LUPIN LIMITED

SAFETY DATA SHEET

Section 1: Identification

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Material	**Repaglinide and Metformin Hydrochloride Tablets 1 mg/500 mg and 2 mg/500 mg**
Manufacturer	**Lupin Limited** Goa - 403722 India
Distributor	Lupin Pharmaceuticals, Inc. 111 South Calvert Street, Harborplace Tower, 21st Floor, Baltimore, Maryland 21202 United States Tel. 001-410-576-2000 Fax. 001-410-576-2221

Section 2: Hazard(s) Identification

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Fire and Explosion	Expected to be non-combustible.
Health	Repaglinide and metformin hydrochloride tablets are contraindicated in: • Severe renal impairment (GFR below 30 mL/min. 1.73 m^2) • Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin • Patients receiving gemfibrozil • Patients with known hypersensitivity to repaglinide, metformin HCl or any inactive ingredients in repaglinide and metformin hydrochloride tablets
Environment	No information is available about the potential of this product to produce adverse environmental effects.

Section 3: Composition / Information on Ingredients

Section 3, Composition/information on ingredients

Ingredients	**CAS**
Repaglinide USP	135062-02-01
Metformin Hydrochloride USP	1115-70-4

Section 4: First-Aid Measures

Section 4, First-aid measures

Ingestion	Harmful if swallowed. May cause hypoglycemia. Gastrointestinal reactions (e.g. diarrhea, nausea, vomiting) are the most common adverse reactions (> 5%) with metformin HCl treatment and are more frequent at higher metformin HCl doses.
Inhalation	None under normal use. Not likely unless the tablets are crushed. Inhalation of dust may cause irritation to the upper airways.
Skin Contact	Not likely unless the tablets are crushed. May then cause slight irritation.
Eye Contact	Not likely unless the tablets are crushed. May then cause temporary irritation.

NOTES TO HEALTH PROFESSIONALS

Medical Treatment	Treat according to locally accepted protocols. For additional guidance, refer to the current prescribing information or to the local poison control information center. Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc.
OVERDOSAGE	**Repaglinide and Metformin Hydrochloride Tablets** No data are available with regard to overdose of repaglinide and metformin hydrochloride tablets. Findings related to the individual active substances are listed below. **Repaglinide** In a clinical trial, dizziness, headache, and diarrhea were reported in subjects receiving increasing doses of repaglinide up to 80 mg a day for 14 days. Hypoglycemia did not occur when meals were given with these high doses. Hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery. There is no evidence that repaglinide is dialyzable using hemodialysis. 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 more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. **Metformin HCl** Overdose of metformin HCl has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in

approximately 10% of cases, but no causal association with metformin HCl has been established. Lactic acidosis has been reported in approximately 32% of metformin HCl 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 HCl overdosage is suspected.

Section 5: Fire-Fighting Measures

Section 5, Fire-fighting measures

Fire and Explosion Hazards	The product is not readily flammable.
Extinguishing Media	Water spray, carbon dioxide, dry chemical powder or appropriate foam.
Special Firefighting Procedures	Positive pressure self-contained breathing apparatus (SCBA) and structural firefighters protective clothing will provide adequate protection.
Hazardous Combustion Products	Hazardous combustion or decomposition products are expected when the product is exposed to fire.

Section 6: Accidental Release Measures

Section 6, Accidental release measures

Personal Precautions	Wear protective clothing and equipment consistent with the degree of hazard.
Environmental Precautions	For large spills, take precautions to prevent entry into waterways, sewers, or surface drainage systems.
Clean-up Methods	Collect and place it in a suitable, properly labeled container for recovery or disposal.

Section 7: Handling and Storage

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Handling	Do not get in eyes, on skin, or on clothing. Use personal protective equipment as required.
Storage	Store at 25°C (77° F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Keep bottles tightly closed. Dispense in tight containers with safety closures.

Section 8: Exposure Controls/Personal Protection

Section 8, Exposure controls/personal protection

Wear appropriate clothing to avoid skin contact. Wash hands and arms thoroughly after handling.

Section 9: Physical and Chemical Properties

Section 9, Physical and chemical properties

Physical Form

Repaglinide and metformin hydrochloride tablets are supplied as biconvex tablets availablein 1 mg/500 mg (yellow) and 2 mg/500 mg (pink) strengths. 1 mg/500 mg tablets are debossed with 'V41' on one side and 'LU' on the other side and 2 mg/500 mg tablets are debossed with 'V42' on one side and 'LU' on the other side. The tablets are colored to indicate strength.

