HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use metformin hydrochloride extended-release tablets safely and effectively. See full prescribing information for metformin hydrochloride extended-release tablets.

Metformin Hydrochloride Extended-Release Tablets USP, 500 mg and 1000 mg
Initial U.S. Approval: 1995

WARNING: LACTIC ACIDOSIS

See full prescribing information for complete boxed warning

- **Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. (5.1)**
- **Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. (5.1)**
- **If acidosis is suspected, discontinue metformin hydrochloride extended-release tablets and hospitalize the patient immediately. (5.1)**

----------RECENT MAJOR CHANGES----------

Dosing and Administration:
Inclusion of the 1000 mg tablet (3) 12/2007

----------INDICATIONS AND USAGE ----------

Metformin hydrochloride is a biguanide indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Important limitations of use:
Not for treatment of type 1 diabetes or diabetic ketoacidosis. (1.1)

----------DOSAGE AND ADMINISTRATION----------

- Administer once daily with the evening meal. (2)
- Individualize the dose based on effectiveness and tolerability, while not exceeding the maximum recommended daily dose of 2000 mg. (2)
- If naive to metformin treatment, initiate with 500 mg daily. (2)
- Swallow whole. Never split, crush or chew. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Extended Release Tablets, 500 mg and 1000 mg (3)

----------CONTRAINDICATIONS ----------

- Renal impairment (4)
- Metabolic acidosis, including diabetic ketoacidosis (4)
- Hypersensitivity to metformin hydrochloride (4)

----------WARNINGS AND PRECAUTIONS----------

- Lactic acidosis: Warn against excessive alcohol intake. metformin hydrochloride is not recommended in hepatic impairment and is contraindicated in renal impairment. Ensure normal renal function before initiating and at least annua ly thereafter. (5.1)
- Temporarily discontinue in patients undergoing radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures necessitating restricted intake of food and fluids. (5.2)
- Vitamin B12 deficiency: Metformin may lower vitamin B12 levels. Monitor hematologic parameters annually. (5.6)
- Macrovascular outcomes: No conclusive evidence of macrovascular risk reduction with metformin hydrochloride or any other antidiabetic drug. (5.8)

----------ADVERSE REACTIONS----------

The incidence and type of adverse reactions reported by >5% of patients for the combined metformin hydrochloride group versus placebo group are hypoglycemia, diarrhea, and nausea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals, Inc. at 1-800-399-2561 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Cationic drugs: May reduce metformin elimination. Use with caution in patients who are taking cationic medications eliminated by renal tubular secretion. (7.1)

----------USE IN SPECIFIC POPULATIONS ----------

- Pediatric Use: Safety and effectiveness in children younger than 18 years of age have not been established. (8.4)
- Geriatric Use: Caution should be used when prescribing metformin hydrochloride extended-release tablets to elderly patients because reduced renal functions are associated with increasing age. (8.5)

See 17 for PATIENT COUNSELING INFORMATION, and FDA approved Patient Information

Revised: 01/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCR BING INFORMATION

WARN NG: Lactic Acidosis

Lactic acidosis is a ra e, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure.
The onset of lactic acidosis is often subt e, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.
Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.
If acidosis is suspected, metformin hydrochloride e tended-release tab ets, should be discontinued and the patient hospita ized immediately [See **WARNINGS and PRECAUTIONS (5.1)**]

1. INDICAT ONS AND USAGE

Metformin hydrochlo ide extended-re ease tablets USP are indicated as an adjunct to diet and exercise to improve glycemic control in adu ts with type 2 diabetes mel itus.

Important Limitations of Use

Metformin hydrochloride extended-release tablets USP should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

2. DOSAGE AND ADMIN STRATION

2.1 Recommended Dosing

Metformin hydrochloride extended-release tab ets shou d be taken once daily with the evening meal. The dosage of metformin hydrochloride extended-release tablets must be individualized on the basis of both e fectiveness and tolerability, whi e not exceeding the maximum recommended daily dose of 2000 mg. The starting dose of metformin hydrochloride extended-release tab ets in patients who are not currently taking metformin is 500 mg once daily, with the evening meal. The dose can be uptitrated in 500 mg increments no sooner than every 1-2 weeks if a higher dose of metformin hydrochloride extended-re ease tab ets is needed and there are no gastrointestinal adverse reactions.

If metformin hydrochloride extended-re ease tab ets are considered appropriate for a patient a ready receiving immediate-release metformin, the patient can be switched to metformin hydrochloride extended-release tablets once daily at the same total daily dose, up to 2000 mg once daily.

Metformin hydroch oride extended-release tab ets must be swal owed who e and never sp it, crushed or chewed. Occasiona ly, the inactive ingredients of metformin hydrochloride extended-release tablets may be e iminated in the feces as an inso uble soft, hydrated mass (See **Patient I formation**). If a dose of metformin hydrochloride extended-release tab et is missed, patients should be cautioned against taking two doses of 2000 mg the same day. Resume dosing as according to prescribing recommendations. [See **PATIENT COUNSELING INFORMAT ON (17)**]

Patients treated with an insulin secretagogue or insulin

Co-administration of metformin hydrochloride extended-release tablets with an insu in secretagogue (e.g., su fonylurea) or insulin may require ower doses of the insulin secretagogue or insu in to reduce the risk of hypoglycemia.

3. DOSAGE FORMS AND STRENGTHS

Metformin hydrochloride extended-release tab ets, 500 mg are available as white to off white, oval shaped, biconvex coated tab et, debossed with "L41" on one side and "LU" on the other side.

Metformin hydrochloride extended-release tablets, 000 mg are availab e as white to off white, oval shaped, biconvex coated tab et, debossed with "L42" on one side and "LU" on the other side

4. CONTRAINDICAT ONS

Metformin hydrochloride extended-re ease tab ets are contraindicated in patients with:

- Renal impairment (e.g., serum creatinine evels ≥ 1.5 mg/dL for men, ≥ 1.4 mg/dL for women or abnormal creatinine c earance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia. [See **WARNINGS AND PRECAUTIONS (5)**]
- Known hypersensitivity to metformin hydroch oride.
- Acute or chronic metabo ic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis shou d be treated with insulin.

5. WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

Lactic acidosis is a serious, metabo ic comp ication that can occur due to m formin accumu ation during treatment with metformin hydrochloride and is fatal in approximately 50% of cases. Lactic acidosis may a so occur in association with a number of pathophysio ogic conditions, including diabetes mel itus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate concentrations (>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 p asma levels >5 mcg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years. In more than 20,000 patient-years exposure to metformin in clinica trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both int insic renal disease and renal hypoperfusion, o ten in the se ting of mu tiple concomitant medical/surgical problems and mu tip e concomitant medications. Patients with congestive heart failure requiring pharmaco ogic management, particularly when accompanied by hypoperfusion and hypoxemia due to unstable or acute failure, are at increased risk of lactic acidosis. The risk of actic 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 hydroch oride. n particular, treatment of the elderly shou d be accompanied by careful monitoring of renal function. Metformin hydrochloride treatme t should not be initiated in any patient unless measurement of creatinine clea ance demonstrates that renal function is not reduced. n addition, metformin hydrochloride should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis.

Because impaired hepatic function may significantly limit the abi ity to clear actate, metformin hydrochloride shou d generally be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients shou d be cautioned against excessive alcohol intake when taking metformin hydrochloride, because alcohol potentiates the effects of metformin on actate metabolism. In addition, metformin hydrochloride should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedu e necessitating restricted intake of food or fluids. Use of topiramate, a carbonic anhydrase inhibitor, in epilepsy and migraine prophylaxis may frequently cause dose-dependent m tabolic acidosis (In control ed trials, 32% and 67% for adjunctive treatment in adults and pediatric patients, respectively, and 15 to 25% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 20 mEq/L; 3% and 11% for adjunctive treatment in adults and pediatric patents, respectively, and 1 to 7% for monotherapy f epilepsy, with decrease in serum bicarbonate to less than 17 mEq/L) and may exacerbate the risk of metformin-induced lactic acidosis. (See 7.1 DRUG INTERACTIONS and 12.5 CLINICAL PHARMACOLOGY) The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as ma aise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis.

Patients should be educated to promptly report these symptoms should they occur. If p esent, metformin hydrochloride should be withdrawn until lactic acidosis is ruled out. Se um e ectrolytes, ketones, b ood glucose, blood pH, lactate levels, and blood metformin levels may be useful. Once a p tient is stabilized on any dose level of metformin hydrochloride, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to recur. Later occurrence of gastrointestinal symptoms could be due to actic acidosis or other serious disease. Levels of fasting venous plasma lactate above the upper limit of normal but ess than 5 mmol/L in patients taking metformin hydrochloride 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 prob ems in samp e handling. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosi ackin 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, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hyd och oride 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 metform n. Such management often esu ts in prompt reversal of symptoms and recovery [See **CONTRAIND CATIONS (4)**]

5.2 Monitoring of Renal Function

M formin is substantia ly e creted by the kidney, and the risk of metfo min ccumulation and la tic acidosis increases with the degree of renal impairment. Therefore metformin hydroch oride is contraindicated in patients with renal impairment.

Before initiation of metformin hydroch oride and at least annually thereafter, renal function shou d be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated (e g , elderly), renal function should be assessed more frequently and metformin hydrochloride discontinued if evidence of renal impairment is present. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptib e to deve oping lactic acidosis.

Use of concomita t medications that may affect renal function or metformin disposition — Concomitant medication(s) that may a fect 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 **DRUG NTERACT ONS (7)**], shou d be used with caution.

Radio ogical studies and surgical procedures

Radiologic studies involving the use of intravascular iodinated contrast materials (for examp e, intravenous urogram, intravenous cholangiography, angiography, and computed tomography) can lead to acute a teration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, metformin hydrochloride should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-eva uated and found to be normal.

Metformin hydroch oride therapy shou d 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.

5.3 Hypoxic States

Ca dio ascular co lapse (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 hydroch oride therapy, the drug shou d be promptly discontinued.

5.4 Alcohol Intake

Alcohol is known to potentiate the effect of metformin on lactate metabo ism. Patients, therefore, should be warned against excessive a cohol intake whi e receiving metformin hydrochloride.

5.5 Impaired Hepatic Function

Because impai ed hepatic function has been associated with some cases of lactic acidosis metformin hydrochloride should genera ly be avoided in patients with clinical or laboratory evidence of hepatic disease.

5.6 Vitamin B_{12} Levels

n controlled, 29-week c inical trials of immediate release metformin, a decrease to subnormal evels of previously no mal serum itamin B_{12} evels, 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 reversib e with discontinuation of metformin hydrochloride or Vitamin B_{12} supplementation. Measurement of hemato ogic parameters on an annual basis is advised in patients on metformin hydrochloride and any apparent abnorma ities should be appropriately investigated nd managed. Cert in individuals (those with inadequate Vitamin B_{12} or ca cium intake or absorption) appear to be predisposed to developing subnormal Vitamin B_{12} leve s. In these patients, routine serum Vitamin B_{12} measurements at two- to three-year interva s may be useful.

5.7 Hypoglycemia

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, b t could occur when caloric intake is deficient, when strenuous exercise is not compensated by ca oric supplementation, or during concomitant use with other glucose- owering agents (such as sulfony ureas and insulin) or ethanol. Elderly, debi itated, or malnourished patients, and those with adrenal or pituitary insufficiency or a cohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in peop e who are taking beta-adrenergic b ocking drugs.

5.8 Macrovascu ar Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with metformin hydrochloride or any other oral anti-diabetic drug.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

n c inical tria s conducted in the U.S., over 000 patients with type 2 diabetes mel itus have been treated with metformin hydrochloride extended- e ease tablets 500-2000 mg/day in active-contro led and placebo-control ed studies with the 500 mg dosage form.

n the 24-week monotherapy trial comparing metformin hydroch oride extended-re ease tablets to immediate-re ease metformin, serious adverse reactions were reported in 3.6% (9/528) of the metformin hydrochloride extended-re ease tablets treated patients compared to 2.9% (5/174) of the patients treated with immediate-release metformin. In the add-on to sulfony urea study, patients receiving background glyburide therapy were randomized to receive add-on treatment of either one of three different regimens of metformin hydrochloride extended-release tab ets or placebo. In total, 431 patients received metformin hydroch oride extended-re ease tablets and glyburide and 144 patients received placebo and glyburide. A serious adverse reaction was reported in 2.1% (9 431) of the metformin hydroch oride extended-re ease tablets and glyburide treated patients compared to 1.4% (2/ 44) of the placebo and glyburide treated patients. When the data from the monotherapy and add-on to su fonylurea clinical tria s were combined, the most frequently (incidence ≥ 0.5 %) reported serious adverse reactions classified by system organ class were gastrointestinal disorders (1.0% of metformin hydroch oride extended-re ease tablets treated patients compared to 0% of patients not treated with metformin hydrochloride) and cardiac disorders (0 4% of metformin hydrochloride extended-re ease tab ets tre ted patients compared to 0.5% of patients not treated with metformin hydrochlo ide). Only 2 serious adverse reactions (unstable angina [n=2] and pancreatitis [n=2]) we e repo ted in more than one metformin hydrochloride extended-re ease tablets treated patient.

