Safety Data Sheet
Glipizide and Metformin Hydrochloride Tablets USP

Strength: 2.5/250mg, 2.5/500mg & 5/500mg.

Pack Size: 90/100/1000 Tablets per bottle for 2.5/250mg, 2.5/500mg & 5/500mg
Unit-dose blister cartons of 100 (10 x 10) unit-dose tablets for 2.5/250mg, 2.5/500mg & 5/500mg

Revision No.: 00

EMERGENCY OVERVIEW

Each Glipizide and Metformin Hydrochloride Tablets USP intended for oral administration contains Glipizide and Metformin Hydrochloride and excipients generally considered to be non- toxic and non-hazardous in small quantities and under conditions of normal occupational exposure.

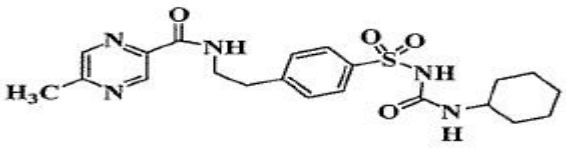
Section 1. Identification

Identification of the product

Product name: Glipizide and Metformin Tablets USP

Formula: $C_{21}H_{27}N_5O_4S$ of Glipizide

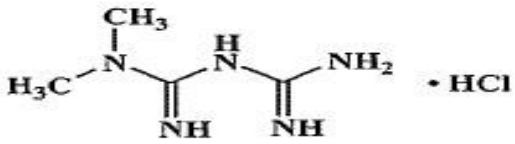
Chemical Name: 1-cyclohexyl-3-[[*p*-[2-(5-methylpyrazinecarboxamido)ethyl]phenyl] sulfonyl]urea



Glipizide

Formula: $C_4H_{12}ClN_5$ of Metformin Hydrochloride

Chemical Name: *N,N*-dimethylimidodicarbonimidic diamide monohydrochloride



Metformin Hydrochloride

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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Contact for information:	Tel.: +91 79 6868100 Fax: +91 79 3750319
Emergency Telephone No.	Tel.: +91 79 6868100
Recommended use / Therapeutic Category	**A**ntihyperglycemic agents with complementary mechanisms of action, to improve glycemic control in patients with type 2 diabetes.
Restriction on Use / Contraindication	Glipizide and metformin hydrochloride tablets are contraindicated in patients with: 1. Severe renal impairment (eGFR below 30 mlL/min/1.73 m^2). 2. Known hypersensitivity to glipizide or metformin hydrochloride. 3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Section 2. Hazard(s) Information

Dose and Administration

General Considerations:

Dosage of glipizide and metformin hydrochloride tablets must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended daily dose of 20 mg glipizide/2000 mg metformin.

Glipizide and metformin hydrochloride tablets should be given with meals and should be initiated at a low dose, with gradual dose escalation as described below, in order to avoid hypoglycemia (largely due to glipizide), reduce GI side effects (largely due to metformin), and permit determination of the minimum effective dose for adequate control of blood glucose for the individual patient.

With initial treatment and during dose titration, appropriate blood glucose monitoring should be used to determine the therapeutic response to glipizide and metformin hydrochloride tablets and to identify the minimum effective dose for the patient. Thereafter, HbA_{1c} should be measured at intervals of approximately 3 months to assess the effectiveness of therapy. The therapeutic goal in all patients with type 2 diabetes is to decrease FPG, PPG, and HbA_{1c} to normal or as near normal as possible. Ideally, the response to therapy should be evaluated using HbA_{1c}, which is a better indicator of long-term glycemic control than FPG alone.

No studies have been performed specifically examining the safety and efficacy of switching to glipizide and metformin hydrochloride tablets therapy in patients taking concomitant glipizide (or other sulfonylurea) plus metformin. Changes in glycemic control may occur in such patients, with either hyperglycemia or hypoglycemia possible. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring.

Adverse Effects

In a double-blind 24-week clinical trial involving glipizide and Metformin hydrochloride tablets as initial therapy, a total of 172 patients received glipizide and metformin hydrochloride tablets, 2.5 mg/250 mg, 173 received glipizide and metformin hydrochloride tablets, 2.5 mg/500 mg, 170 received glipizide, and 177 received metformin.

In a double-blind 18-week clinical trial involving glipizide and metformin hydrochloride tablets as second-line therapy, a total of 87 patients received glipizide and metformin hydrochloride tablets, 84 received glipizide, and 75 received metformin.

