

LACHMAN CONSULTANT SERVICES, INC.  
Westbury, NY 11590

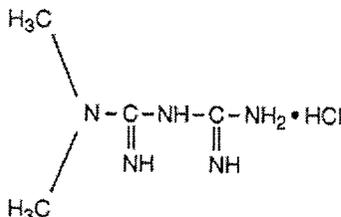
**ATTACHMENT 2**

# METFORMIN HYDROCHLORIDE EXTENDED-RELEASE TABLETS

Rx only

## DESCRIPTION

Metformin hydrochloride extended-release tablets are 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  $\text{C}_4\text{H}_{11}\text{N}_5 \cdot \text{HCl}$  and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

Metformin hydrochloride extended-release tablets contain 500 mg and 1000 mg of metformin hydrochloride as the active ingredient. Each tablet contains the inactive ingredients [Inactive ingredients will be included in the insert at time of submission of the ANDA]

## System Components and Performance

[System components and performance information will be included in the insert at the time of submission of the ANDA].

## 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 hours to 8 hours. At steady state, the AUC and  $C_{max}$  are less than dose proportional for metformin hydrochloride extended-release tablets within the range of 500 mg to 2000 mg administered once daily. Peak plasma levels are approximately 0.6, 1.1, 1.4, and 1.8 mcg/mL for 500, 1000, 1500, and 2000 mg once-daily doses, respectively. The extent of metformin absorption (as measured by AUC) from metformin hydrochloride extended-release tablets at a 2000 mg once-daily dose is similar to the same total daily dose administered as metformin hydrochloride tablets 1000 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 tablet 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  $654 \pm 358$  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.

## Special 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 is comparable to those in healthy normal adults.

### Renal Insufficiency

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance (see **Table 1**; also see **WARNINGS**).

### Hepatic Insufficiency

No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency.

### 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**). Metformin hydrochloride extended-release tablet treatment should not be initiated in patients  $\geq 80$  years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced. (See **WARNINGS** and **DOSAGE AND ADMINISTRATION**.)

Table 1. Select Mean ( $\pm$ S.D.) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of Metformin Hydrochloride Tablets			
Subject Groups: Metformin Hydrochloride Tablets dose <sup>a</sup> (number of subjects)	$C_{max}^b$ (mcg/mL)	$T_{max}^c$ (hrs)	Renal Clearance (mL/min)
Healthy, nondiabetic adults: 500 mg single dose (24) 850 mg single dose (74) <sup>d</sup> 850 mg three times daily for 19 doses <sup>e</sup> (9) (continued)	1.03 ( $\pm$ 0.33) 1.60 ( $\pm$ 0.38) 2.01 ( $\pm$ 0.42)	2.75 ( $\pm$ 0.81) 2.64 ( $\pm$ 0.82) 1.79 ( $\pm$ 0.94)	600 ( $\pm$ 132) 552 ( $\pm$ 139) 642 ( $\pm$ 173)
Table 1. Select Mean ( $\pm$ S.D.) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of Metformin Hydrochloride Tablets			
Subject Groups: Metformin Hydrochloride Tablets dose <sup>a</sup> (number of subjects)	$C_{max}^b$ (mcg/mL)	$T_{max}^c$ (hrs)	Renal Clearance (mL/min)

<b>Adults with type 2 diabetes:</b>			
850 mg single dose (23)	1.48 (±0.5)	3.32 (±1.08)	491 (±138)
850 mg three times daily for 19 doses <sup>e</sup> (9)	1.90 (±0.62)	2.01 (±1.22)	550 (±160)
<b>Elderly<sup>f</sup>, healthy nondiabetic adults:</b>			
850 mg single dose (12)	2.45 (±0.70)	2.71 (±1.05)	412 (±98)
<b>Renal-impaired adults:</b>			
850 mg single dose			
Mild (CL <sub>cr</sub> <sup>g</sup> 61-90 mL/min) (5)	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Moderate (CL <sub>cr</sub> 31-60 mL/min) (4)	4.12 (±1.83)	3.75 (±0.50)	108 (±57)
Severe (CL <sub>cr</sub> 10-30 mL/min) (6)	3.93 (±0.92)	4.01 (±1.10)	130 (±90)

<sup>a</sup> All doses given fasting except the first 18 doses of the multiple dose studies

<sup>b</sup> Peak plasma concentration;

<sup>c</sup> Time to peak plasma concentration;

<sup>d</sup> Combined results (average means) of five studies: mean age 32 years (range 23-59 years)

<sup>e</sup> Kinetic study done following dose 19, given fasting

<sup>f</sup> Elderly subjects, mean age 71 years (range 65-81 years)

<sup>g</sup> CL<sub>cr</sub> = creatinine clearance normalized to body surface area of 1.73 m<sup>2</sup>

### Pediatrics

No pharmacokinetic data from studies of pediatric patients are currently available.