Adverse reactions reported in greater than 5% of patients treated with metformin hyd och oride extended-release tablets that were more common in the combined m tformin hydrochlo ide extended-release tablets and glyburide group than in the placebo and glyburide group are shown in Tab e 1.

n 0.7% of patients treated with metformin hydroch oride extended-release tablets and glyburide, diarrhea was responsible for discontinuation of study medication compared to no patients in the placebo and glyburide group.

Table 1: Treatment-Emergent Adverse Reactions Repo ted By >5%* of Patients for the Combined Metformin Hydrochlo ide Extended-Release Tablets Groups Versus Placebo Group

Adverse Reaction	Metformin Hydrochloride E tended-Release Tablets + Glyburide (n = 431)	P acebo + Glyburide (n = 144)
Hypoglycemia	13.7%	4.9%
Diarrhea	12.5%	5.6%
Nausea	6.7%	4.2%

* AR's that were more common n the metformin hydrochloride extended-release tablets treated than in the placebo-treated patients.

6.2 Laboratory Tests

Vitamin B_{12} concentrations

Metformin may lower serum vitamin B_{12} conce trations. Measurement of hemato ogic parameters on an annual basis is advised in patients on metformin hydrochloride extended-re ease tablets and any apparent abnormalities should be appropriately investigated and managed [See **WARN NGS AND PRECAUTIONS (5.6)**]

7. DRUG INTERACTIONS

7.1 Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic m tabolic acidosis. Concomitant use of these drugs may induce metabo ic acidosis. Use these drugs with caution in patients treated with metformin, as the risk of lactic acidosis may increase.

7.2 Cationic Drugs

Cationic drugs (e.g., ami oride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancom cin) that are e iminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Although such interactions remain theoretica (except for cimetidine), careful patient monitoring and dose adju tment of metformin hydrochloride and/ or the interfering drug is recommended in patients who are taking cationic medications that a e excreted via the proximal renal tubular secretory system.

7.3 Drugs Hecting Glycemic Control

Certain drugs tend to produce hyperglycemia and may lead to oss of glycemic control. These drugs include the thiazides and other diuretics, co ticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered to a patient receiving metformin hydrochloride, the patient shou d be closely obser ed for oss of blood glucose control. When such drugs are withdrawn from a patient receiving metfo min hydrochloride, the patient should be observed closely for hypoglycemia.

8. USE N SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg kg/day, which represent 3 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparison for rats and rabbits, respectively. However, because animal reproduction studies are not always predictive of human response, Metformin HCl shou d not be used during pregnancy unless clearly needed.

8.2 Labor and Delivery

The safety and e fectiveness of metformin hydroch oride used during labor and delivery has not been eva uated in human studies.

8.3 Nursing Mothers

Studies in lactating rats show that metformin is excreted into milk and reaches leve s compar b e to those in plasma. Similar studies have not been conducted in nursing mothers. Thus, the potential for hypoglycemia in nursing infants after Metformin HCl Oral Solution may exist.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been estab ished. Metfo min hydroch oride is not recommended in pediatric patients below the age of 8 years.

8 5 Geriatric Use

C inical studies of metformin hydroch oride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported c inical experience has not identified di ferences in esponses between the elderly and younger patients. n general, dose se ection for an elderly patient should be cautious, usu lly starting at the ow end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other d ug therapy and the higher risk of lactic acidosis. [See **WARNINGS AND PRECAUT ONS (5)**]

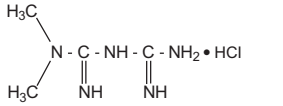
10. OVERDOSAGE

No cases of overdose were reported during metformin hyd och oride extended-re ease tablets clinical tria s. It would be expected that adverse reactions of a more intense character including epigastric discomfort, nausea, and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen. Shou d those symptoms persist, lactic acidosis shou d be exc uded.

Ove dose of m tformin hydrochloride has occurred, inc uding ingestion of mou ts 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 repo ted in approximately 32% of metformin overdose cases [See **WARNINGS AND PRECAUT ONS (5.1)**] Metformin is dialyzab e with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

11. DESCRIPTION

Metformin hydrochloride extended-re ease tablets USP are o ral nithyperglycemic medication used in the management of type 2 diabetes. Metformin hydroch oride (N,N-dimethylimidodicarbonimidic diamide hydroch oride) is not chemically or pharmaco ogica ly related to any other classes of oral antihyperglycemic agents. The structural formula of metformin hydroch oride (metformin HCl) is as shown:



Metformin HCl is a white to off-white crysta line compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 65.63. Metformin HCl is freely solub e in water and is practica ly 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 hydroch oride extended-release tablets are modified release dosage forms that cont in 500 mg or 1000 mg of metformin HCl. Each tablet contains ammonio methacrylate copolymer, colloidal silicon dioxide, dibutyl sebacate, hypromel ose, magnesium stearate, microcrystalline cel ulose, povidone and talc.

USP dissolution test for metformin hydrochloride extended-re ease tab ets is pending.

Metformin hydrochloride extended-release tablets USP, 500 and 000 mg t b ets both utilize polymer-based, oral drug delivery systems, which allow de ivery of metformin HCl to the upper gastrointestinal (GI) tract.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of A tion

Metformin is a biguanide that improves glucose tolerance in patients with type 2 diabetes, owering both basal and postprandial plasma g ucose. Metformin decreases hepatic glucose production, decre ses intestinal absorption of g ucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metfo min does not produce hypoglycemia in patients with type 2 diabetes or in healthy subjects except in special circumst nces, [see **WARNINGS AND PRECAUTIONS (5)**] and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin evels and day ong plasma insulin response may actua ly decrease.

