SAFETY DATA SHEET
Metformin Hydrochloride Extended-Release Tablets
Strength: 500 mg and 750 mg **Revision No.:** 00

EMERGENCY OVERVIEW

Metformin hydrochloride extended-release tablets contain the antihyperglycemic agent metformin, which is a biguanide, in the form of monohydrochloride. The chemical name of metformin hydrochloride is *N*,*N*-dimethylimidodicarbonimidic diamide hydrochloride.

Section 1. IDENTIFICATION OF THE PRODUCT

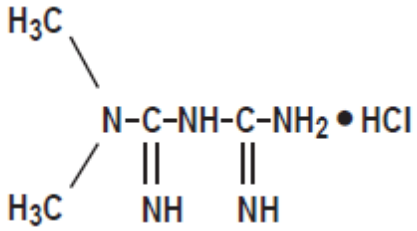
Product Name: Metformin Hydrochloride Extended-Release Tablets: 500 mg and 750 mg

Active Pharmaceutical Ingredient: Metformin Hydrochloride USP

Formula: $C_4H_{11}N_5 \cdot HCl$

Chemical Name: N,N-dimethyl-imidodicarbonimidic diamide, monohydrochloride; 1,1-Dimethylbiguanide hydrochloride

Structure:



Manufacturer / supplier identification

Company: Cadila Healthcare Ltd. Ahmedabad, India

Address: Sarkhej – Bavla. N.H. 8A, Moraiya. Tal. Sanand. Dist. Ahmedabad – 382210. State: Gujarat. India

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

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

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

Recommended usage: Pregnancy
Risk Summary
Limited data with metformin hydrochloride extended-release tablets in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and

major birth defect or miscarriage risk. There are risks to the mother and fetus associated with poorly controlled diabetes mellitus in pregnancy

No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during the period of organogenesis at doses up to 2 times and 5times, respectively, a 2,550 mg clinical dose, based on body surface area.

The estimated background risk of major birth defects is 6% to 10% in women with pre-gestational diabetes mellitus with an HbA1C >7 and has been reported to be as high as 20% to 25% in women with a HbA1C >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly-controlled diabetes mellitus in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes mellitus increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human Data

Published data from postmarketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Metformin hydrochloride did not adversely affect development outcomes when administered to pregnant rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 times and 5 times a 2,550 mg clinical dose based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Lactation

Risk Summary

Limited published studies report that metformin is present in human milk [see Data]. However, there is insufficient information to determine the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for metformin hydrochloride extended-release tablets and any potential adverse effects on the breastfed child from metformin hydrochloride extended-release tablets or from the underlying maternal condition.

Data

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1.

However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin hydrochloride extended-release tablets may result in ovulation in some anovulatory women.

Pediatric Use

Metformin Hydrochloride Extended-Release Tablets

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

Renal Impairment

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Metformin hydrochloride extended-release tablets are contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m2

Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Metformin hydrochloride extended-release tablets are not recommended in patients with hepatic impairment.

Restriction on Use / Contraindications:

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

• Severe renal impairment (eGFR below 30 mL/min/1.73 m2• Hypersensitivity to metformin.

• Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

Section 2. HAZARDS IDENTIFICATION

Dosage and Administration:

Adult Dosage

Metformin Hydrochloride Extended-Release Tablets

- Swallow metformin hydrochloride extended-release tablets whole and never crush, cut or chew.
- The recommended starting dose of metformin hydrochloride extended-release tablets are 500 mg orally once daily with the evening meal.
- Increase the dose in increments of 500 mg weekly on the basis of glycemic control and tolerability, up to a maximum of 2,000 mg once daily with the evening meal.
- If glycemic control is not achieved with metformin hydrochloride extended-release tablets 2,000 mg once daily, consider a trial of

metformin hydrochloride extended-release tablets 1,000 mg twice daily. If higher doses are required, switch to metformin hydrochloride tablets at total daily doses up to 2,550 mg administered in divided daily doses, as described above.

- Patients receiving metformin hydrochloride tablets may be switched to metformin hydrochloride extended-release tablets once daily at the same total daily dose, up to 2,000 mg once daily.

