extended-release tablets increased by approximately 50% when given with food, there was no effect of food on C_{max} and T_{max} of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of metformin hydrochloride extended-release tablets.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady state plasma concentrations of metformin are reached within 24 to 48 hours and are generally < 1 mcg/mL. During controlled clinical trials of metformin hydrochloride tablets, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism and Elimination

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. Renal clearance (see **Table 1**) 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

Patients with Type 2 Diabetes

In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects (see **Table 1**), nor is there any accumulation of metformin in either group at usual clinical doses.

The pharmacokinetics of metformin hydrochloride extended-release tablets in patients with type 2 diabetes are comparable to those in healthy normal adults.

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 1**; also see **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **DOSAGE AND ADMINISTRATION**).

Hepatic Impairment

No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency (see **PRECAUTIONS**).

Geriatrics

Limited data from controlled pharmacokinetic studies of metformin hydrochloride tablets in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see **Table 1**; also see **WARNINGS, PRECAUTIONS,** and **DOSAGE AND ADMINISTRATION**).

Table 1: Select Mean (± S.D.) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of Metformin Hydrochloride Tablets

Subject Groups: Metformin Hydrochloride Tablets Dose * (number of subjects)	**C_{max}† (mcg/mL)**	**T_{max}‡ (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) §	1.60 (± 0.38)	2.64 (± 0.82)	552 (± 139)
850 mg three times daily for 19 doses ¶ (9)	2.01 (± 0.42)	1.79 (± 0.94)	642 (± 173)
Adults with type 2 diabetes:			
850 mg single dose (23)	1.48 (± 0.5)	3.32 (± 1.08)	491 (± 138)
850 mg three times daily for 19 doses ¶ (9)	1.90 (± 0.62)	2.01 (± 1.22)	550 (± 160)
Elderly #, 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**			
Mild (CL_{cr}Þ 61 to 90 mL/min) (5)	1.86 (± 0.52)	3.20 (± 0.45)	384 (± 122)
Moderate (CL_{cr} 31 to 60 mL/min) (4)	4.12 (± 1.83)	3.75 (± 0.50)	108 (± 57)
Severe (CL_{cr} 10 to 30 mL/min) (6)	3.93 (± 0.92)	4.01 (± 1.10)	130 (± 90)

* All doses given fasting except the first 18 doses of the multiple dose studies

† Peak plasma concentration

‡ Time to peak plasma concentration

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

¶ Kinetic study done following dose 19, given fasting

\# Elderly subjects, mean age 71 years (range 65 to 81 years)

Þ CL cr = creatinine clearance normalized to body surface area of 1.73 m 2

Pediatrics

After administration of a single oral metformin hydrochloride 500 mg tablet with food, geometric mean metformin C_{max} and AUC differed less than 5% between pediatric type 2 diabetic patients (12 to 16 years of age) and gender- and weight-matched healthy adults (20 to 45 years of age), all with normal renal function.

Gender

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender (males = 19, females = 16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin hydrochloride tablets was comparable in males and females.

Race

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin hydrochloride tablets in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n = 249), blacks (n = 51), and Hispanics (n = 24).

Clinical Studies

Metformin Hydrochloride Extended-Release Tablets

A 24-week, double-blind, placebo-controlled study of metformin hydrochloride extended-release tablets, taken once daily with the evening meal, was conducted in patients with type 2 diabetes who had failed to achieve glycemic control with diet and exercise (HbA $_{1C}$ 7.0% to 10.0%, FPG 126 to 270 mg/dL). Patients entering the study had a mean baseline HbA $_{1C}$ of 8.0% and a mean baseline FPG of 176 mg/dL. After 12 weeks treatment, mean HbA $_{1C}$ had increased from baseline by 0.1% and mean FPG decreased from baseline by 2 mg/dL in the placebo group, compared with a decrease in mean HbA $_{1C}$ of 0.6% and a decrease in mean FPG of 23 mg/dL in patients treated with metformin hydrochloride extended-release tablets 1,000 mg once daily. Subsequently, the treatment dose was increased to 1,500 mg once daily if 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 HbA $_{1C}$ had increased 0.2% from baseline in placebo patients and decreased 0.6% with metformin hydrochloride extended-release tablets.

