LUPIN LIMITED

SAFETY DATA SHEET

Section 1: Identification

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Material	**Amlodipine, Valsartan and Hydrochlorothiazide Tablet USP 5 mg/160 mg/12.5 mg; 10 mg/160 mg/12.5 mg; 5 mg/160 mg/25 mg; 10 mg/160 mg/25 mg and 10 mg/320 mg/25 mg**
Manufacturer	**Lupin Limited** Goa - 403 722 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	Do not use in patients with anuria, hypersensitivity to other sulfonamide-derived drugs, or hypersensitivity to any component of this product. Do not coadminister aliskiren with amlodipine, valsartan and hydrochlorothiazide in patients with diabetes.
Environment	No information is available about the potential of this product to produce adverse environmental effects.

Section 3: Composition/Information on Ingredients

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Ingredients	**CAS**
Amlodipine Besylate USP	111470-99-6
Valsartan USP	137862-53-4
Hydrochlorothiazide USP	00058-93-5

Section 4: First-Aid Measures

Section 4, First-aid measures

Ingestion	Get medical attention. Do not induce vomiting unless directed by medical personnel. Never give anything by mouth to an unconscious person.
Inhalation	Remove to fresh air, If not breathing, give artificial respiration. Get medical attention.

Skin Contact

Wash off immediately with plenty of water. Continue to rinse for at least 15 minutes. Immediately take off all contaminated clothing. Get medical attention if irritation develops and persists.

Eye Contact

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

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

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur institute supportive treatment.

Amlodipine

Single oral doses of amlodipine maleate equivalent to 40 mg/kg and 100 mg/kg amlodipine in mice and rats, respectively, caused deaths. Single oral doses equivalent to 4 or more mg/kg amlodipine in dogs (11 or more times the maximum recommended human dose on a mg/m^2 basis) caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension. In humans, experience with intentional overdosage of amlodipine is limited. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, initiate cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption.

Valsartan

Depressed level of consciousness, circulatory collapse, and shock have been reported.

Valsartan is not removed from the plasma by hemodialysis.

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 31 times, respectively, the MRHD on a mg/m^2 basis) (Calculations assume an oral dose of 320 mg/day and a 60 -kg patient).

Hydrochlorothiazide

The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The most common signs and symptoms observed in patients are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive

diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

The oral LD_{50} of hydrochlorothiazide is greater than 10 g/kg in both mice and rats, 2000 and 4000 times, respectively, the MRHD on a mg/m^2 basis (Calculations assume an oral dose of 25 mg/day and a 60-kg patient).

Valsartan and Hydrochlorothiazide
In rats and marmosets, single oral doses of valsartan up to 1524 and 762 mg/kg in combination with hydrochlorothiazide at doses up to 476 and 238 mg/kg, respectively, were very well tolerated without any treatment-related effects. These no adverse effect doses in rats and marmosets, respectively, represent 46.5 and 23 times the MRHD of valsartan and 188 and 113 times the MRHD of hydrochlorothiazide on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60 kg patient.)

Section 5: Fire-Fighting Measures

Section 5, Fire-fighting measures

Fire and Explosion Hazards	Assume that this product is capable of sustaining combustion.
Extinguishing Media	Water spray, carbon dioxide, dry chemical powder or appropriate foam.
Special Firefighting Procedures	For single units (packages): No special requirements needed. For larger amounts (multiple packages/pallets) of product: Since toxic, corrosive or flammable vapors might be evolved from fires involving this product and associated packaging, self-contained breathing apparatus and full protective equipment are recommended for firefighters.
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 suitable protective clothing, gloves and eye/face protection.
Environmental Precautions	Avoid release to the environment.
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	Minimize dust generation and accumulation. If tablets or capsules are crushed and/or broken, avoid breathing dust and avoid contact with eyes, skin, and clothing. When handling, use appropriate personal protective equipment. Wash hands and any exposed skin.
Storage	Store at 20°C-25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Dispense in tight container (USP).