Recommendations for Use in Renal Impairment

- Assess renal function prior to initiation of metformin hydrochloride extended-release tablets and periodically thereafter.
- Metformin hydrochloride extended-release tablets are contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m2.
- Initiation of metformin hydrochloride extended-release tablets in patients with an eGFR between 30 mL/minute/1.73 m2 to 45 mL/minute/1.73 m2 is not recommended.
- In patients taking metformin hydrochloride extended-release tablets whose eGFR later falls below 45 mL/min/1.73 m2, assess the benefit risk of continuing therapy.
- Discontinue metformin hydrochloride extended-release tablets if the patient's eGFR later falls below 30 mL/minute/1.73 m2

Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue metformin hydrochloride extended-release tablets at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 mL/min/1.73 m2 and 60 mL/min/1.73 m2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin hydrochloride extended-release tablets if renal function is stable

Adverse Effects:

The following adverse reactions are also discussed elsewhere in the labeling:

- Lactic Acidosis
- Vitamin B12 Deficiency
- Hypoglycemia

Clinical Studies Experience

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

Metformin Hydrochloride Extended-Release Tablets

In placebo-controlled trials, 781 patients were administered metformin hydrochloride extended-release tablets. Adverse reactions reported in greater than 5% of the metformin hydrochloride extended-release tablets patients, and that were more common in metformin hydrochloride extended-release tablets- than placebo-treated patients, are listed in Table 2.

Table 2

Adverse Reactions from Clinical Trials of Metformin Hydrochloride Extended-

Release Tablets Occurring >5% and More Common than Placebo in Patients with Type 2 Diabetes Mellitus

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

Over Dose Effect:

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

Pregnancy Comments:

Limited data with metformin hydrochloride extended-release tablets in pregnant women are not sufficient to determine a drug-Associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk. There are risks to the mother and fetus associated with poorly controlled diabetes mellitus in pregnancy

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Clinical Considerations

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Warnings & Precautions: Lactic Acidosis: • Vitamin B12 Deficiency: Metformin may lower vitamin B12 levels. Measure hematological parameters annually and vitamin B12 at 2 to 3 year intervals and manage any abnormalities.
• Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Increased risk of hypoglycemia when used in combination

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

Section 3. COMPOSITION / INFORMATION ON INGREDIENTS

Component	Exposure Limit	CAS No.
Principle Component :		
Metformin (hydrochloride)	Not Found	1115-70-4
Inactive ingredients :		
Hypromellose	Not Found	9004-65-3
IPA	Not Found	67-63-0
Povidone	Not Found	9003-39-8
MCC	Not Found	9004-34-6
Glyceryl behenate	Not Found	77538-19-3

Section 4. FIRST - AID MEASURES

Description of First Aid Measures

Eye Contact: Hold eyelids apart and flush eyes with plenty of water for at least 15 minutes. Have eyes examined and tested by medical personnel

Skin Contact: Immediately wash skin with soap and plenty of water for at least 15 minutes. Remove contaminated clothing. Get medical attention if symptoms occur. Wash clothing before reuse..

Ingestion: Wash out mouth with water provided person is conscious. Never give anything by mouth to an unconscious person. Get medical attention. Do NOT induce vomiting unless directed to do so by medical personnel.

Inhalation: Remove to fresh air. If not breathing, give artificial respiration or give oxygen

by trained personnel. Get immediate medical attention..

Section 5. FIRE FIGHTING MEASURES

Extinguishing Media:	Use alcohol-resistant foam, carbon dioxide, water, or dry chemical spray. Use water spray to cool fire-exposed containers.
Hazardous Combustion Products:	Not applicable
Fire Fighting Procedures:	As in any fire, wear self-contained breathing apparatus pressure-demand (NIOSH approved or equivalent), and full protective gear to prevent contact with skin and eyes
Fire / Explosion Hazards:	Not applicable

Section 6. ACCIDENTAL RELEASE MEASURES

Protective Precautions, Protective Equipment and Emergency Procedures:	Avoid raising and breathing dust, and provide adequate ventilation. As conditions warrant, wear a NIOSH approved self-contained breathing apparatus, or respirator, and appropriate personal protection (rubber boots, safety goggles, and heavy rubber gloves).
Environmental. Precautions:	Take steps to avoid release into the environment, if safe to do so
Methods and Material For Containment and Cleaning Up:	Contain spill and collect, as appropriate. Transfer to a chemical waste container for disposal in accordance with local regulations.