1 mg repaglinide/500 mg metformin HCl tablets (yellow)	Bottles of 100 NDC 68180-490-01
	Bottles of 500 NDC 68180-490-02
	Bottles of 1000 NDC 68180-490-03
2 mg repaglinide/500 mg metformin HCl tablets (pink)	Bottles of 100 NDC 68180-491-01
	Bottles of 500 NDC 68180-491-02
	Bottles of 1000 NDC 68180-491-03

Section 10: Stability and Reactivity

Section 10, Stability and reactivity

Stable under recommended storage conditions.

Section 11: Toxicological Information

Section 11, Toxicological information

Carcinogenesis, Mutagenesis, Impairment of Fertility

Repaglinide and Metformin Hydrochloride Tablets
No animal studies have been conducted with the combined products in repaglinide and metformin hydrochloride tablets to evaluate carcinogenesis, mutagenesis and impairment of fertility. The following data are based on findings in studies performed with the individual components.

Repaglinide
In a 104-week carcinogenicity study in rats at doses up to 120 mg/kg/day, the incidences of benign adenomas of the thyroid and liver were increased in male rats. The higher incidences of thyroid and

liver tumors in male rats were not seen at lower dose of 30 mg/kg/day and 60 mg/kg/day respectively (which are over 15 and 30 times, respectively, clinical exposures on a mg/m^2 basis).

In a 104-week carcinogenicity study in mice at doses up to 500 mg/kg/day, no evidence of carcinogenicity was found in mice (which is approximately 125 times clinical exposure on a mg/m^2 basis).

Repaglinide was non-genotoxic in a battery of *in vivo* and *in vitro* studies: Bacterial mutagenesis (Ames test), *in vitro* forward cell mutation assay in V79 cells (HGPRT), *in vitro* chromosomal aberration assay in human lymphocytes, unscheduled and replicating DNA synthesis in rat liver, and *in vivo* mouse and rat micronucleus tests.

In a rat fertility study, repaglinide was administered to male and female rats at doses up to 300 and 80 mg/kg/day, respectively. No adverse effects on fertility were observed (which are over 40 times clinical exposure on a mg/m^2 basis).

Metformin HCl

In a 104-week carcinogenicity study in rats at doses up to 900 mg/kg/day, the incidences of benign stromal uterine polyps were increased in female rats at 900 mg/kg/day (which is approximately four times the maximal recommended human daily dose of 2000 mg of metformin HCl component of repaglinide and metformin hydrochloride tablets on a mg/m^2 basis).

In a 91-week carcinogenicity study in mice at doses up to 1500 mg/kg/day, no evidence of carcinogenicity was found in mice (which is approximately four times the maximal recommended human daily dose of 2000 mg of metformin HCl component of repaglinide and metformin hydrochloride tablets on a mg/m^2 basis).

There was no evidence of a mutagenic potential of metformin HCl alone in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

In a rat fertility study, metformin HCl was administered to male and female rats at doses up to 600 mg/kg/day. No adverse effects on fertility were observed (which is approximately three times the maximal recommended human daily dose of 2000 mg of metformin HCl component of repaglinide and metformin hydrochloride tablets on a mg/m^2 basis).

Section 12: Ecological Information

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No relevant studies identified.

Section 13: Disposal Considerations

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Incinerate in an approved facility. Follow all federal state and local environmental regulations.

Section 14: Transport Information

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IATA/ICAO - Not Regulated

IATA Proper shipping Name	:	N/A
IATA UN/ID No	:	N/A
IATA Hazard Class	:	N/A
IATA Packaging Group	:	N/A
IATA Label	:	N/A

IMDG - Not Regulated

IMDG Proper shipping Name	:	N/A
IMDG UN/ID No	:	N/A
IMDG Hazard Class	:	N/A
IMDG Flash Point	:	N/A
IMDG Label	:	N/A

DOT - Not Regulated

DOT Proper shipping Name	:	N/A
DOT UN/ID No	:	N/A
DOT Hazard Class	:	N/A
DOT Flash Point	:	N/A
DOT Packing Group	:	N/A
DOT Label	:	N/A

Section 15: Regulatory Information

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This Section Contains Information relevant to compliance with other Federal and/or state laws.

Section 16: Other Information

Section 16, Other information

The above information is believed to be correct but does not purport to be all-inclusive and shall be used only as a guide. Nothing herein shall be deemed to create any warranty, express or implied. It is the responsibility of the user to determine the applicability of this information and the suitability of the material or product for any particular purpose.

Lupin shall not be held liable for any damage resulting from handling or from contact with the above product. Lupin reserves the right to revise this SDS.