12.3 Pharmacokinetics

Absorption and Bioavai ability

Fol owing a single oral dose f 000 mg (2x500 mg tablets) metformin hydroch oride extended-release tab ets after a meal, the time to reach maximum plasma metformin concentration (T_{max}) is achieved at approximately 7 to 8 hours.

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In both single and mu tiple-dose studies in hea thy subjects, once daily 000 mg (2x500 mg tablets) dosing provides equivalent systemic exposure, as measured by area-under the-curve (AUC), and up to 35% higher $C_{ss,max}$ of metformin relative to the immediate release given as 500 mg twice daily Metformin hydrochloride extended-re ease tab ets must be administered immediately after a meal to maximize therapeutic benefit.

Single oral doses of metformin hydrochloride extended-release tablets from 500 mg to 2500 mg resulted in less than proportional increase in both AUC and C_{max}. Low fat and high fat meals increased the systemic exposure (s measured by AUC) from metformin hydrochloride extended re ease tab ets by about 38% and 73%, respectively, elative to fasting. Both mea s prolonged metformin T_{max} by approximately 3 hours but C_{max} was not affected.

In a two-way, sing e-dose crossover study in healthy vo unteers, the 000 mg tablet was found to be bioequivalent to two 500 mg tablets under fed conditions based on equivalent C_{max} and AUCs for the two formulations.

Distribution

The app rent volume of distribution (V_d) of metformin fol owing single oral doses of 850 mg immediate release metformin hydrochloride averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most ikely as a function of time. At usual c inical doses and dosing schedu es of metformin, ste dy state plasma concentrations of metformin are reached within 24 to 48 hours and are generally < 1 mcg/mL. During controlled clinical trials, which served as the basis of approval for metformin, maximum metformin plasma evels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism

Intravenous single-dose studies in healthy subjects demonstrate that metformin is excreted unchanged in the urine od does not undergo hepatic metabolism (no metabo ites have been identified in humans), nor biliary excretion. Metabolism studies with extended-release metformin tab ets have not been conducted.

Excretion

Renal c earance is approximately 3 5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin e imination. Fo lowing oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma e imination ha f-life of approximately 6.2 hours. n blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

12.4 Specific Populations

Renal impairment

Fo lowing a single dose administration of metformin hydroch oride extended-release tablets, 500 mg in patients with mi d and moderate renal failure (based on measured creatinine c earance), the oral and renal c earance of metformin we e decreased by 33% and 50% and 16% and 53%, respectively (See **WARN NGS AND PRECAUTIONS (5)**. Metformin peak and systemic exposure was 27% and 6 % greater, respectively in mild renal impaired and 74% and 2.36 fold greater in moderate renal impaired patients as compared to hea thy subjects.

Use of metformin in patients with renal impairment increases the risk for lactic acidosis.

Metformin hydrochloride extended-release tablets are contraindicated in patients with enal impairment. [See **CONTRAINDICATIONS (4) and WARNINGS AND PRECAUTIONS (5.2)**]

Hepatic Impairment

No pharmacokinetic studies of metformin hydroch oride extended-re ease tab ets have been conducted in subjects with hepatic impairment. Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Metfo min hydrochloride extended-release tablets are not recommended in patients with hepatic impairment. [See **WARNINGS AND PRECAUTIONS (5.5)**]

Geriatrics

Limited data from control ed pharmacokinetic studies of metformin hydroch oride in hea thy e derly subjects suggest that total plasma c earance of metformin is decreased by 35%, the half-life is pro onged by 64% and C_{max} is increased by 76%, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function. Metformin treatment should not be initiated in patients of any age un ess measurement of creatinine c earance demonstrates that renal function is normal [See **WARNINGS AND PRECAUTIONS (5)** and **DOSAGE AND ADMINISTRATION (2)**]

Gender

In the pharmacokinetic studies in healthy volunteers, there were no important differences between male and female subjects with respect to metformin AUC and $t_{1/2}$. However, C_{ss} for m tformin was 40% higher in fema e subjects as compared to ma es. The gender differences for C_{max} a e unlikely to be c inica ly important. Similarly, in control ed clinical tudies in patients with type 2 diabetes, the antihyperglycemic effect of metformin hydrochloride tab ets was comparable in males and fema es.

Race

There were no definitive conclusions on the differences between the races with respect to the pharmacokinetics of metformin because of the imbalance in the respective sizes of the racial groups. However, the data suggest a trend towa ds higher metformin C_{max} nd AUC values for metformin are obtained in Asian subjects when compared to Caucasian, Hispanic and Black subjects. The differences between the Asian and Caucasian groups are un likely to be clinically important. In control ed c inical studies of metformin hydrochloride in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n = 249), blacks (n = 51) and Hispanics (n = 24).

Pediatrics

No pharmacokinetic data from studies of metformin hydroch oride extended-release tablets in pediatric subjects are availab e.

12.5 Drug Interactions

Specific pharmacokinetic drug intera tion studies with metformin hydrochloride extended- e ease tablets have not been performed except for one with glyburide. However, such studies have been performed on metformin.