A 16-week, double-blind, placebo-controlled, dose-response study of metformin hydrochloride extended-release tablets, taken once daily with the evening meal or twice daily with meals, was conducted in patients with type 2 diabetes who had failed to achieve glycemic control with diet and exercise (HbA $_{1C}$ 7.0% to 11.0%, FPG 126 to 280 mg/dL). Changes in glycemic control and body weight are shown in **Table 2**.

Table 2: Summary of Mean Changes from Baseline * in HbA $_{1C}$, Fasting Plasma Glucose, and Body Weight at Final Visit (16-week study)

	Metformin Hydrochloride 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 $_{1C}$ (%)	**(n = 115)**	**(n = 115)**	**(n = 111)**	**(n = 125)**	**(n = 112)**	**(n = 111)**
Baseline	8.2	8.4	8.3	8.4	8.4	8.4
Change at FINAL VISIT	-0.4	-0.6	-0.9	-0.8	-1.1	0.1
p-value †	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	-
FPG (mg/dL)	**(n = 126)**	**(n = 118)**	**(n = 120)**	**(n = 132)**	**(n = 122)**	**(n = 113)**
Baseline	182.7	183.7	178.9	181.0	181.6	179.6
Change at FINAL	-15.2	-19.3	-28.5	-29.9	-33.6	-7.6

VISIT	-15.2	-19.3	-28.5	-29.9	-33.6	7.6
p-value †	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	-
Body Weight (lbs)	**(n = 125)**	**(n = 119)**	**(n = 117)**	**(n = 131)**	**(n = 119)**	**(n = 113)**
Baseline	192.9	191.8	188.3	195.4	192.5	194.3
Change at FINAL VISIT	-1.3	-1.3	-0.7	-1.5	-2.2	-1.8
p-value †	NS ‡	NS ‡	NS ‡	NS ‡	NS ‡	-

* All patients on diet therapy at Baseline

† All comparisons versus Placebo

‡ Not statistically significant

Compared with placebo, improvement in glycemic control was seen at all dose levels of metformin hydrochloride extended-release tablets and treatment was not associated with any significant change in weight (see **DOSAGE AND ADMINISTRATION** for dosing recommendations for metformin hydrochloride extended-release tablets).

A 24-week, double-blind, randomized study of metformin hydrochloride extended-release tablets, taken once daily with the evening meal, and metformin hydrochloride tablets, taken twice daily (with breakfast and evening meal), was conducted in patients with type 2 diabetes who had been treated with metformin hydrochloride tablets 500 mg twice daily for at least 8 weeks prior to study entry. The metformin hydrochloride tablets dose had not necessarily been titrated to achieve a specific level of glycemic control prior to study entry. Patients qualified for the study if HbA_{1C} was ≤ 8.5% and FPG was ≤ 200 mg/dL. Changes in glycemic control and body weight are shown in **Table 3**.

Table 3: Summary of Mean Changes from Baseline * in HbA_{1C}, Fasting Plasma Glucose, and Body Weight at Week 12 and at Final Visit (24-week study)

	Metformin Hydrochloride Tablets	**Metformin Hydrochloride Extended-Release Tablets**	
	500 mg Twice Daily	**1,000 mg Once Daily**	**1,500 mg Once Daily**
Hemoglobin A_{1C} (%)	**(n = 67)**	**(n = 72)**	**(n = 66)**
Baseline	7.06	6.99	7.02
Change at 12 Weeks	0.14	0.23	0.04
(95% CI)	(-0.03, 0.31)	(0.10, 0.36)	(-0.08, 0.15)
Change at FINAL VISIT	0.14 †	0.27	0.13
(95% CI)	(-0.04, 0.31)	(0.11, 0.43)	(-0.02, 0.28)
FPG (mg/dL)	**(n = 69)**	**(n = 72)**	**(n = 70)**
Baseline	127.2	131.0	131.4
Change at 12 Weeks	12.9	9.5	3.7
(95% CI)	(6.5, 19.4)	(4.4, 14.6)	(-0.4, 7.8)
Change at FINAL VISIT	14.0	11.5	7.6
(95% CI)	(7.0, 21.0)	(4.4, 18.6)	(1.0, 14.2)

Body Weight (lbs)	**(n = 71)**	**(n = 74)**	**(n = 71)**
Baseline	210.3	202.8	192.7
Change at 12 Weeks	0.4	0.9	0.7
(95% CI)	(-0.4, 1.5)	(0.0, 2.0)	(-0.4, 1.8)
Change at FINAL VISIT	0.9	1.1	0.9
(95% CI)	(-0.4, 2.2)	(-0.2, 2.4)	(-0.4, 2.0)

* All patients on metformin hydrochloride tablets 500 mg twice daily at Baseline

† n = 68

After 12 weeks of treatment, there was an increase in mean HbA_{1C} in all groups; in the metformin hydrochloride extended-release tablets 1,000 mg group, the increase from baseline of 0.23% was statistically significant (see **DOSAGE AND ADMINISTRATION**).

