# Material Safety Data Sheet

According to (EC) No 1907/2006 (REACH) and 1272/2008 (CLP)

## ISOSORBIDI DINITRAS DILUTUS



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Version: 00

MAGIS PHARMA

## SECTION 1: IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/UNDERTAKING

### 1.1 Product identifier

| | |
|---|---|
| Product name: | Isosorbide dinitrate, diluted 40%<br>Isosorbidi dinitras dilutus<br>Verdund isosorbidedinitraat 40%<br>Isosorbide (dinitrate d') dilué 40%<br>Verdünntes Isosorbiddinitrat 40% |
| N° CAS: | 87-33-2 |
| N° EC: | 201-740-9 |

### 1.2 Relevant identified uses of the substance/mixture and uses advised against

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|---|---|
| Identified uses: | Active Pharmaceutical Ingredient or Excipient. |

### 1.3 Details of the supplier of the safety data sheet

| | |
|---|---|
| Company: | FAC SECUNDUM ARTEM NV<br>Oostmalsebaan 1c (unit 5)<br>2960 Sint-Lenaarts<br>Belgium |
| Telephone: | (+32) (0)3 457 11 76 |
| Email: | info@magis-pharma.be |
| Web page: | www.magis-pharma.be |

### 1.4 Emergency telephone number

| | | |
|---|---|---|
| Public utility foundation: | Belgisch Antigifcentrum | Centre Antipoisons Belge |
| Telephone: | (+32) (0)70 245 245 | (Service 24/7) |
| Web page: | www.antigifcentrum.be | www.centreantipoisons.be |

## SECTION 2: HAZARDS IDENTIFICATION

### 2.1 Classification of the substance/mixture

**Classification according to (EC) n° 1272/2008**

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|---|---|
| Flam. Sol. 1 | H228 |
| Acute Tox. 4 | H302 |

### 2.2 Label elements

**Labelling according to (EC) n° 1272/2008**

Hazard pictogram(s):

Signal word(s): Danger

Hazard statements:

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| H228 | Flammable solid. |
| H302 | Harmful if swallowed. |

Precautionary statements:

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| P241 | Use explosion-proof electrical/ventilating/lighting/equipment. |

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| P210 | Keep away from heat, hot surfaces, sparks, open flames and other ignition sources. No smoking. |
| P280 | Wear protective gloves/protective clothing/eye protection/face protection. |
| P301+P312 | IF SWALLOWED: Call a POISON CENTER if you feel unwell. |
| P370+P378 | In case of fire: Use dry chemicals (powders) or carbon dioxide to extinguish. |
| Additional applicable label elements: | Not applicable. |

### 2.3 Other hazards

The mixture is solid: consider - and if needed control - the formation of dusts during the use. A chemical safety report is not required for this mixture, therefore PBT and vPvB assessments were not performed. No other hazards are identified.

## SECTION 3: COMPOSITION/INFORMATION ON INGREDIENTS

### 3.1 Substances

Not applicable.

### 3.2 Mixtures

| | |
|---|---|
| Product name: | Isosorbide dinitrate |
| IUPAC name: | (3S,3aS,6R,6aS)-3-(nitrooxy)-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3-yl nitrate |
| Synonyms: | Sorbide nitrate<br>Isordil |
| N° CAS: | 87-33-2 |
| N° EC: | 201-740-9 |
| Molecular Formula: | $C_6H_8N_2O_8$ |
| Content: | 40% |

| | |
|---|---|
| Product name: | Lactose monohydrate |
| IUPAC name: | (2*R*,3*R*,4*S*,5*R*,6*S*)-2-(hydroxymethyl)-6-[(2*R*,3*S*,4*R*,5*R*,6*S*)-4,5,6-trihydroxy-2-(hydroxymethyl)oxan-3-yl]oxyoxane-3,4,5-triol;hydrate |
| Synonyms: | Lactose<br>D-Lactose monohydrate |
| N° CAS: | 10039-26-6 |
| N° EC: | 200-559-2 |
| Molecular Formula: | $C_{12}H_{22}O_{11}$ , $H_2O$ |
| Content: | 60% |