Table 2: Effect of Coadministered Drug on P asma Metformin Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug[a]	Dose of Metformin[a]	Geomet ic Mean Rat o (ratio with/ without coadministered drug) No effect = 1.00	
			AUC[b]	C_{max}
No dosing adjustments required for the fo lowing:				
Glybur de	5 mg	500 mg[4]	0.98[2]	0.99[2]
Furosemide	40 mg	850 mg	1.09[2]	1.22[2]
N fedipine	10 mg	850 mg	1.16	1.21
Proprano ol	40 mg	850 mg	0 90	0.94
Ibuprofen	400 mg	850 mg	1.05[2]	1.07[2]
Cationic drugs eliminated by renal tubu ar secretion may reduce metformin elimination: use with caution. [See **WARN NGS AND PRECAUTIONS (5)** and **DRUG INTERACTIONS (7)**]				
Cimetidine	400 mg	850 mg	1 40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis: use with caution [See **WARNINGS AND PRECAUTIONS (5)** and **DRUG INTERACTIONS (7)**]				
Topiramate	100 mg	500 mg[4]	1.25[2]	1.17

1. All metformin and coadm n stered drugs were given as sing e doses
2. AUC – AUC $_{\infty}$
3. Ratio of arithmetic means
4. Metformin hydrochloride extended-re ease tab ets, 500 mg
5. t steady state with topiramate 00 mg every 12 hours and metformin 500 mg every 2 hours; AUC – $AUC_{0,t,s,s}$

Table 3: Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug[a]	Dose of Metformin[a]	Geometric Mean Ratio (ratio with without coadministered drug) No effect = 1.00	
			AUC[b]	C
No dosing adjustments required for the fo lowing:				
Glyburide	5 mg	500 mg[4]	0.78[2]	0.63[2]
Furosemide	40 mg	850 mg	0.87[2]	0.69[2]
Nifedipine	10 mg	850 mg	1. 0[2]	1.08
Proprano ol	40 mg	850 mg	1.01[4]	0.94
Ibuprofen	400 mg	850 mg	0.97[2]	1.01[5]
C met d ne	400 mg	850 mg	0.95[2]	1.01

1. A l metformin and coadm nistered drugs were given as sing e doses
2. AUC – AUC
3. Ratio of arithmetic means, p-va ue of difference < 0.05
4. $AUC_{0,24}$ hr reported
5. Ratio of arithmetic means

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term carcinogenicity studies have been perfo med in Sprague Daw ey rats at doses of 50, 300, and 450 mg/kg/ day in males and 150, 450, 900, and 200 mg/kg/day in females. These doses are approximately 2, 4, and 8 times m ma es, and 3, 7, 2, and 16 times in females of the maximum recommended human daily dose of 2000 mg based on body surface a ea comparisons. No evidence of carcinogenicity with metformin was found in either ma e or female rats. A ce cinogenicity study was also performed in Tg.AC transgenic mice at doses up to 2000 mg applied dermally. No evidence of ca cinogenicity was observed in ma e or female mice.

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

14. CLINICAL STUDIES

Metformin hyd roch oride extended-re ease tab ets have been studied as mon therapy and in combination with a su fonylurea and insulin. Other formulations of metformin have been studied with other classes of antihyperglycemic agents, either as immediate or as extended re ease tab ets.

Double-Blind, Randomized, Parallel Group Clinical Trial to Compare the Efficacy, Safety, and Tolerability of Metformin ER (M-ER) Tablets and Metformin Immediate Release (M-IR) Tablets in the Treatment of Type 2 Diabetes Me litus

In a mu ticenter, randomized, double-blind, active-contro led, dose-ranging, para el group trial metformin hydrochloride extended-release tab ets 1500 mg once daily, metformin hydrochloride extended-release tablets 500 per day in divided doses (500 mg in the morning and 000 mg in the evening), and metformin hydrochloride extended-release tablets A 2000 mg once daily were compared to immediate-release metformin 500 mg per day in divided doses (500 mg in the morning and 000 mg in the evening). This trial enrol ed patients (n = 338) who were newly diagnosed with diabetes, patients treated only with diet and e ercise, patients treated with a single anti-diabetic medication (su fonylureas, alpha-glucosidase inhibitors, thiazolidinediones, or meglitinides), and patients (n = 368) receiving metformin up to 500 mg/ day p us a sulfony ureas at a dose equal to or ess than one-half the maximum dose. Patients who were enro led on monotherapy or combination anti-diabetic therapy underwent a 6-week washout. Patients randomized to metformin hydrochloride extended-release tab ets began titration from 000 mg day up to their assigned treatment dose over 3 weeks. Patients randomized to immediate-re ease metformin initiated 500 mg twice daily for 1 week followed by 500 mg with breakfa t and 000 mg with dinner for the second week. The 3-week treatment period was fo lowed by an additional 21-week period at the randomized dose. For HbA1c and fasting plasma glucose, each of the metformin hydrochloride extended-release tablets regimens was at least as effective as immediate-release metformin. Additiona ly, once daily dosing of metformin hydrochloride extended-re ease tablets was as e fective as twice daily dosing of the immediate release metformin formulation.

Table 4: Mean ± SE Changes f om Baseline to Final Visit in HbA_{1c} Fasting P asma G ucose and Body Weight for the Metformin Hydrochloride E tended-Release Tablets and Metformin Immediate-Release Treatment Groups (First 24-Week Study)

Parameter	Metformin Hydrochlor de E tended-Release Tab ets			Metformin immediate release
	1500 mg once daily (n = 178)	1500 mg in divided doses (n = 182)	2000 mg once daily (n =172)	1500 mg in divided doses (n = 174)
HbA_{1c} (%)				
N	169	175	59	170
Base ine	8.2 ± 0 3	8.5 ± 0 2	8.3 ± 0 2	8.7 ± 0.3
Mean Change ± SE at Final V s t	-0.7 ± 0.1	-0.7 ± 0.1	-1.1 ± 0.1	0.7 ± 0.1
Mean D fference ± SE from Metformin IR	-0 0 ± 0.1	-0 0 ± 0.1	-0 4 ± 0.1	N/A
98.4% CI for Difference	(-0.3, 0.3)	(-0.3, 0.3)	(-0.7, -0.1)	
Fasting Plasma Glucose (mg/dL)				
N	175	179	170	172
Base ne	190 ± 10	192 3 ± 0	184 ± 10	97 ± 11
Mean Change ± SE at Final Visit	-39 ± 4	-32 ± 4	-42 ± 5	-32 ± 5
Mean Difference ± SE from Metformin IR	-6 ± 4	0 ± 4	-10 ± 4	N/A
95% CI for D fference	(- 5, 2)	(-8, 9)	(-19, -1)	
Body Weight (kg)				
N	176	180	171	173
Base ne	88.2 ± 3.7	90 5 ± 3.7	87.7 ± 3.7	88.7 ± 3.9
Mean Change ± SE at Final Visit	-0 9 ± 0 4	-0.7 ± 0 4	-1.1 ± 0 4	-0 9 ± 0.4
Mean Difference ± SE from Metformin IR	-0.1 ± 0 4	0.2 ± 0.4	-0.3 ± 0 4	N/A
95% CI for D fference	(-0 9, 0.7)	(-0 6, 0 9)	(-1.0, 0.5)	