Section 7. HANDLING AND STORAGE

Precautions To Be Taken in Handling:	Avoid breathing dust/fume/gas/mist/vapours/spray. Avoid prolonged or repeated exposure.
Precautions To Be Taken in Storing:	Keep container tightly closed. Store in accordance with information listed on the product insert.

Section 8. EXPOSURE CONTROLS / PERSONAL PROTECTION

Engineering Controls:	Use process enclosures, local exhaust ventilation, or other engineering controls to control airborne levels below recommended exposure limits.
Environmental Exposure Controls:	Refer to specific Member State legislation for requirements under Community environmental legislation.
Eye Protection:	Safety glasses
Protective Gloves:	Compatible chemical-resistant gloves
Other Protective Clothing:	Lab coat
Engineering Controls (Ventilation etc.):	Use process enclosures, local exhaust ventilation, or other engineering controls to control airborne levels below recommended exposure limits.
Work/Hygienic/Maintenance Practices:	Do not take internally. Facilities storing or utilizing this material should be equipped with an eyewash

and a safety shower. Wash thoroughly after handling. No data available.

Respiratory Equipment (Specify Type): NIOSH approved respirator, as conditions warrant.

Section 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance

Physical state Tablets

Description Metformin Hydrochloride Extended-release Tablets, USP

- Metformin Hydrochloride Extended-release Tablets USP, 500 mg are white to off-white, capsule shaped, uncoated tablets, debossed with "63" on one side and "Z" on the other side.

• Metformin Hydrochloride Extended-release Tablets USP, 750 mg are and are supplied as follows:

Metformin Hydrochloride Extended-release Tablets, USP

Metformin Hydrochloride Extended-release Tablets USP, 500 mg are white to off-white, capsule shaped, uncoated tablets, debossed with "63" on one side and "Z" on the other side and are supplied as follows.

NDC 72578-035-01 in bottles of 100 tablets

NDC 72578-035-05 in bottles of 500 tablets

Metformin Hydrochloride Extended-release Tablets USP, 750 mg are white to off-white, capsule shaped, uncoated tablets, debossed with "Z", "C" on one side and "20" on the other side and are supplied as follows.

NDC 72578-036-01 in bottles of 100 tablets

NDC 72578-036-05 in bottles of 500 tablets

Pure/Mixture Mixture

Section 10. STABILITY AND REACTIVITY

The product is stable

Section 11. TOXICOLOGICAL INFORMATION

Information ON Toxicological Effects:

The toxicological effects of this product have not been thoroughly studied. Metformin (hydrochloride) - Toxicity Data: Oral LD50 (rat): 1 g/kg; Intraperitoneal LD50 (rat): 500mg/kg; Subcutaneous LD50 (rat): 300 mg/kg; Oral LD50 (mouse): 1450 mg/kg; Intraperitoneal
LD50 (mouse): 420 mg/kg; Subcutaneous LD50 (mouse): 225 mg/kg;

Chronic Toxicological Effects:

Metformin (hydrochloride) - Investigated as a drug and primary irritant. Only select Registry of Toxic Effects of Chemical Substances (RTECS) data is presented here. See actual entry in RTECS for complete information. Metformin (hydrochloride) RTECS Number: DU1800000

Section 12. ECOLOGICAL INFORMATION

Toxicity: Avoid release into the environment.

Persistence and Degradability: Runoff from fire control or dilution water may cause pollution.

Bioaccumulative Potential:	No data available
Mobility in Soil:	No data available..
Results of PBT and vPvB	No data available
No **assessment:**	No data available.

Section 13. DISPOSAL CONSIDERATION

Disposal Recommendations	. Dispose in accordance with local, state, and federal regulations

Section 14. TRANSPORT INFORMATION

The following refers to all modes of transportation unless specified below. Not regulated for transport under USDOT, EUADR, IATA, or IMDG regulations.

Section 15. REGULATORY INFORMATION

Generic Medicine, ANDA Number	077-078 (750 mg) 077-060 (500 mg)

Section 16. OTHER INFORMATION

None

Date of issue: 19th August, 2019 **Supersedes edition:** NA

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