## SECTION 4: FIRST AID MEASURES

### 4.1 Description of first aid measures

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| General notes: | In case of doubt or in the presence of symptoms, contact a physician, and show him/her the material safety data sheet. In case of severe symptoms, call your local health care emergency number. Call a poison control centre in order to receive toxicological advice for the clinical management of poisoning. Do not administer anything by mouth to an unconscious person. |

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| After inhalation: | Move the person to fresh air. In case of respiratory symptoms (cough, dyspnoea), place the person in a semi-seated position and administer oxygen. Provide artificial respiration if the person is not breathing. |
| After skin contact: | Flush the skin with copious amounts of water (and soap, if possible) for at least 15 minutes. Consult a physician if there are symptoms of skin irritation and/or pain. |
| After eye contact: | Remove contact lenses, if present and easy to do. Flush the eyes, kept open, with copious amounts of running water for at least 15 minutes. Consult a physician, especially if there are symptoms of eye irritation and/or pain. |
| After ingestion: | Do not induce emesis. Do not administer anything by mouth unless advised to do so by a poison control centre. Rinse the mouth and consult a physician. |

### 4.2 Most important symptoms and effects, both acute and delayed

Most important symptoms and effects, both acute and delayed, are described in section 11.

### 4.3 Indication of any immediate medical attention and special treatment needed

Need for immediate medical attention

If the victim has severe symptoms, immediately call your local health care emergency number to request the intervention of a physician. In any case, refer to a poison control centre for advice and medical toxicology specialist from the early stages of the rescue. Consult a physician if in any case any symptoms, even mild, persists.

Special treatment needed and antidotes to be available on the workplace

Freshwater for washing skin and eye. Oxygen. Activated charcoal, to be administered after toxicological advice.

Personal protective equipment for first aid responders

Wear appropriate protective equipment to prevent the contamination of the first aid responder from the victim.

Removal and handling of contaminated clothing and shoes

In case of gross contamination, remove clothing and shoes. Place them into a suitable, closed, temporary storage away from the working area.

## SECTION 5: FIREFIGHTING MEASURES

### 5.1 Extinguishing media

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| Suitable extinguishing media: | As the substance is a solid material, the most suitable extinguishing media are water and dry chemicals (powders); foam and carbon dioxide are less effective. In the choice of extinguishing media, consider the other materials involved in the fire. |
| Unsuitable extinguishing media: | None. |

### 5.2 Special hazards arising from the substance/mixture

In the case of fire, irritant or toxic fumes may develop from the substance and from the other materials involved in the fire.

Hazardous combustion products: carbon oxides ($CO_x$), nitrogen oxides ($NO_x$).

### 5.3 Advice for firefighters

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| Surrounding fires: | Move all people away and stay upwind of the fire. Do not enter closed rooms without adequate protection. Use jets of water to cool the containers to prevent product decomposition and the development of substances potentially hazardous for health. Always wear full fire prevention gear. Collect extinguishing water to prevent it from draining into the sewer system. Dispose of contaminated water used for extinction and the remains of the fire according to applicable regulations. |

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| Protection against fire: | Hardhat with visor, fireproof clothing (fireproof jacket and trousers with straps around arms, legs and waist), work gloves (fireproof, cut proof and dielectric), a depressurized mask with facemask covering the whole face of the operator or a self-respirator (self-protector) in the event of large quantities of fume. |
| Hazardous combustion products: | Not available. |

## SECTION 6: ACCIDENTAL RELEASE MEASURES

### 6.1 Personal precautions, protective equipment and emergency procedures

**For non-emergency personnel**

Eliminate sources of ignition (cigarettes, flames, sparks, etc.) from the area in which the leak occurred. Send away individuals who are not suitably equipped.