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

HOW SUPPLIED

Amlodipine, valsartan and hydrochlorothiazide tablets USP, are available as film-coated tablets containing amlodipine besylate equivalent to 5 mg or 10 mg of amlodipine free-base with valsartan 160 mg or 320 mg and hydrochlorothiazide 12.5 mg or 25 mg, providing for the following available combination: 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg and 10/320/25 mg. All strengths are packaged in bottles of 30, 90 and 500 tablets.

Amlodipine, valsartan and hydrochlorothiazide tablets USP, 5 mg/160 mg/12.5 mg – White to off-white, capsule shaped, film coated, biconvex tablets, debossed with 'LU' on one side and 'W41' on the other side.

Bottles of 30	NDC 68180-771-06
Bottles of 90	NDC 68180-771-09
Bottles of 500	NDC 68180-771-02

Amlodipine, valsartan and hydrochlorothiazide tablets USP, 10 mg/160 mg/12.5 mg – Mustard colored, capsule shaped, film coated, biconvex tablets, debossed with 'LU' on one side and 'W43' on the other side.

Bottles of 30	NDC 68180-772-06
Bottles of 90	NDC 68180-772-09
Bottles of 500	NDC 68180-772-02

Amlodipine, valsartan and hydrochlorothiazide tablets USP, 5 mg/160 mg/25 mg – Yellow colored, capsule shaped, film coated, biconvex tablets, debossed with 'LU' on one side and 'W42' on the other side.

Bottles of 30	NDC 68180-773-06
Bottles of 90	NDC 68180-773-09
Bottles of 500	NDC 68180-773-02

Amlodipine, valsartan and hydrochlorothiazide tablets USP, 10 mg/160 mg/25 mg – Beige colored, capsule shaped, film coated, biconvex tablets, debossed with 'LU' on one side and 'W44' on the other side.

Bottles of 30	NDC 68180-774-06
Bottles of 90	NDC 68180-774-09
Bottles of 500	NDC 68180-774-02

Amlodipine, valsartan and hydrochlorothiazide tablets USP, 10 mg/320 mg/25 mg – Light brick red colored, capsule shaped, film coated, biconvex tablets, debossed with 'LU' on one side and 'W45' on the other side.

Bottles of 30	NDC 68180-775-06
Bottles of 90	NDC 68180-775-09
Bottles of 500	NDC 68180-775-02

Section 10: Stability and Reactivity

Section 10, Stability and reactivity

The product is stable and non-reactive under normal conditions of use, storage and transport.

Section 11: Toxicological Information

Section 11, Toxicological information

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with amlodipine/valsartan/hydrochlorothiazide
No carcinogenicity, mutagenicity, or fertility studies have been conducted with this combination. However, these studies have been conducted for amlodipine, valsartan and hydrochlorothiazide alone. Based on the preclinical safety and human pharmacokinetic studies, there is no indication of any toxicologically significant adverse interaction between these components.

Studies with amlodipine
Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m^2 basis, similar to the MRHD of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m^2 basis, about 2.5 times the MRHD. (Calculations based on a 60 kg patient.)

Mutagenicity studies conducted with amlodipine maleate revealed no drug-related effects at either the gene or chromosome level.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 10 times the MRHD of 10 mg/day on a mg/m^2 basis).

Studies with valsartan
There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at concentrations calculated to provide doses of up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.4 and 6 times, respectively, the MRHD of 320 mg/day on a mg/m^2 basis (Calculations based on a 60 kg patient).

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* and *E. coli*, a gene mutation test with

Chinese hamster V79 cells, a cytogenetic test with Chinese hamster ovary cells, and a rat micronucleus test.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses of up to 200 mg/kg/day. This dose is about 6 times the MRHD on a mg/m^2 basis.

Studies with hydrochlorothiazide
Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella Typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and Mouse Lymphoma Cell (mutagenicity) assays and in the Aspergillus Nidulans non-disjunction assay.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed via diet at doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation. These doses of hydrochlorothiazide in mice and rats are 19 and 1.5 times, respectively, the MRHD on a mg/m^2 basis (Calculations assume an oral dose of 25 mg/day and a 60-kg patient).

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.