### 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<sub>1c</sub> 7.0-10.0%, FPG 126-270 mg/dL). Patients entering the study had a mean baseline HbA<sub>1c</sub> of 8.0% and a mean baseline FPG of 176 mg/dL. After 12 weeks treatment, mean HbA<sub>1c</sub> 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<sub>1c</sub> of 0.6% and a decrease in mean FPG of 23 mg/dL in patients treated with metformin hydrochloride extended-release tablets 1000 mg once daily. Subsequently, the treatment dose was increased to 1500 mg once daily if HbA<sub>1c</sub> was ≥7.0% but <8.0%

(patients with HbA<sub>1c</sub> ≥8.0% were discontinued from the study). At the final visit (24-week), mean HbA<sub>1c</sub> 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<sub>1c</sub> 7.0-11%, FPG 126-280 mg/dL). Changes in glycemic control and body weight are shown in **Table 2**.

<b>Table 2. Summary of Mean Changes from Baseline* in HbA<sub>1c</sub>, Fasting Plasma Glucose, and Body Weight at Final Visit (16-week study)</b>						
	<b>Metformin Hydrochloride Extended-Release Tablets</b>					<b>Placebo</b>
	<b>500 mg Once Daily</b>	<b>1000 mg Once Daily</b>	<b>1500 mg Once Daily</b>	<b>2000 mg Once Daily</b>	<b>1000 mg Twice Daily</b>	
<b>Hemoglobin A<sub>1c</sub> (%)</b>	<b>(n=115)</b>	<b>(n=115)</b>	<b>(n=111)</b>	<b>(n=125)</b>	<b>(n=112)</b>	<b>(n=111)</b>
Baseline Change at	8.2	8.4	8.3	8.4	8.4	8.4
FINAL VISIT	-0.4	-0.6	-0.9	-0.8	-1.1	0.1
p-value <sup>a</sup>	<0.001	<0.001	<0.001	<0.001	<0.001	-
<b>FPG (mg/dL)</b>	<b>(n=126)</b>	<b>(n=118)</b>	<b>(n=120)</b>	<b>(n=132)</b>	<b>(n=122)</b>	<b>(n=113)</b>
Baseline Change at	183.7	183.7	178.9	181.0	181.6	179.6
FINAL VISIT	-15.2	-19.3	-28.5	-29.9	-33.6	7.6
p-value <sup>a</sup>	<0.001	<0.001	<0.001	<0.001	<0.001	-
<b>Body Weight (lbs)</b>	<b>(n=125)</b>	<b>(n=119)</b>	<b>(n=117)</b>	<b>(n=131)</b>	<b>(n=119)</b>	<b>(n=113)</b>
Baseline Change at	192.9	191.8	188.3	195.4	192.5	194.3
FINAL VISIT	-1.3	-1.3	-0.7	-1.5	-2.2	-1.8
p-value <sup>a</sup>	NS**	NS**	NS**	NS**	NS**	-

\* All patients on diet therapy at Baseline

<sup>a</sup> 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 tablet 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<sub>1c</sub> was ≤8.5% and FPG was ≤200 mg/dL. Changes in glycemic control and body weight are shown in **Table 3**.

