

SAFETY DATA SHEET

Product Name

Bosentan Tablets for Oral suspension 32 mg

SECTION 1. IDENTIFICATION

Product name : Bosentan Tablets for Oral suspension 32 mg

Manufacturer or supplier's details:

Company name of supplier	:	Natco Pharma Limited
Address	:	Natco Pharma Limited. Plot No. 89 & 90, JNPC SEZ, Ramky Pharma City, Parawada Visakhapatnam- -531019 Andhra Pradesh, India.

Recommended use of the chemical and restrictions on use

Recommended use : Finished Pharmaceutical Product This SDS is only intended for occupational use and not for consumer use (see patient packaging insert for consumer use). This SDS is written to provide environmental, health and safety information for personnel that will be handling this finished pharmaceutical product. For health and safety information during manufacturing of this product we refer to the appropriate SDS for each component. This dosage form is exempt from the requirements of the OSHA Hazard Communication Standard (US OSHA Standard 29 CFR Part 1910.1200).



SECTION 2. HAZARDS IDENTIFICATION

GHS classification in accordance with 29 CFR 1910.1200

Eye irritation	:	Category 2A
Skin sensitisation	:	Category 1
Reproductive toxicity	:	Category 2

GHS label elements

Medicinal products in the finished state, intended for the final user, are not subject to GHS labelling.

Hazard pictograms	:	 
Signal word	:	Warning
Hazard statements	:	H317 May cause an allergic skin reaction. H319 Causes serious eye irritation. H361d Suspected of damaging the unborn child.
Precautionary statements	:	Prevention: P201 Obtain special instructions before use. P202 Do not handle until all safety precautions have been read and understood.

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	<p>P261 Avoid breathing dust/ fume/ gas/ mist/ vapours/ spray. P264 Wash skin thoroughly after handling. P272 Contaminated work clothing should not be allowed out of the workplace. P280 Wear protective gloves/ protective clothing/ eye protection/ face protection.</p> <p>Response: P302 + P352 IF ON SKIN: Wash with plenty of soap and water. P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P308 + P313 IF exposed or concerned: Get medical advice/ attention. P333 + P313 If skin irritation or rash occurs: Get medical advice/ attention. P337 + P313 If eye irritation persists: Get medical advice/ attention. P363 Wash contaminated clothing before reuse.</p>
Storage	: P405 Store locked up.
Disposal	: P501 Dispose of contents/ container to an approved waste disposal plant.
Other hazards	: None known

SECTION 3. COMPOSITION/INFORMATION ON INGREDIENTS

Substance / Mixture	: Mixture
Chemical nature	: Solid
Substance name	: Bosentan Tablets for Oral suspension 32 mg

Hazardous components

Chemical name	CAS-No.	Concentration (% w/w)
Microcrystalline Cellulose	9004-34-6	>=30 - < 50
Bosentan monohydrate	157212-55-0	>=10 - < 20
Magnesium Stearate	557-04-0	>=1 - < 5
Colloidal Silicon dioxide	7631-86-9	>=1 - < 5

SECTION 4. FIRST AID MEASURES

If inhaled	: If breathed in, move person into fresh air. Consult a physician
In case of skin contact	: Take off contaminated clothing and shoes immediately. Wash off immediately with plenty of water. If symptoms persist, call a physician. Wash contaminated clothing before reuse
In case of eye contact	: Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. Remove contact lenses. Consult a physician.
If swallowed	: If swallowed, rinse mouth with water (only if the person is conscious). Call a physician immediately.
Most important symptoms and effects, both acute and delayed	: Eye irritation sensitising effects
Notes to physician	: Treat symptomatically

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SECTION 5. FIREFIGHTING MEASURES

Suitable extinguishing media	:	Use extinguishing measures that are appropriate to local circumstances and the surrounding environment.
Hazardous combustion products	:	No information available.
Further information	:	No information available.
Special protective equipment for firefighters	:	In the event of fire, wear self-contained breathing apparatus.

SECTION 6. ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures	:	In the event of an accidental release the emergency response team must respond based on a risk assessment and use personal protective equipment as appropriate. Avoid dust formation. Avoid breathing dust. Evacuate personnel to safe areas.
Environmental precautions	:	Should not be released into the environment
Methods and materials for containment and cleaning up	:	Large spills: Sweep up or vacuum with HEPA filter or via wet cleaning into suitable containers for disposal. Pick up and arrange without creating dust. Keep in properly labelled containers.
	:	Small spills: Moisten a towel, cover the spill, pick up the spill or use HEPA vacuum.
	:	Large spills + Small spills: Keep in suitable, closed containers for disposal. Treat recovered material as described in the section "Disposal considerations".