Changes in lipid parameters in the previously described placebo-controlled dose-response study of metformin hydrochloride extended-release tablets are shown in **Table 4**.

Table 4: Summary of Mean Percent Changes from Baseline * in Major Lipid Variables at Final Visit (16-week study)

	Metformin Hydrochloride 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**	
Total Cholesterol (mg/dL)	**(n = 120)**	**(n = 113)**	**(n = 110)**	**(n = 126)**	**(n = 117)**	**(n = 110)**
Baseline	210.3	218.1	214.6	204.4	208.2	208.6
Mean % Change at FINAL VISIT	1.0%	1.7%	0.7%	-1.6%	-2.6%	2.6%
Total Triglycerides (mg/dL)	**(n = 120)**	**(n = 113)**	**(n = 110)**	**(n = 126)**	**(n = 117)**	**(n = 110)**
Baseline	220.2	211.9	198.0	194.2	179.0	211.7
Mean % Change at FINAL VISIT	14.5%	9.4%	15.1%	14.9%	9.4%	10.9%
LDL-Cholesterol (mg/dL)	**(n = 119)**	**(n = 113)**	**(n = 109)**	**(n = 126)**	**(n = 117)**	**(n = 107)**
Baseline	131.0	134.9	135.8	125.8	131.4	131.9
Mean % Change at FINAL VISIT	-1.4%	-1.6%	-3.5%	-3.3%	-5.5%	3.2%
HDL-Cholesterol (mg/dL)	**(n = 120)**	**(n = 108)**	**(n = 108)**	**(n = 125)**	**(n = 117)**	**(n = 108)**
Baseline	40.8	41.6	40.6	40.2	42.4	39.4
Mean % Change at FINAL VISIT	6.2%	8.6%	5.5%	6.1%	7.1%	5.8%

* All patients on diet therapy at Baseline

Changes in lipid parameters in the previously described study of metformin hydrochloride tablets and metformin hydrochloride extended-release tablets are shown in **Table 5**.

Table 5: Summary of Mean Percent Changes from Baseline * in Major Lipid Variables at Final Visit (24-week study)

	Metformin Hydrochloride Tablets	Metformin Hydrochloride Extended-Release Tablets	
	500 mg Twice Daily	1,000 mg Once Daily	1,500 mg Once Daily
Total Cholesterol (mg/dL)	**(n = 68)**	**(n = 70)**	**(n = 66)**
Baseline	199.0	201.9	201.6
Mean % Change at FINAL VISIT	0.1%	1.3%	0.1%
Total Triglycerides (mg/dL)	**(n = 68)**	**(n = 70)**	**(n = 66)**
Baseline	178.0	169.2	206.8
Mean % Change at FINAL VISIT	6.3%	25.3%	33.4%
LDL-Cholesterol (mg/dL)	**(n = 68)**	**(n = 70)**	**(n = 66)**
Baseline	122.1	126.2	115.7
Mean % Change at FINAL VISIT	-1.3%	-3.3%	-3.7%
HDL-Cholesterol (mg/dL)	**(n = 68)**	**(n = 70)**	**(n = 65)**
Baseline	41.9	41.7	44.6
Mean % Change at FINAL VISIT	4.8%	1.0%	-2.1%

* All patients on metformin hydrochloride tablets 500 mg twice daily at Baseline

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

1. Severe renal impairment (eGFR below 30 mL/min/1.73 m^2) (see **WARNINGS** and **PRECAUTIONS**).
2. Known hypersensitivity to metformin hydrochloride.
3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

WARNINGS

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 PRECAUTIONS).

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**, **CONTRAINDICATIONS**, and **PRECAUTIONS**).

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 **PRECAUTIONS**).