A Double Blind, Randomized, Parallel-Group Study to Compare the Safety, Efficacy, and Tolerability of Metformin E tended Release (M-ER) Tablets in Combination with a Sulfonylurea (SU) and SU Alone in the Management of Patients with Type 2 Diabetes Mellitus

a double-b ind, randomized, placebo-control ed (glyburide add-on) mu ticenter trial, patients with type 2 diabetes mel itus who were newly diagnosed or treated with diet and exercise (n = 144), or who were receiving monotherapy with metformin, su fonylureas, alpha-glucosidase inhibitors, thiazo idinediones, or meglinitides, or treated with combination therapy consisting of metformin/glyburide at doses up to 000 mg metformin + 0 mg glyburide per day (or equivalent doses of glipizide or g imepi ide up to ha f the maximum therapeutic dose (n = 421) were enrolled. A l patients were stabilized on glyburide for a 6-week run-in period, and then randomized to 1 of 4 treatments: placebo + glyburide (glyburide a one ; metformin hydrochloride extended-re ease tablets 500 mg once a day + glyburide, metformin hydrochloride extended- e ease tablets 2000 mg once a day + glyburide, or metformin hydroch oride extended-re ease tablets 000 mg twice a day + glyburide. A 3-week metformin hydroch oride extended-release tablets titration phase was fol owed by a 21-week maintenance treatment phase. Use of insu in nd oral hypoglycemic agents other than the study drugs were prohibited. The difference in the change from Baseline in HbA1c evels between the combined metformin hydrochloride extended-re ease tablets + glyburide groups and the glyburide only group was statistically significant at week 24 (p<0.001). The changes in glycemic control across the three metformin hydroch oride extended-release tablets + glyburide groups were comparable.

Table 5: Mean ± SE Changes from Baseline to Final Visit in HbA1c, Fasting Plasma Glucose and Body Weight for the Metformin Hydrochloride Extended-Release Tab ets/Glyburide Groups and Placebo/Glyburide Treatment Group (Second 24-Week Study)

Parameter	Metformin Hydrochloride Extended-Release Tab ets + Glyburide*			Placebo/ Glyburide* (n = 144)
	1500 mg QD (n =144)	1000 mg BID (n = 141)	2000 mg QD (n = 146)	
HbA_{1c} (%)				
N	136	36	44	141
Baseline	7 9 ± 0.1	7.8 ± 0.1	7.7 ± 0.1	8.1 ± 0.1
Mean Change ± SE at Final Visit	-0.7 ± 0.1	-0.8 ± 0.1	-0.7 ± 0.1	-0.1 ± 0.1
Mean Difference ± SE from Glyburide Alone	-0.8 ± 0.1	-0.9 ± 0.1	-0.8 ± 0.1	N/A
95% CI for D fference	(-1.0, -0.6)	(-1.1, -0.7)	(-1.0, -0.6)	
p-va ue for pairwise compar son	< 0.001	< 0.001	< 0.001	
Fasting Plasma Glucose (mg/dL)				
N	43	41	45	144
Base ne	63 ± 5	63 ± 5	59 ± 5	164 ± 5
Mean Change ± SE at Final Visit	-14 ± 4	- 6 ± 4	-9 ± 4	6 ± 4
Mean Difference ± SE from Glyburide Alone	-29.2 ± 4.9	-31.2 ± 40 9	-24 9 ± 4.9	N/A
95% CI for D fference	(-39, -20)	(-41, -22)	(-35, - 5)	
p-va ue for pairwise compar son	< 0.001	< 0.001	< 0.001	
Body We ght (kg)				
N	43	41	46	144
Base ne	89 4 ± 11 2	03.7 ± 11.2	02 9 ± 11.2	95.6 ± 8.0
Mean Change ± SE at Final Visit	0 3 ± 1.1	0.1 ± 1.1	0 ± 1.1	0.7 ± 1.0
Mean Difference ± SE from Glyburide Alone	-0.4 ± 0 5	-0.6 ± 0.5	-0.7 ± 0.5	N/A
95% CI for D fference	(-1 5, 0.6)	(-1.7, 0 4)	(-1 8, 0 3)	
p-va ue for pairwise compar son	0.4 0	0.230	0. 56	

* - Glyburide was adm n stered as 10 mg at breakfast and 5 mg at dinner.

A 24-week, doub e blind, placebo-contro led trial of immediate release metformin plus insulin versus insu in plus placebo was conducted in patients with type 2 diabetes who failed to achieve adequate glycemic control on insulin alone. Patients randomized to receive metformin plus insulin achieved a mean reduction in HbA_{1c} of 2.10%, compared to a 1.58% reduction in HbA_{1c} achie ed by insu in plus placebo. The improvement in glycemic control w s achieved at the final study visit with 6% ess insu in, 93 0 U/day vs. 110.6 U/day, metformin plus insulin versus insulin p us placebo, respectively, p=0.04.

A second double-blind, placebo-control ed study (n=51), with 16 weeks of randomized treatme t, demonstrated that in patients with type 2 diabetes control ed on insu in for 8 weeks with an average HbA_{1c} of 7 46 ± 0.97%, the addition of metformin m intained similar glycemic control (HbA $_{1c}$ 7.15 ± 0.61 versus 6.97 ± 0.62 for m tformin plus insulin and placebo p us insu in, respectively) with 9% ess insu in versus baseline (reduction of 23.68 ± 30.22 versus an increase of 0.43 ± 25 20 units for metformin p us insu in and placebo plus insulin, p 0 01). In addition, this study demonstrated that the combination of metformin plus insulin resulted in reduction in body weight of 3.11 ± 4.30 lbs, compared to an increase of 1.30 ± 6.08 bs for placebo p us insu in, p=0.01.

16. HOW SUPPLIED/STORAGE AND HANDLING

Metformin hydrochloride extended-release tablets USP, 500 mg are availab e as white to o f white, oval shaped, biconvex coated tablet, debossed with "L4 " on one side and "LU" on the other side.

Metformin hydrochloride extended-release tab ets USP, 000 mg are available as white to off white, oval shaped, biconvex coated tablet, debossed with "L42" on one side and "LU" on the other side.