SECTION 7. HANDLING AND STORAGE

Advice on protection against fire and explosion	:	No data available
Advice on safe handling	:	Do not break, crush or spill this Finished Pharmaceutical Product. To avoid thermal decomposition, do not overheat. Use personal protective equipment as required. Keep away from heat and sources of ignition. Avoid inhalation, ingestion and contact with skin and eyes
Conditions for safe storage	:	To maintain product quality, do not store in heat or direct sunlight. Store in original container. Keep away from heat and sources of ignition. Keep containers tightly closed in a dry, cool and well-ventilated place

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SECTION 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Components with workplace control parameters

Components	CAS-No.	Value type (Form of exposure)	Control parameters / Permissible concentration	Basis
Microcrystalline Cellulose	9004-34-6	TWA	10 mg/m ³	ACGIH
			10 mg/m ³	ACGIH
		TWA (Respirable)	5 mg/m ³	NIOSH REL
		TWA (total)	10 mg/m ³	NIOSH REL
		TWA (total dust)	15 mg/m ³	OSHA Z-1
		TWA (respirable fraction)	5 mg/m ³	OSHA Z-1
		TWA (Total dust)	15 mg/m ³	OSHA P0
		TWA (respirable dust fraction)	5 mg/m ³	OSHA P0
Bosentan monohydrate	157212-55-0	TWA	50 microgram per cubic meter	OEL/PBOEL HHC
Magnesium Stearate	557-04-0	TWA (Inhalable fraction)	10 mg/m ³	ACGIH
		TWA (Respirable fraction)	3 mg/m ³	ACGIH
Colloidal Silicon dioxide	112945-52-5	TWA (Dust)	20 Million particles per cubic foot (Silica)	OSHA Z-3
		TWA (Dust)	80 mg/m ³ % SiO ₂ (Silica)	OSHA Z-3
		TWA	6 mg/m ³ (Silica)	NIOSH REL

Engineering measures: All personal protective equipment should be based on a risk assessment. Consult a Environment Health Safety expert if necessary.

Personal protective equipment

Respiratory protection : Engineering controls should always be the primary method of controlling exposures. If respiratory protective equipment is needed for certain activities, the type as well as the corresponding protection factor will depend upon the risk assessment and air concentrations, hazards, physical and warning properties of substances pre- sent. No personal respiratory protective equipment normally required.

Hand protection

Remarks : No special precautions required.

Eye protection : No special precautions required.

Skin and body protection : No special precautions required.

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Protective measures : The type of protective equipment must be selected based on the Environmental Health and Safety risk assessment. Consult a environmental Health and Safety expert if necessary.

Hygiene measures : Handle in accordance with good industrial hygiene and safety

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

- Appearance : tablet
- Colour : Off white to pale yellow coloured
- Odour : No data available
- Odour Threshold : No data available
- pH : No data available
- Melting point/freezing point : No data available
- Boiling point/boiling range : No data available
- Flash point : No data available
- Evaporation rate : No data available
- Upper explosion limit : No data available
- Lower explosion limit : No data available
- Vapour pressure : No data available
- Relative vapour density : No data available
- Relative density : No data available
- Density : No data available
- Solubility(ies) Water solubility : No data available
- Partition coefficient: n- octanol/water : No data available
- Auto-ignition temperature : No data available
- Decomposition temperature : No data available
- Viscosity Viscosity, dynamic : No data available
- Viscosity, kinematic : No data available
- Explosive properties : No data available
- Oxidizing properties : No data available

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SECTION 10. STABILITY AND REACTIVITY

- Reactivity : None reasonably foreseeable.
- Chemical stability : Stable under normal conditions.
- Possibility of hazardous reactions : No dangerous reaction known under conditions of normal use.
- Conditions to avoid : To avoid thermal decomposition, do not overheat. Heat, flames and sparks.
- Incompatible materials : None known.
- Hazardous decomposition products : None known.