PRECAUTIONS

General

• 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. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (> 5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio; metformin plasma levels were generally > 5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of metformin hydrochloride extended-release tablets. In metformin hydrochloride extended-release 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 hydrochloride is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

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

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

• Renal impairment

The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment.

The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include (see **DOSAGE AND ADMINISTRATION, CLINICAL PHARMACOLOGY**):

- 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**).
- 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. 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 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 cause prerenal azotemia. When such an event occurs, discontinue metformin hydrochloride extended-release tablets.

• Excessive alcohol intake

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, 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.

Vitamin B_{12} levels

In controlled clinical trials of metformin hydrochloride tablets of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin hydrochloride tablets or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on metformin hydrochloride extended-release tablets and any apparent abnormalities should be appropriately investigated and managed (see **PRECAUTIONS: Laboratory Tests**).

Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at 2- to 3-year intervals may be useful.

Hypoglycemia

Hypoglycemia does not occur in patients receiving metformin hydrochloride extended-release tablets alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol.

Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Macrovascular outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with metformin hydrochloride extended-release tablets or any other antidiabetic drug.

Information for Patients

Patients should be informed of the potential risks and benefits of metformin hydrochloride extended-release tablets and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function, and hematologic parameters.

The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the **WARNINGS** and **PRECAUTIONS** sections, should be explained to patients. Patients should be advised to discontinue metformin hydrochloride extended-release tablets immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of metformin hydrochloride extended-release tablets, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Patients should be counselled against excessive alcohol intake, either acute or chronic, while receiving metformin hydrochloride extended-release tablets.

Metformin hydrochloride extended-release tablets alone do not usually cause hypoglycemia, although it may occur when metformin hydrochloride extended-release tablets are used in conjunction with oral sulfonylureas and insulin. When initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. (See **Patient Information** printed below.)

Patients should be informed that metformin hydrochloride extended-release tablets must be swallowed whole and not crushed or chewed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that may resemble the original tablet.

Laboratory Tests

Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control (see also **DOSAGE AND ADMINISTRATION**).

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, vitamin B_{12} deficiency should be excluded.

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 of metformin hydrochloride extended-release tablets may be required until renal function has been confirmed to be normal (see **PRECAUTIONS**).

Drug Interactions (Clinical Evaluation of Drug Interactions Conducted with Metformin Hydrochloride Tablets)

Glyburide

In a single-dose interaction study in type 2 diabetes patients, coadministration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain (see **DOSAGE AND ADMINISTRATION: Concomitant Metformin Hydrochloride Extended-Release Tablets and Oral Sulfonylurea Therapy in Adult Patients**).

Furosemide

A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine

A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Drugs that reduce metformin clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Other

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

Carbonic anhydrase inhibitors

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

Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving metformin hydrochloride extended-release tablets.

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 4 times 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 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 3 times the maximum recommended human daily dose based on body surface area comparisons.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. Because animal reproduction studies are not always predictive of human response, metformin hydrochloride extended-release tablets should not be used during pregnancy unless clearly needed.

There are no adequate and well-controlled studies in pregnant women with metformin hydrochloride extended-release tablets. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nursing Mothers

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If metformin hydrochloride extended-release tablets are discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

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

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, although other reported clinical experience has not identified differences in responses between the elderly and younger patients.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients (see **WARNINGS, PRECAUTIONS,** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

In worldwide clinical trials over 900 patients with type 2 diabetes have been treated with metformin hydrochloride extended-release tablets in placebo- and active-controlled studies. In placebo-controlled trials, 781 patients were administered metformin hydrochloride extended-release tablets and 195

patients received placebo. Adverse reactions reported in greater than 5% of the metformin hydrochloride extended-release tablets patients, and that were more common in metformin hydrochloride extended-release tablets- than placebo-treated patients, are listed in **Table 6**.

Table 6: Most Common Adverse Reactions (> 5.0 Percent) in Placebo-Controlled Studies of Metformin Hydrochloride Extended-Release Tablets *

Adverse Reaction	Metformin Hydrochloride Extended-Release Tablets (n = 781)	Placebo (n = 195)
	% of Patients	
Diarrhea	9.6	2.6
Nausea/Vomiting	6.5	1.5

* Reactions that were more common in metformin hydrochloride extended-release tablets- than placebo-treated patients.