<b>Table 3. Summary of Mean Changes from Baseline in HbA<sub>1c</sub>, Fasting Plasma Glucose, and Body Weight at Week 12 and at Final Visit (24-week study)</b>		
	<b>Metformin Hydrochloride Extended-Release Tablets</b>	
	<b>1000 mg Once Daily</b>	<b>1500 mg Once Daily</b>
<b>Hemoglobin A<sub>1c</sub> (%)</b>	<b>(n=72)</b>	<b>(n=66)</b>
Baseline	6.99	7.02
Change at 12 Weeks	0.23	0.04
(95% CI)	(0.10, 0.36)	(-0.08, 0.15)
Change at FINAL VISIT	0.27	0.13
(95% CI)	(0.11, 0.43)	(-0.02, 0.28)
<b>FPG (mg/dL)</b>	<b>(n=72)</b>	<b>(n=70)</b>
Baseline	131.0	131.4
Change at 12 Weeks	9.5	3.7
(95% CI)	(4.4, 14.6)	(-0.4, 7.8)
Change at FINAL VISIT	11.5	7.6
(95% CI)	(4.4, 18.6)	(1.0, 14.2)
<b>Body Weight (lbs)</b>	<b>(n=74)</b>	<b>(n=71)</b>
Baseline	202.8	192.7
Change at 12 Weeks	0.9	0.7
(95% CI)	(0.0, 2.0)	(-0.4, 1.8)
Change at FINAL VISIT	1.1	0.9
(95% CI)	(-0.2, 2.4)	(-0.4, 2.0)

After 12 weeks of treatment there was an increase in mean HbA<sub>1c</sub> in all groups in the metformin hydrochloride extended-release tablets 1000 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**.

<b>Table 4. Summary of Mean Percent Changes from Baseline* in Major Lipid Variables at Final Visit (16-week study)</b>						
	<b>Metformin Hydrochloride Extended-Release Tablets</b>					
	<b>500 mg Once Daily</b>	<b>1000 mg Once Daily</b>	<b>1500 mg Once Daily</b>	<b>2000 mg Once Daily</b>	<b>1000 mg Twice Daily</b>	<b>Placebo</b>
<b>Total Cholesterol (mg/dL)</b>	<b>(n=120)</b>	<b>(n=113)</b>	<b>(n=110)</b>	<b>(n=126)</b>	<b>(n=117)</b>	<b>(n=110)</b>
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%
<b>Total Triglycerides (mg/dL)</b>	<b>(n=120)</b>	<b>(n=113)</b>	<b>(n=110)</b>	<b>(n=126)</b>	<b>(n=117)</b>	<b>(n=110)</b>
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%
<b>(continued)</b>						

<b>Table 4. Summary of Mean Percent Changes from Baseline* in Major Lipid Variables at Final Visit (16-week study)</b>						
	<b>Metformin Hydrochloride Extended-Release Tablets</b>					
	<b>500 mg Once Daily</b>	<b>1000 mg Once Daily</b>	<b>1500 mg Once Daily</b>	<b>2000 mg Once Daily</b>	<b>1000 mg Twice Daily</b>	<b>Placebo</b>
<b>LDL-Cholesterol (mg/dL)</b>	<b>(n=119)</b>	<b>(n=113)</b>	<b>(n=109)</b>	<b>(n=126)</b>	<b>(n=117)</b>	<b>(n=107)</b>
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%
<b>HDL-Cholesterol (mg/dL)</b>	<b>(n=120)</b>	<b>(n=108)</b>	<b>(n=108)</b>	<b>(n=125)</b>	<b>(n=117)</b>	<b>(n=108)</b>
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 extended-release tablets is shown in **Table 5**.

<b>Table 5. Summary of Mean Percent Changes from Baseline in Major Lipid Variables at Final Visit (24-week study)</b>		
	<b>Metformin Hydrochloride Extended-Release Tablets</b>	
	<b>1000 mg Once Daily</b>	<b>1500 mg Once Daily</b>
<b>Total Cholesterol (mg/dL)</b>	<b>(n=70)</b>	<b>(n=66)</b>
Baseline	201.9	201.6
Mean % change at FINAL VISIT	1.3%	0.1%
<b>Total Triglycerides (mg/dL)</b>	<b>(n=70)</b>	<b>(n=66)</b>
Baseline	169.2	206.8
Mean % change at FINAL VISIT	25.3%	33.4%
<b>LDL-Cholesterol (mg/dL)</b>	<b>(n=70)</b>	<b>(n=66)</b>
Baseline	126.2	115.7
Mean % change at FINAL VISIT	-3.3%	-3.7%
<b>HDL-Cholesterol (mg/dL)</b>	<b>(n=70)</b>	<b>(n=65)</b>
Baseline	41.7	44.6
Mean % change at FINAL VISIT	1.0%	-2.1%

## INDICATIONS AND USE

Metformin hydrochloride extended-release tablets, as monotherapy, are indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. Metformin hydrochloride extended-release tablets are indicated in patients 17 years of age and older. Metformin hydrochloride extended-release tablets may be used concomitantly with a sulfonylurea or insulin to improve glycemic control in adults (17 years of age and older).