They are supp ied as fol ows:

Strength	Package	NDC Code
500 mg	Bo ttes of 00	68180 338-01
500 mg	Bo ttes of 500	68180 338-02
500 mg	Bo ttes of 000	68180 338-03
1000 mg	Bo ttes of 90	68180 339-09
1000 mg	Bo ttes of 00	68180 339-01
1000 mg	Bo ttes of 500	68180 339-02

Store at 25°C (77°F ; excursions permitted to 15° to 30°C (59° to 86°F ; see [USP Contro led Room Temperature.]

17. PATIENT COUNSELING INFORMAT ON

nformation for Patients

- Patients shou d be informed of the potential risks and benefits of metformin hydrochloride extended-re ease tab ets and of a ternative modes of therapy. They shou d a so be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, and hemog obin A C. During periods of stress such as fever, trauma, infe tion, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.
- The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the metformin hydrochloride extended-release tablets sections, should be explained to patients. Patients should be dvised to discontinue metformin hydrochloride extended-release tab ets immediately and to promptly notify their he th practitioner if unexplained hyperventilation, mya gia, malaise, unusual sommolence, or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of metformin hydrochloride extended-re ease tablets, gastrointestinal symptoms, which are common during initiation of metformin therapy, are un ikely to recur. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.
- Patients shou d be advised to notify their hea th practitioner or ca l the Poison Control Center immediately in case of metformin hydrochloride extended re ease tab ets overdose
- Patients should be informed about the importance of regular testing of renal function and hematological par meters when receiving t eatment with metfo min hydrochloride extended-re ease tab ets.
- Patients should be counseled against excessive a cohol intake, either acute or chronic, while receiving metformin hydrochloride extended-release tablets.
- Metformin hydrochloride extended-release tablets alone do not usually cause hypoglycemia, a though it may occur when metformin hydrochloride extended-release tablets is used in conjunction with insu in secretagogues, such as sulfonylureas and insulin.
- Patients shou d be informed that metformin hydrochloride extended-release tab ets must be swa lowed whole and not crushed or chewed, and that the inactive ing edients may occasionally be e iminated in the feces as an inso uble soft, hydrated mass that may resemble the original tablet.

Manufactured for:
Lupin Pharmaceutica s, Inc.
Baltimore, Maryland 2 202
United States

Manufa tured by:
Lupin Limited
Goa 403 722
NDIA

January 2012 ID#: 227224

PAT ENT INFORMAT ON

Metformin Hydrochloride Extended-Release Tablets, USP 500 mg and 1000 mg

Read the patient info rmation that comes with metformin hydroch oride extended-release tab ets 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 ta king with your doctor about your medical condition or treatment. 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 is the most important information I should know abo t metformin hydrochloride extended-release tablets? Serious side effects can happen in people taking metformin hydrochloride e tended-release tab ets, including:

Lactic Acidosis. Metformin hydrochloride, the medicine in metformin hydrochloride extended-release tablets can cause a rare, but serious condition ca led lactic acidosis (a bui dup of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

Stop taking metformin hydrochloride e tended-release tablets and call your doctor right away if you get any of the fol owing symptoms of lactic acidosis:

- feel very weak or tired
- have unusua (not normal) muscle pain
- have trouble b eathing
- have unusual sleepiness or sleep longer than usual
- have unexplained stomach or intestinal prob ems with nausea and vomiting, or diarrhea
- feel co d, especia ly in your arms and legs
- feel dizzy or ightheaded
- have a s ow or irregular heartbeat

You have a higher chance for ge ting actic acidosis with metformin hydrochloride extended-release tablets if you:

- have kidney prob ems. People whose kidneys are not working properly should not take metformin hydroch oride extended-release tablets.
- have liver problems
- have congestive heart failure that requires treatments with medicines
- drink a lot of alcoho (very often or short term "binge" drinking)
- get dehydrated (ose 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 ce tain x-ray tests with injectable dyes or contrast agent
- have surgery
- have a heart attack, severe infection, or stroke

What is e metformin hydrochloride e tended-release tab ets?

- Metfo min hydroch oride extended-release tab ets are a prescription medicine that contains metformin hydrochloride used with diet and exercise to he p control high blood sugar in adults with type 2 diabetes.
- Metfo min hydrochloride extended-re ease tab ets are not for peop e with type 1 diabetes.
- Metfo min hydrochloride e tended-release tablets are not for people with diabetic ketoacidosis (increased ketones in your b ood or urine).

It is not known if metformin hydrochloride extended-release tablets are safe and effective in children younger than 18 years o d.

Who should not take metformin hydrochloride extended-release tablets?
Do not take metformin hydroch oride e tended-release tablets if you:

- have kidney p oblems
- are a iergic to the metformin hydroch oride in metformin hydrochloride extended-release tablets or any of the ingredients in metfo min hydrochloride extended-release tablets. See the end of this eaflet for a list of ingredients in metformin hydrochloride extended- e ease tab ets.
- you are going to get an injection of dye or contrast agents for an x-ray procedure, metformin hydroch oride extended-release tablets wi l need to be stopped for a short time. Talk to your doctor about when you should stop metformin hydroch oride extended-release tab ets and when you shou d start metformin hydroch oride extended-release tablets again. See "What is the most important information I should know about metformin hydrochloride extended-release tablets?"
- have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in your blood or urine).

What shou d I tell my doctor before taking metformin hydrochloride e tended-release tablets?

Before you take metformin hydroch oride extended-release tablets, tell your doctor if you:

- have type 1 diabetes. Metformin hydrochloride extended-release tablets shou d not be used to treat people with type 1 diabetes.
- have a history or risk for diabetic ketoacidosis (high evels of certain acids, known as ketones, in the blood or urine). Metformin hydrochloride extended-release tablets should not be used for the treatment of diabetic ketoacidosis.
- have kidney problems
- have liver prob ems
- have heart prob ems, including congestive heart failure.
- drink a coho l very often, or drink a ot of a coho l in short term (binge) drinking
- are taking insu in
- have any other medical conditions
- **are pregnant or planning to become pregnant.** It is not known if metformin hydroch oride extended-release tablets can harm your unborn baby. f you are pregnant, talk with your doctor about the best way to control your blood sug r while you are pregnant.
- **are breastfeeding or plan to breastfeed.** It is not known if metformin hydrochloride extended-release tablets passes into your breast milk. Ta k with your doctor about the best way to feed your baby while you take metfo min hydrochloride extended-re ease tab ets.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supp ements. Know the medicines you take. Keep a list of them to show your doctor and pharmacist. Talk to your doctor before you start any new medicine.