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

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of hyperglycemia in patients with type 2 diabetes with metformin hydrochloride extended-release tablets or any other pharmacologic agent. Dosage of metformin hydrochloride extended-release tablets must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily doses. The maximum recommended daily dose of metformin hydrochloride extended-release tablets in adults is 2,000 mg.

Metformin hydrochloride extended-release tablets should generally be given once daily with the evening meal. Metformin hydrochloride extended-release tablets should be started at a low dose, with gradual dose escalation, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient.

During treatment initiation and dose titration (see **Recommended Dosing Schedule**), fasting plasma glucose should be used to determine the therapeutic response to metformin hydrochloride extended-release tablets and identify the minimum effective dose for the patient. Thereafter, glycosylated

hemoglobin should be measured at intervals of approximately 3 months. **The therapeutic goal should be to decrease both fasting plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of metformin hydrochloride extended-release tablets, either when used as monotherapy or in combination with sulfonylurea or insulin.**

Monitoring of blood glucose and glycosylated hemoglobin will also permit detection of primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication, and secondary failure, i.e., loss of an adequate blood glucose lowering response after an initial period of effectiveness.

Short-term administration of metformin hydrochloride extended-release tablets may be sufficient during periods of transient loss of control in patients usually well-controlled on diet alone.

Metformin hydrochloride extended-release tablets must be swallowed whole and never crushed or chewed. Occasionally, the inactive ingredients of metformin hydrochloride extended-release tablets will be eliminated in the feces as a soft, hydrated mass. (See **Patient Information** printed below.)

Recommended Dosing Schedule

Adults

The usual starting dose of metformin hydrochloride extended-release tablets is 500 mg once daily with the evening meal. In general, clinically significant responses are not seen at doses below 1,500 mg per day. Dosage increases should be made in increments of 500 mg weekly, up to a maximum of 2,000 mg once daily with the evening meal. The dosage of metformin hydrochloride extended-release tablets must be individualized on the basis of both effectiveness and tolerability. If glycemic control is not achieved on metformin hydrochloride extended-release tablets 2,000 mg once daily, a trial of metformin hydrochloride extended-release tablets 1,000 mg twice daily should be considered. If higher doses of metformin are required, metformin hydrochloride tablets should be used at total daily doses up to 2,550 mg administered in divided daily doses, as described above. (See **CLINICAL PHARMACOLOGY: Clinical Studies.**)

Patients receiving metformin hydrochloride tablets treatment may be safely switched to metformin hydrochloride extended-release tablets once daily at the same total daily dose, up to 2,000 mg once daily. Following a switch from metformin hydrochloride tablets to metformin hydrochloride extended-release tablets, glycemic control should be closely monitored and dosage adjustments made accordingly (see **CLINICAL PHARMACOLOGY: Clinical Studies**).

Pediatrics

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

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 **WARNINGS** and **PRECAUTIONS**).

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.

Concomitant Metformin Hydrochloride Extended-Release Tablets and Oral Sulfonylurea Therapy in Adult Patients

If patients have not responded to 4 weeks of the maximum dose of metformin hydrochloride extended-release tablets monotherapy, consideration should be given to gradual addition of an oral sulfonylurea while continuing metformin hydrochloride extended-release tablets at the maximum dose, even if prior primary or secondary failure to a sulfonylurea has occurred. Clinical and pharmacokinetic drug-drug interaction data are currently available only for metformin plus glyburide (glibenclamide).

With concomitant metformin hydrochloride extended-release tablets and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. However, attempts should be made to identify the minimum effective dose of each drug to achieve this goal. With concomitant metformin hydrochloride extended-release tablets and sulfonylurea therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken. (See Package Insert of the respective sulfonylurea.)

If patients have not satisfactorily responded to 1 to 3 months of concomitant therapy with the maximum dose of metformin hydrochloride extended-release tablets and the maximum dose of an oral sulfonylurea, consider therapeutic alternatives including switching to insulin with or without metformin hydrochloride extended-release tablets.