## CONTRAINDICATIONS

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

1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels  $\geq 1.5$  mg/dL [males],  $\geq 1.4$  mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see **WARNINGS** and **PRECAUTIONS**).

2. Congestive heart failure requiring pharmacologic treatment.
3. Known hypersensitivity to metformin hydrochloride.
4. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Metformin hydrochloride extended-release tablets should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated materials, because use of such products may result in acute alteration of renal function. (See also **PRECAUTIONS**.)

## **WARNINGS**

### **Lactic Acidosis:**

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with metformin hydrochloride extended-release tablets; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels ( $>5$  mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels  $>5$  mcg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure, who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin hydrochloride extended-release tablets and by use of the minimum effective dose of metformin hydrochloride extended release tablets. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin hydrochloride extended-release tablet treatment should not be initiated in patients  $\geq 80$  years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin hydrochloride extended-release tablets should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin hydrochloride extended -

release tablets should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin hydrochloride extended-release tablets, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin hydrochloride extended-release tablets should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see also PRECAUTIONS).

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). Metformin hydrochloride extended-release tablets should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin hydrochloride extended release tablets, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin hydrochloride extended-release tablets do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. (See also PRECAUTIONS.)

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin hydrochloride extended release tablets, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See also CONTRAINDICATIONS and PRECAUTIONS).

## PRECAUTIONS

### General

**Monitoring of renal function** — Metformin hydrochloride is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive

metformin hydrochloride extended-release tablets. In patients with advanced age, metformin hydrochloride extended-release tablets should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those  $\geq 80$  years of age, renal function should be monitored regularly and, generally, metformin hydrochloride extended-release tablets should not be titrated to the maximum dose (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

Before initiation of metformin hydrochloride extended-release tablets therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and metformin hydrochloride extended-release tablets discontinued if evidence of renal impairment is present.

***Use of concomitant medications that may affect renal function or metformin disposition*** — Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see **PRECAUTIONS: Drug Interactions**), should be used with caution.

***Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials)*** — Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see **CONTRAINDICATIONS**). Therefore, in patients in whom any such study is planned, metformin hydrochloride extended-release tablets should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstated only after renal function has been re-evaluated and found to be normal.

***Hypoxic states*** — Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on metformin hydrochloride extended-release tablet therapy, the drug should be promptly discontinued.

***Surgical procedures*** — Metformin hydrochloride extended-release tablet therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

***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 of metformin hydrochloride extended-release tablets.

***Impaired hepatic function*** — Since impaired hepatic function has been associated with some cases of lactic acidosis, metformin hydrochloride extended-release tablets should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

***Vitamin B<sub>12</sub> levels*** — In controlled clinical trials of metformin hydrochloride tablets of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B<sub>12</sub> levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B<sub>12</sub> absorption from the B<sub>12</sub>-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<sub>12</sub> 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<sub>12</sub> or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B<sub>12</sub> levels. In these patients, routine serum Vitamin B<sub>12</sub> measurements at two- to three-year intervals may be useful.

***Change in clinical status of patients with previously controlled type 2 diabetes*** — A patient with type 2 diabetes previously well controlled on metformin hydrochloride extended-release tablets who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, metformin hydrochloride extended-release tablets must be stopped immediately and other appropriate corrective measures initiated (see also **WARNINGS**).

***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 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.

***Loss of control of blood glucose*** — When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold metformin hydrochloride extended-release tablets and temporarily administer insulin. Metformin hydrochloride extended-release tablets may be reinstated after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with either metformin hydrochloride extended-release tablets or sulfonylurea monotherapy, combined therapy with metformin hydrochloride extended-release tablets and sulfonylurea may result in a response. Should secondary failure occur with combined metformin hydrochloride extended-release tablet/sulfonylurea therapy, it may be necessary to consider therapeutic alternatives including initiation of insulin therapy.

### **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 counseled against excessive alcohol intake, either acute or chronic, while receiving Metformin hydrochloride extended-release tablets.

Metformin hydrochloride extended-release tablets alone does 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.