Metformin hydrochloride extended-release tablets may affect the way other medicines work, and other medicines may a fect how metformin hydroch oride extended-release tablets works.

How should I take metformin hydrochloride extended-release tablets?

- Take metformin hydrochloride extended-re ease tab ets exactly as your doctor tells you.
- Metfo min hydrochloride extended-re ease tab ets should be taken 1 time per day with your evening meal.
- Swa low metformin hydrochloride extended-release tablets whole. Do not crush, cut, dissolve, or chew metfo min hydrochloride extended-re ease tab ets.
- Te l your doctor if you cannot swallow tab ets whо e. Your doctor may prescribe a different medicine for you.
- You may sometimes pass an inso uble so t, hydrated mass in your stools (bowel movement) that looks like metfo min hydrochloride extended-re ease tab ets. It is normal to see this in your stool.
- When your body is under some type of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these prob ems.
- Your doctor should do blood tests to check how we l your kidneys and liver are working befo e and du ing your treatment with metformin hydrochloride extended-re ease tab ets.
- Your healthcare provider will check your diabetes with regular b ood tests, inc uding your b ood sugar evels and your hemog obin A C.
- Fo low your doctor's instructions for treating b ood sugar that is too ow (hypoglycemia). Talk to your do tor if low blood sugar is a prob em for you. See **"What are the possible side effects of metformin hydrochloride extended-release tablets?"**
- Check your blood sugar regularly and as your doctor te ls you to.
- Take your prescribed diet and exercise program and test your blood sugar regularly while taking metformin hydrochloride extended-release tablets.
- If you miss a dose of metformin hydrochloride extended-release tablets, resume dosing according to schedule.
- If you take too much metformin hydroch oride extended-release tablets, call your doctor, or go to the nearest hospital emergency room right away.

What are the side effects of metformin hydroch oride e tended-release tablets?
Metformin hydroch oride e tended-release tablets can cause se ious side effects, including:

- See **"What is the most important information I should know about metformin hydrochloride e tended-release tablets?"**
- **Low blood sugar (hypoglycemia).** If you take metformin hydroch oride extended-release tablets with another medicine that can cause low b ood sugar, such as su fonylureas or insulin, you have a higher isk of having low blood sugar. Te l your doctor if you take other di betes medicines. If you have symptoms of ow blood sugar, you shou d check your b ood sugar and treat if ow, then ca l your doctor. Symptoms of ow blood sugar include:
  - o shaking
  - o sweating
  - o rapid heartbeat
  - o change in vision
  - o hunger
  - o headache
  - o change in mood

Common side e fects of metformin hydrochloride e tended-release tab ets include:

- hypoglycemia
- diarrhea
- nausea
- upset stomach or stomach pain

Taking metformin hydroch oride extended-release tablets with your evening meal can help lessen the common stomach side effects of metformin that usua ly happens at the beginning of treatment. f you have unexplained stom ch problems, tell your doctor. Stomach problems that start later, during treatment may be a sign of something more serious.

Tell your doctor if these symptoms return, as they may be symptoms of lactic acidosis.

Tell your doctor if you have side effects that bother you or that do not go away.

These are not a l of the possib e side effects of metformin hydrochloride extended-re ease tab ets. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA- 088.

How should I store metformin hydrochloride extended-release tablets?

- Store at 25°C (77°F ; excursions permitted to 5° to 30°C (59° to 86°F ; see [USP Contro led Room Temperature.]

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

General information about the s fe and e fective use of metformin hydrochlo ide extended-release tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information eaflet. Do not use metformin hydrochloride extended-release tablets for a condition for which it was not prescribed.

Do not give metformin hydroch oride extended-release tablets to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information summarizes the most important information about metformin hydrochloride extended-release tab ets. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about metformin hydrochloride extended-release tablets that is w itten for health professionals.

For more information, go to www.lupinpharmaceuticals.com or ca l 1-800-399-2561.

What are the ingredients in metformin hydrochloride e tended-release tablets?

Active ingredient: 500 mg or 1000 mg of metformin HCl

Inactive ngredient: E ch tablet contains ammonio methacrylate copolymer, col oidal si icon dioxide, dibutyl sebacate, hypromellose, magnesium stearate, microcrystal ine cellulose, povidone and talc. Metformin hydrochloride extended-re ease t ab ets 500 mg and 000 mg tablets both utilize advanced, polymer-based, oral d ug delivery systems, which a low de ivery of metformin HCl to the upper GI tract.

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as we l as it should. Your body can also make too much sugar. When this happens, sugar (glucose) bui ds up in the blood. This can lead to serious medical problems.

The main goal of treating diabetes is to lower your b ood sugar to a normal level.

High b ood sugar can be owered by diet and exercise, and by certain medicines when necessary.

Talk to your doctor about how to prevent, recognize, and take care of ow b ood sugar (hypoglycemia), high blood sugar (hyperglycemia), and problems you have because of your diabetes.

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Manufa tured by:
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TEMPLE Packaging P t. Ltd. 28476001 Email:-temple@bom4.vsnl.net.in			
Customer: Lupin Pharma		**Location:** Goa	
Product Code & Name: 227224 Metformin Hydrochloride Tab-With USP (Outsert-Back)			
SAP Code: xxxxxxxxxx		**File No:** xxx	
Version No.: 3		**Open Size:** 480 x 320 mm	
Date: 05.01.2012		**Folding Size:** 35 x 33 mm	
Font: Helvetica Condensed		**Pharma code:** 000	
Colours: 1(Black)		**Perforation:** No	
Substrate: 40 gsm Bible Paper		**Gluing:** Yes	
Artwork Sr. No.: xxx			
Artwork Status: In process			
Note - This approval will be considered for final printing. Please recheck for corrections indicated earlier, in this proof also.			
Prepared by : Sanjay	**Checked by:**	**Approved by:**	
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JAMES T BARLOW
01/11/2012