SECTION 11. TOXICOLOGICAL INFORMATION**ACUTE TOXICITY:****Components:****Microcrystalline Cellulose:** Acute oral toxicity : LD50 (Rat): > 5,000 mg/kg**Bosentan monohydrate:** Acute oral toxicity : LDLo (Rat): > 3,000 mg/kg (Assessment: The substance or mixture has no acute oral toxicity)**Colloidal Silicon dioxide:**

Acute oral toxicity : Remarks: No data available

Acute inhalation toxicity : Remarks: No data available

Acute dermal toxicity : Remarks: No data available

Acute toxicity (other routes of administration) : Remarks: No data available

Skin corrosion/irritation**Components:****Microcrystalline Cellulose:**

Species: Rabbit Remarks: No skin irritation

Bosentan monohydrate: Species: Rabbit Result: No skin irritation**Colloidal Silicon dioxide:** Remarks: No data available**SERIOUS EYE DAMAGE/EYE IRRITATION****Components:****Microcrystalline Cellulose:** Species: Rabbit Remarks: No eye irritation**Bosentan monohydrate:** Species: Rabbit & Result: No eye irritation**Colloidal Silicon dioxide:** Remarks: No data available

SAFETY DATA SHEET**Product Name****Bosentan Tablets for Oral suspension 32 mg****Respiratory or skin sensitisation****Components:**

Microcrystalline Cellulose: Species: Guinea pig Remarks: Did not cause sensitisation on laboratory animals.

Bosentan monohydrate: Species: Guinea pig Result: May cause sensitisation by skin contact.

Colloidal Silicon dioxide: Remarks: No data available

GERM CELL MUTAGENICITY**Components:**

Bosentan monohydrate: Germ cell mutagenicity - Assessment : No evidence of mutagenicity based on in vitro and in vivo studies and expert judgment.

Colloidal Silicon dioxide: Genotoxicity in vitro : Remarks: No data available

CARCINOGENICITY**Components:**

Bosentan monohydrate: Carcinogenicity - Assessment: No evidence of carcinogenicity.

Colloidal Silicon dioxide: Remarks: No data available

IARC: No component of this product present at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by IARC.

OSHA No component of this product present at levels greater than or equal to 0.1% is on OSHA's list of regulated carcinogens.

NTP: No component of this product present at levels greater than or equal to 0.1% is identified as a known or anticipated carcinogen by NTP.

REPRODUCTIVE TOXICITY:**Components:****Bosentan monohydrate:**

Reproductive toxicity-Assessment -: Some evidence of adverse effects on development, based on animal experiments

Teratogenicity-Assessment : Some evidence of adverse effects on development, based on animal experiments

Colloidal Silicon dioxide:

Effects on fertility: Remarks: No data available

Effects on foetal development: Remarks: No data available

SAFETY DATA SHEET**Product Name****Bosentan Tablets for Oral suspension 32 mg****STOT - single exposure****Components:****Colloidal Silicon dioxide:** Remarks: No data available**STOT - repeated exposure****Components:****Colloidal Silicon dioxide:** Remarks: No data available**Repeated dose toxicity:** No data available**Aspiration toxicity:** No data available**SECTION 12. ECOLOGICAL INFORMATION****ECOTOXICITY:****Components:****Colloidal Silicon dioxide:****Toxicity to fish :** Remarks: No data available**Bosentan monohydrate:****Toxicity to fish :** (Oncorhynchus mykiss (rainbow trout)): > 100 mg/l Exposure time: 96 h

Test Type: LC50

Method: OECD Test Guideline 203

NOEC: < 100 mg/l

Exposure time: 96 h

Method: OECD Test Guideline 203

Toxicity to daphnia and other aquatic invertebrates:

EC50 (Daphnia magna (Water flea)): 66 mg/l

Exposure time: 48 h

Method: OECD Test Guideline 202

EC0 (Daphnia magna (Water flea)): 33 mg/l

Exposure time: 48 h

Method: OECD Test Guideline 202

Toxicity to microorganisms: EC50 (activated sludge): > 100 mg/l Exposure time: 3 h Test Type:**Respiration inhibition Method:** OECD Test Guideline 209

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Colloidal Silicon dioxide:

Toxicity to fish : (Brachydanio rerio (zebrafish)): > 10,000 mg/l Exposure time: 96 h Test Type: LC50

Toxicity to daphnia and other aquatic invertebrates : Remarks: No data available

Toxicity to algae : Remarks: No data available

Persistence and degradability**Components:****Bosentan monohydrate:**

Biodegradability : Result: Not readily biodegradable.