Concomitant Metformin Hydrochloride Extended-Release Tablets and Insulin Therapy in Adult Patients

The current insulin dose should be continued upon initiation of metformin hydrochloride extended-release tablets therapy. Metformin hydrochloride extended-release tablets therapy should be initiated at 500 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of metformin hydrochloride extended-release tablets should be increased by 500 mg after approximately 1 week and by 500 mg every week thereafter until adequate glycemic control is achieved. The maximum recommended daily dose is 2,000 mg for metformin hydrochloride extended-release tablets. It is recommended that the insulin dose be decreased by 10% to 25% when fasting plasma glucose concentrations decrease to less than 120 mg/dL in patients receiving concomitant insulin and metformin hydrochloride extended-release tablets. Further adjustment should be individualized based on glucose-lowering response.

Specific Patient Populations

Metformin hydrochloride extended-release tablets are not recommended for use in pregnancy. Metformin hydrochloride extended-release tablets are not recommended in pediatric patients (below the age of 17 years).

The initial and maintenance dosing of metformin hydrochloride extended-release tablets should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function.

HOW SUPPLIED

Metformin hydrochloride extended-release tablets USP, **500 mg** are oval white tablets, with "OE" debossed on one side and "584" debossed on the other side.

They are available as follows:

Bottles of 100 NDC 51224-007-50
Bottles of 500 NDC 51224-007-60

Metformin hydrochloride extended-release tablets USP, **750 mg** are white, capsule shaped tablets, with "OE" debossed on one side and "585" debossed on the other side.

They are available as follows:

Bottles of 100 NDC 51224-107-50
Bottles of 500 NDC 51224-107-60

Storage

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.]

Dispense in well-closed, light-resistant containers.

Manufactured by: **CSPC Ouyi Pharmaceutical Co., Ltd.**
Shijiazhuang, Hebei, China, 052160

Manufactured for: **TAGI Pharma, Inc.**
South Beloit, IL 61080

Rev. 05/2017

Patient Information

Metformin Hydrochloride Extended-Release Tablets, USP
(met for' min hye" droe klor' ide)

Read this information carefully before you start taking this medicine and each time you refill your prescription. There may be new information. This information does not take the place of your doctor's advice. Ask your doctor or pharmacist if you do not understand some of this information or if you want to know more about this medicine.

What are metformin hydrochloride extended-release tablets?

Metformin hydrochloride extended-release tablets are used to treat type 2 diabetes. This is also known as non-insulin-dependent diabetes mellitus. People with type 2 diabetes are not able to make enough insulin or respond normally to the insulin their bodies make. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems including kidney damage, amputations, and blindness. Diabetes is also closely linked to heart disease. The main goal of treating diabetes is to lower your blood sugar to a normal level.

High blood sugar can be lowered by diet and exercise, by a number of medicines taken by mouth, and by insulin shots. Before you take metformin hydrochloride extended-release tablets, try to control your diabetes by exercise and weight loss. While you take your diabetes medicine, continue to exercise and follow the diet advised for your diabetes. No matter what your recommended diabetes management plan is, studies have shown that maintaining good blood sugar control can prevent or delay complications of diabetes, such as blindness.

Metformin hydrochloride extended-release tablets help control your blood sugar in a number of ways. These include helping your body respond better to the insulin it makes naturally, decreasing the amount of sugar your liver makes, and decreasing the amount of sugar your intestines absorb. Metformin hydrochloride extended-release tablets do not cause your body to make more insulin. Because of this,

when taken alone, they rarely cause hypoglycemia (low blood sugar), and usually do not cause weight gain. However, when they are taken with a sulfonylurea or with insulin, hypoglycemia is more likely to occur, as is weight gain.

Tell your doctor if you are pregnant or plan to become pregnant. Metformin hydrochloride extended-release tablets may not be right for you. Talk with your doctor about your choices. You should also discuss your choices with your doctor if you are nursing a child.

Can metformin hydrochloride extended-release tablets be used in children?

Metformin hydrochloride extended-release tablets have not been studied in children.

How should I take metformin hydrochloride extended-release tablets?

Your doctor will tell you how much medicine to take and when to take it. You will probably start out with a low dose of the medicine. Your doctor may slowly increase your dose until your blood sugar is better controlled. You should take metformin hydrochloride extended-release tablets with meals.

Your doctor may have you take other medicines along with metformin hydrochloride extended-release tablets to control your blood sugar. These medicines may include insulin shots. Taking metformin hydrochloride extended-release tablets with insulin may help you better control your blood sugar while reducing the insulin dose.