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.

(See **Patient Information** Printed Below.)

### **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 hydrochloride tablet therapy, if this is suspected, Vitamin B<sub>12</sub> deficiency should be excluded.

### **Drug Interactions (clinical evaluation of drug interactions done with metformin hydrochloride tablets)**

**Glyburide** — In a single-dose interaction study in type 2 diabetes subjects, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C<sub>max</sub> 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**).

**Furosemide** — A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C<sub>max</sub> by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C<sub>max</sub> 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 co-administered chronically.

**Nifedipine** — A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C<sub>max</sub> and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T<sub>max</sub> and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

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

**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.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when co-administered 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.

#### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 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 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 three times the maximum recommended human daily dose based on body surface area comparisons.

## **Pregnancy**

### **Teratogenic Effects: Pregnancy Category B.**

Recent information 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 two and six times the maximum recommended human daily dose of 2000 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. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, metformin hydrochloride extended-release tablets should only be used in patients with normal renal function (see **CONTRAINDICATIONS, WARNINGS, and CLINICAL PHARMACOLOGY: Pharmacokinetics**). Because aging is associated with reduced renal function metformin hydrochloride extended-release tablets should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of metformin hydrochloride extended-release tablets (see also **WARNINGS 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 patients, and that were more common in metformin hydrochloride extended-release tablet-than placebo-treated patients, are listed in **Table 6**.

<b>Table 6. Most Common Adverse Reactions (&gt;5.0%) In Placebo-Controlled Studies of Metformin Hydrochloride Extended-Release Tablets*</b>		
	<b>Metformin Hydrochloride Extended-Release Tablets n=781</b>	<b>Placebo n=195</b>
<b>Adverse Reaction</b>	<b>% of Patients</b>	
Diarrhea	9.6	2.6
Nausea/Vomiting	6.5	1.5

\* Reactions that were more common in metformin hydrochloride extended-release tablet-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  $\geq 1.0\%$  -  $\leq 5.0\%$  of metformin hydrochloride extended-release tablet 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.

### **Pediatric Patients**

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

## OVERDOSAGE

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 dose. The maximum recommended daily dose of metformin hydrochloride extended-release tablets in adults is 2000 mg.

Metformin hydrochloride extended-release tablets should generally be given once daily with the evening meal. Metformin hydrochloride extended-release 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 three 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** — In general, clinically significant responses are not seen at doses below 1500 mg per day. However, a lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms.

The usual starting dose of metformin hydrochloride extended-release tablets is 500 mg once daily with the evening meal. Dosage increases should be made in increments of 500 mg weekly, up to a maximum of 2000 mg once daily with the evening meal. If glycemic control is not achieved on metformin hydrochloride extended-release 2000 mg once daily, a trial of metformin hydrochloride extended-release 1000 mg twice daily should be considered. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In a randomized trial, patients currently treated with metformin hydrochloride tablets were switched to metformin hydrochloride extended-release tablets. Results of this trial suggest that patients receiving metformin hydrochloride tablet treatment may be safely switched to metformin hydrochloride extended-release tablets once daily at the same total daily dose, up to 2000 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.

#### **Transfer From Other Antidiabetic Therapy**

When transferring patients from standard oral hypoglycemic agents other than chlorpropamide to metformin hydrochloride extended-release tablets, no transition period generally is necessary. When transferring patients from chlorpropamide, care should be exercised during the first two weeks because of the prolonged retention of chlorpropamide in the body, leading to overlapping drug effects and possible hypoglycemia.

#### **Concomitant Metformin Hydrochloride Extended-release Tablets and Oral Sulfonylurea Therapy in Adult Patients**

If patients have not responded to four weeks of the maximum dose of metformin hydrochloride extended-release tablet 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 tablet 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 tablet 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 one to three 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 2000 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. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of metformin hydrochloride extended-release tablets.

Monitoring of renal function is necessary to aid in prevention of lactic acidosis, particularly in the elderly. (See **WARNINGS**.)

### **HOW SUPPLIED**

Metformin Hydrochloride Extended-Release Tablets 1000 mg, capsule shaped tablets are to be determined.

Package Size to be determined

Store at 20 – 25° C (68 – 77° F) (See USP Controlled Room Temperature).

Dispense in a tightly-closed, light-resistant container (USP).

Manufactured by:

August 2003