Biodegradation: 0 %

Exposure time: 28 d

Method: OECD Test Guideline 301F

Result: Not inherently biodegradable.

Biodegradation: 0 %

Exposure time: 28 d

Method: OECD Test Guideline 302C

Silicon, amorphous: Biodegradability : Remarks: No data available

BIOACCUMULATIVE POTENTIAL**Components:**

Magnesium Stearate: Partition coefficient: n- octanol/water : Remarks: No data available

Colloidal Silicon dioxide: Bioaccumulation : Remarks: No data available

Partition coefficient: n- octanol/water : Remarks: No data available

MOBILITY IN SOIL**Components:****Other adverse effects**

Product: Ozone-Depletion Potential : Regulation: 40 CFR Protection of Environment; Part 82
Protection of Stratospheric Ozone - CAA Section 602 Class I Substances

Remarks: This product neither contains, nor was manufactured with a Class I or Class II ODS as defined by the U.S. Clean Air Act Section 602 (40 CFR 82, Subpt. A, App.A + B).

**SAFETY DATA SHEET****Product Name****Bosentan Tablets for Oral suspension 32 mg****SECTION 13. DISPOSAL CONSIDERATIONS****Disposal methods**

Waste from residues : In accordance with National, Federal, State and Local regulations

Contaminated packaging : Empty containers should be taken to an approved waste handling site for recycling or disposal.

SECTION 14. TRANSPORT INFORMATION**International Regulations**

UNRTDG Not regulated as a dangerous good

IATA-DGR Not regulated as a dangerous good

IMDG-Code Not regulated as a dangerous good

Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code

Not applicable for product as supplied.

National Regulations

49 CFR Not regulated as a dangerous good

SECTION 15. REGULATORY INFORMATION

EPCRA - Emergency Planning and Community Right-to-Know Act

SARA 302 Extremely Hazardous Substances Threshold Planning Quantity

This material does not contain any components with a section 302 EHS TPQ.

SARA 311/312 Hazards :

Serious eye damage or eye irritation Respiratory or skin sensitisation Reproductive toxicity

SARA 313 :

This material does not contain any chemical components with known CAS numbers that exceed the threshold (De Minimis) reporting levels established by SARA Title III, Section 313.

Clean Air Act

This product neither contains, nor was manufactured with a Class I or Class II ODS as defined by the U.S. Clean Air Act Section 602 (40 CFR 82, Subpt. A, App.A+B). This product does not contain any hazardous air pollutants (HAP), as defined by the U.S. Clean Air Act Section 112 (40 CFR 61). This product does not contain any chemicals listed under the U.S. Clean Air Act Section 112(r) for Accidental Release Prevention (40 CFR 68.130, Subpart F). This product does not contain any chemicals listed under the U.S. Clean Air Act Section 111 SOCM I Intermediate or Final VOC's (40 CFR 60.489).



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Clean Water Act

This product does not contain any Hazardous Substances listed under the U.S. Clean Water Act, Section 311, Table 116.4A. This product does not contain any Hazardous Chemicals listed under the U.S. Clean Water Act, Section 311, Table 117.3. This product does not contain any toxic pollutants listed under the U.S. Clean Water Act Section 307

US State Regulations

Massachusetts Right To Know: Cellulose 9004-34-6

Pennsylvania Right To Know:

Microcrystalline Cellulose 9004-34-6

Anhydrous Dibasic calcium Phosphate 7757-93-9

Bosentan monohydrate 157212-55-0 & 74811-65-7

California Prop 65 This product does not contain any chemicals known to State of California to cause cancer, birth defects, or any other reproductive harm.

Other regulations: Restricted to professional users.

This product is not subject to TSCA and TSCA 12(b) Export notification because Food, Drugs and cosmetic products are exempt.