Hypoglycemia:
In a controlled initial therapy trial of glipizide and metformin hydrochloride tablets, 2.5 mg/250 mg and 2.5 mg/500 mg the numbers of patients with hypoglycemia documented by symptoms (such as dizziness, shakiness, sweating, and hunger) and a fingerstick blood glucose measurement ≤50 mg/dL were 5 (2.9%) for glipizide, 0 (0%) for metformin, 13 (7.6%) for glipizide and metformin hydrochloride tablets, 2.5 mg/250 mg, and 16 (9.3%) for glipizide and metformin hydrochloride tablets, 2.5 mg/500 mg.

Gastrointestinal Reactions:
Among the most common clinical adverse events in the initial therapy trial were diarrhea and nausea/vomiting; the incidences of these events were lower with both glipizide and metformin hydrochloride tablets dosage strengths than with metformin therapy.

Over Dose Effects

Glipizide
Overdosage of sulfonylureas, including glipizide, can produce hypoglycemia. Mild hypoglycemic symptoms, without loss of consciousness or neurological findings, should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns.

Metformin Hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts > 50 g. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established.

Contraindications

Glipizide and metformin hydrochloride tablets are contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mlL/min/1.73 m^2).
- Known hypersensitivity to glipizide or metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Medical condition

People who have a condition known as glucose-6-phosphate dehydro genase (G6PD) deficiency and who take glipizide and metformin hydrochloride may develop hemolytic anemia (fast breakdown of red blood cells). G6PD deficiency usually runs in families. Tell your doctor if you or any members of your family have been diagnosed with G6PD deficiency before you start taking Glipizide and metformin hydrochloride tablets.

Glipizide and metformin hydrochloride tablets rarely cause serious side effects. Metformin, one of the medicines in glipizide and metformin hydrochloride can cause a rare but serious condition called lactic acidosis (a buildup of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

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

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

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

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

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

Glipizide and metformin hydrochloride can have other serious side effects. See “What are the possible side effects of glipizide and metformin hydrochloride?”

Pregnancy Comments

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

Glipizide was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5 to 50 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide.

Metformin alone was not teratogenic in rats or rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the MRHD dose of 2000 mg of the metformin component of glipizide and metformin hydrochloride tablets based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nonteratogenic Effects:
Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives.

Pregnancy Category **C**

Section 3. Composition / information on ingredient

Component	Exposure Limit	CAS No.
Principle Component :		
Glyburide (Micronised)	Not Found	10238-21-8
Metformin Hydrochloride	Not Found	1115-70-4
Inactive Ingredients		
Microcrystalline Cellulose (Comprecel M101D+) NF	Not Found	9004-34-6
Croscarmellose Sodium [AcDiSol] NF	Not Found	74811-65-7
Calcium Carbonate (Scoralite LL250)	Not Found	1317-65-3
Povidone (Piasdone K-29/32) USP	Not Found	94800-10-9
Microcrystalline Cellulose (Comprecel Ml02D+) NF	Not Found	9004-34-6

Magnesium Stearate (Vegetable Grade) NF	Not Found	557-04-0
Opadry II White 33F28398 (Colorcon)	Not Found	----------
Opadry II Orange 31 F530003 (Colorcon)	Not Found	----------
Opadry II Green31F510000 (Colorcon)	Not Found	----------

Section 4. First - aid measures

General

Inhalation

Remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Seek medical attention.

Contact with skin

Wash skin with soap and water. Remove contaminated clothing and shoes. If irritation occurs or persists, get medical attention.

Contact with eyes
Immediately flush eyes with water for at least 15 minutes. If irritation occurs or persists, get medical attention.

Ingestion
Get medical attention immediately. Do not induce vomiting unless directed by medical personnel. Never give anything by mouth to an unconscious person.

Overdose Treatment

Glipizide
Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery. Clearance of glipizide from plasma would be prolonged in persons with liver disease. Because of the extensive protein binding of glipizide, dialysis is unlikely to be of benefit.

Metformin Hydrochloride:
Overdose of metformin hydrochloride has occurred, including ingestion of amounts > 50 g. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. 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.

Section 5. Fire - fighting measures

Flash point	Not Found	**Upper Flammable Limit:**	Not Found
Auto-Ignition Temperature:	Not Found	**Lower Flammable Limit:**	Not Found
Extinguishing Media	Use carbon dioxide, dry chemical, or water spray. Also use alcohol - resistant foam.	**Fire and Explosion Hazard**	No Data available.
Fire Fighting Procedure	As with all fires, evacuate personnel to a safe area. Fire fighter should use self- contained breathing equipment and protective clothing.		

Section 6. Accidental Release Measures

Spill Response

Health and Safety Precautions: Personnel involved in clean-up should wear appropriate personal protective equipment.
Measures for Cleaning / Collecting: Contain the source of spill if it is safe to do so. Collect spilled material by a method that controls dust generation. A damp cloth or a filtered vacuum should be used to clean spills of dry solids. Clean spill area thoroughly.
Measures for Environmental Protections:
Place waste in an appropriately labeled, sealed container for disposal. Care should be taken to avoid environmental release.
Additional Consideration for Large Spills:
Non-essential personnel should be evacuated from affected area. Report emergency situations immediately. Clean-up operations should only be undertaken by trained personnel.