Continue your exercise and diet program and test your blood sugar regularly while taking metformin hydrochloride extended-release tablets. Your doctor will monitor your diabetes and may perform blood tests on you from time to time to make sure your kidneys and your liver are functioning normally. There is no evidence that metformin hydrochloride extended-release tablets cause harm to the liver or kidneys.

Tell your doctor if you:

- have an illness that causes severe vomiting, diarrhea or fever, or if you drink a much lower amount of liquid than normal. These conditions can lead to severe dehydration (loss of water in your body). You may need to stop taking metformin hydrochloride extended-release tablets for a short time.
- plan to have surgery or an x-ray procedure with injection of dye (contrast agent). You may need to stop taking metformin hydrochloride extended-release tablets for a short time.
- start to take other medicines or change how you take a medicine. Metformin hydrochloride extended-release tablets can affect how well other drugs work, and some drugs can affect how well metformin hydrochloride extended-release tablets work. Some medicines may cause high blood sugar.

Metformin hydrochloride extended-release tablets must be swallowed whole and never crushed or chewed. Occasionally, the inactive ingredients of metformin hydrochloride extended-release tablets may be eliminated as a soft mass in your stool that may look like the original tablet; this is not harmful and will not affect the way metformin hydrochloride extended-release tablets work to control your diabetes.

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 side effects of metformin hydrochloride extended-release tablets?

- **Lactic acidosis. Metformin, the active ingredient in metformin hydrochloride extended-release tablets, can cause a rare but serious condition called lactic acidosis (a buildup of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.**

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

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

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

- have severe kidney problems, or your kidneys are affected by certain x-ray tests that use injectable dye
- have liver problems
- drink alcohol very often, or drink a lot of alcohol in short-term "binge" drinking
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids
- have surgery
- have a heart attack, severe infection, or stroke

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

Other Side Effects. Common side effects of metformin hydrochloride extended-release tablets include diarrhea, nausea, and upset stomach. These side effects generally go away after you take the medicine for a while. Taking your medicine with meals can help reduce these side effects. Tell your doctor if the side effects bother you a lot, last for more than a few weeks, come back after they've gone away, or start later in therapy. You may need a lower dose or need to stop taking the medicine for a short period or for good.

About 3 out of every 100 people who take metformin hydrochloride extended-release tablets have an unpleasant metallic taste when they start taking the medicine. It lasts for a short time.

Metformin hydrochloride extended-release tablets rarely cause hypoglycemia (low blood sugar) by themselves. However, hypoglycemia can happen if you do not eat enough, if you drink alcohol, or if you take other medicines to lower blood sugar.

General advice about prescription medicines

If you have questions or problems, talk with your doctor or other healthcare provider. You can ask your doctor or pharmacist for the information about metformin hydrochloride extended-release tablets that is written for healthcare professionals. 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 share your medicine with other people.

Manufactured by:
CSPC Ouyi Pharmaceutical Co., Ltd.
Shijiazhuang, Hebei, China, 052160

Manufactured for:
TAGI Pharma, Inc.
South Beloit, IL 61080

Rev. 05/2017

Principal Display Panel

NDC: 70934-117-30

METFORMIN HYDROCHLORIDE

metformin hydrochloride tablet, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70934-117(NDC:51224-107)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
METFORMIN HYDROCHLORIDE (UNII: 786Z46389E) (METFORMIN - UNII:9100L32L2N)	METFORMIN HYDROCHLORIDE	750 mg

Inactive Ingredients	
Ingredient Name	**Strength**
COPOVIDONE K25-31 (UNII: D9C330MD8B)	
CARBOXYMETHYLCELLULOSE SODIUM, UNSPECIFIED FORM (UNII: K679OBS311)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics			
Color	white	**Score**	no score
Shape	OVAL	**Size**	21mm
Flavor		**Imprint Code**	OE;585
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70934-117-30	30 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	05/09/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078321	05/09/2018	

Labeler - Denton Pharma, Inc. DBA Northwind Pharmaceuticals (080355546)

Registrant - Denton Pharma, Inc. DBA Northwind Pharmaceuticals (080355546)

Establishment

Name	Address	ID/FEI	Business Operations
Denton Pharma, Inc. DBA Northwind Pharmaceuticals		080355546	repack(70934-117)

Revised: 12/2019 Denton Pharma, Inc. DBA Northwind Pharmaceuticals