California Permissible Exposure Limits for Chemical Contaminants

Microcrystalline Cellulose 9004-34-6

Magnesium Stearate 557-04-0

Colloidal Silicon dioxide 112945-52-5

SECTION 16. OTHER INFORMATION**Full text of other abbreviations**

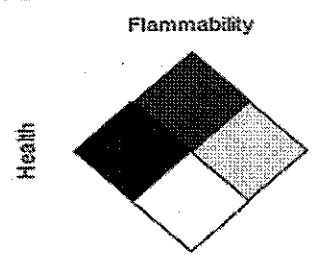
AICS - Australian Inventory of Chemical Substances; ASTM - American Society for the Testing of Materials; bw - Body weight; CERCLA - Comprehensive Environmental Response, Compensation, and Liability Act; CMR - Carcinogen, Mutagen or Reproductive Toxicant; DIN - Standard of the German Institute for Standardisation; DOT - Department of Transportation; DSL - Domestic Substances List (Canada); ECx - Concentration associated with x% response; EHS - Extremely Hazardous Substance; ELx - Loading rate associated with x% response; EmS - Emergency Schedule; ENCS - Existing and New Chemical Substances (Japan); ErCx - Concentration associated with x% growth rate response; ERG - Emergency Response Guide; GHS - Globally Harmonized System; GLP - Good Laboratory Practice; HMIS - Hazardous Materials Identification System; IARC - International Agency for Research on Cancer; IATA - International Air Transport Association; IBC - International Code for the Construction and Equipment of Ships carrying Dangerous Chemicals in Bulk; IC50 - Half maximal inhibitory concentration; ICAO - International Civil Aviation Organization; IECSC - Inventory of Existing Chemical Substances in China; IMDG - International Maritime Dangerous Goods; IMO - International Maritime Organization; ISHL - Industrial Safety and Health Law (Japan); ISO - International Organisation for

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Standardization; KECI - Korea Existing Chemicals Inventory; LC50 - Lethal Concentration to 50 % of a test population; LD50 - Lethal Dose to 50% of a test population (Median Lethal Dose); MARPOL - International Convention for the Prevention of Pollution from Ships; MSHA - Mine Safety and Health Administration; n.o.s. - Not Otherwise Specified; NFPA - National Fire Protection Association; NO(A)EC - No Observed (Adverse) Effect Concentration; NO(A)EL - No Observed (Adverse) Effect Level; NOELR - No Observable Effect Loading Rate; NTP - National Toxicology Program; NZIoC - New Zealand Inventory of Chemicals; OECD - Organization for Economic Co-operation and Development; OPPTS - Office of Chemical Safety and Pollution Prevention; PBT - Persistent, Bioaccumulative and Toxic substance; PICCS - Philippines Inventory of Chemicals and Chemical Substances; (Q)SAR - (Quantitative) Structure Activity Relationship; RCRA - Resource Conservation and Recovery Act; REACH - Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals; RQ - Reportable Quantity; SADT - Self-Accelerating Decomposition Temperature; SARA - Superfund Amendments and Reauthorization Act; SDS - Safety Data Sheet; TCSI - Taiwan Chemical Sub- stance Inventory; TSCA - Toxic Substances Control Act (United States); UN - United Nations; UNRTDG - United Nations Recommendations on the Transport of Dangerous Goods; vPvB - Very Persistent and Very Bioaccumulative

Further information

<p>NFPA:</p> <div style="text-align: center;"> <p>Flammability</p>  <p>Health Instability</p> <p>Special hazard.</p> </div>	<p>HMIS® IV:</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="background-color: black; color: white; padding: 5px;">HEALTH</td> <td style="width: 40px; height: 30px; border: 1px solid black;"></td> <td style="width: 40px; height: 30px; border: 1px solid black;"></td> </tr> <tr> <td style="background-color: black; color: white; padding: 5px;">PHYSICAL HAZARD</td> <td style="width: 40px; height: 30px; border: 1px solid black;"></td> <td style="width: 40px; height: 30px; border: 1px solid black;"></td> </tr> </table> <p>HMIS® ratings are based on a 0-4 rating scale, with 0 representing minimal hazards or risks, and 4 representing significant hazards or risks. The "X" represents a chronic hazard, while the "/" represents the absence of a chronic hazard.</p>	HEALTH			PHYSICAL HAZARD		
HEALTH							
PHYSICAL HAZARD							

The information provided in this Safety Data Sheet is correct to the best of our knowledge, information and belief at the date of its publication. The information given is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and is not to be considered a warranty or quality specification. The information relates only to the specific material designated and may not be valid for such material used in combination with any other materials or in any process, unless specified in the text.

Natco pharma Limited

Authorized signatory: 