Section 7. Handling and Storage

Storage

Store at 20° to 25° C (68° to 77° F) [See USP Controlled Room Temperature].
Dispense in a tight container

Incompatibilities: Not available.

Section 8. Exposure controls / personal protection

Respiratory Protection If applicable Occupational Exposure Limit (OEL) is exceeded, wear an appropriate respirator with a protection factor sufficient to control exposures to below the OEL.

Skin Protection Impervious protective clothing is recommended if skin contact with drug product is possible and for bulk processing operations. Wear protective clothing when working with large quantities. Individuals with known sensitivity should wear long sleeves to avoid skin contact. Wash hand and arms throughly after handling materials.

Eye protection Eye protection is not normally necessary. If concerned wear protective goggles or glasses. Wash hands prior to touching eye and in particular handling contact lenses.

Protective Clothing Protective clothing is not normally necessary, however it is good practice to use apron.

Engineering Control General room ventilation is adequate unless the process generates dust, mist or fumes.

Section 9. Physical and chemical properties

Appearance Glipizide and Metformin Hydrochloride Tablets USP, 2.5 mg/250 mg are pink-colored, biconvex, modified capsule-shaped, film-coated tablet, debossed with "ZE68" on one side and plain on other side.

Glipizide and Metformin Hydrochloride Tablets USP, 2.5 mg/500 mg are white-colored, biconvex, modified capsule-shaped, film-coated tablet, debossed with "ZE67" on one side and plain on other side.

Glipizide and Metformin Hydrochloride Tablets USP, 5 mg/500 mg are pink-colored, biconvex, modified capsule-shaped, film-coated tablet, debossed with "ZE66" on one side and plain on other side.

Solubility in water	No Data Available	**Odour**	Odourless
Boiling point	No Data Available	**Melting Point**	No Data Available
Evaporation rate	No Data Available	**Vapour density**	No Data Available
Reactivity in water	No Data Available	**Evaporation rate**	No Data Available
% Volatile by volume	No Data Available	**Specific gravity**	No Data Available
		Vapour pressure	No Data Available

Other information Not applicable

Section 10. Stability and Reactivity

Condition to avoid	Avoid exposure to extreme heat, light and moisture.	**Stable**	Product is stable under normal condition.
Decomposition Products	No Data Available	**Hazardous Reaction**	No data available.
Incompatibilities:	No Data Available.		

Section 11. Toxicological information

General

Glipizide

Glipizide was found to be mildly fetotoxic in rat reproductive studies at all dose levels (550 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of glipizide. In studies in rats and rabbits, no teratogenic effects were found.

Metformin Hydrochloride

Metformin alone was not teratogenic in rats or rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the MRHD dose of 2000 mg of the metformin component of METAGLIP based on body surface area comparisons for rats and rabbits, respectively.

Target organ

Glipizide and metformin hydrochloride tablets are not recommended for use during pregnancy or for use in pediatric patients. The initial and maintenance dosing of glipizide and metformin hydrochloride tablets should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment requires a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of glipizide and metformin hydrochloride tablets to avoid the risk of hypoglycemia. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly.

Other

Carbonic Anhydrase Inhibitors

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

Alcohol
Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving glipizide and metformin hydrochloride.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No animal studies have been conducted with the combined products in glipizide and metformin hydrochloride tablets. The following data are based on findings in studies performed with the individual products.

Glipizide:
A 20-month study in rats and an 18-month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and in vivo mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

Metformin Hydrochloride:
Long-term carcinogenicity studies were performed with metformin alone 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 4 times the maximum recommended human daily dose of 2000 mg of the metformin component of glipizide and metformin hydrochloride tablets based on body surface area comparisons. No evidence of carcinogenicity with metformin alone was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin alone in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day of metformin alone.

Section 12. Ecological information

Do not allow product to enter drinking water supplies, waste water or soil.

Section 13. Disposal Consideration

Dispose the waste in accordance with all applicable Federal, State and Local laws.

Section 14. Transport Information

The product is not hazardous when shipping via air (IATA), ground (DOT), or sea (IMDG).

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Section 15. Regulatory Information

Generic Medicine. Approved by USFDA & the ANDA Number is 078905

Section 16. Other information

None

Date of issue: 25/05/2016 **Supersedes edition:** New addition

The information contained herein is based on the state of our knowledge. It Characterises the product with regard to the appropriate safety precautions. It does not represent a guarantee of the properties of the product.