**For emergency responders**

Do not handle damaged containers or leaked product before donning appropriate protective gear (section 8 of the safety data sheet) to prevent any contamination of skin, eyes and personal clothing. If there are no contraindications, spray powder with water to prevent the formation of dust and provide sufficient ventilation.

### 6.2 Environmental precautions

The product must not penetrate the sewer system, surface water, ground water and neighbouring areas.

### 6.3 Methods and material for containment and cleaning up

Appropriate advice on how to contain a spill: Make sure the leakage site is well aired.

Appropriate advice on how to clean up a spill: Use spark proof mechanical tools to collect the leaked product and place in a plastic container. If there are no contraindications, use jets of water to eliminate product residues.

Any other information relating to spills and releases, including advice on inappropriate containment or clean up techniques: Contaminated material should be disposed of in compliance with the provisions set forth in section 13.

### 6.4 Reference to other sections

For any other information on risks for the environment, see section 12.

For any other information on health risks, see section 11.

For any other information on personal protection, see section 8

For any other information on disposal, see section 13.

## SECTION 7: HANDLING AND STORAGE

### 7.1 Precautions for safe handling

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| Precautions for safe handling: | Measures to prevent fire: Eliminate sources of ignition (cigarettes, flames, sparks, etc.). Wear antistatic cloths and shoes when handling this substance. Use antistatic primary packaging. Avoid shaking the powder or creating dust clouds. Ground and bound equipment; work as much as possible with inertization systems to avoid the formation of potentially explosive atmospheres. Use spark proof mechanical tools to collect the leaked product.<br>Measures to prevent aerosol and dust generation: Avoid shaking packaging when filling/empting them. Keep containers tightly sealed when not in use. |

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| Personal protection: | Advice on general occupational hygiene: Do not eat, drink and smoke in work areas. Wash hands after use. Remove contaminated clothing and protective equipment before entering eating areas. |
| Technical protective measures: | Measures to protect the environment: General ventilation; LEV; filters or water scrubbers on exhaust ventilation. |
| Handling: | Not available. |

**7.2 Conditions for safe storage, including any incompatibilities**

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| Storage: | Packaging materials: Double black antistatic polythene bag of hygienic type (inner packaging); fibre (outer packaging). |
| Conditions for safe storage, including any incompatibilities: | The mixture should be stored in a manner to prevent degradation, contamination, and cross-contamination, keeping material in properly labelled tightly closed containers.<br>The mixture stored in fibre drums should be stored off the floor and suitably spaced to permit cleaning and inspection.<br>Requirements for storage rooms and vessels: There should not be present sources of ignition (cigarettes, flames, sparks, etc.). |
| Storage – away from: | Protected from light. Store away from incompatible materials (section 10). |

**7.3 Specific end use(s)**

Active Pharmaceutical Ingredient or Excipient

## SECTION 8: EXPOSURE CONTROLS/PERSONAL PROTECTION

**8.1 Control parameters**

Occupational exposure limit values

Limit value – 8h: 250 µg/m$^3$ (Internal method)

The substance (ISDN) has not a national occupational exposure limit value that corresponds to a Community OEL or a relevant national limit and an Indicative Occupational Exposure Limit Value (IOELV) has not been proposed by the European Commission not yet been transposed into individual Member States national law. The reported limit value is obtained applying a calculation model that includes the following three levels approaches:

- Level I – calculation based on Therapeutic Dose approach
- Level II – calculation based on “banding approach”
- Level III – calculation based on NOAEL or LOAEL approach

OELMIX is calculated as the ratio of OELISDN: %ISDN in the mixture.

Information on monitoring procedures

The main currently recommended monitoring (air monitoring, room air monitoring) are:

- UNI EN 481:1994 Workplace atmospheres. Size fraction definitions for measurement of airborne particles.
- UNI EN 482:1998 Workplace atmospheres. General requirements for the performance of procedures of chemical agents.
- UNI EN 689:1997 Workplace Atmosphere – Guide to assessing inhalation exposure to chemical compounds with the purpose of

comparing them to the limit values and measuring strategies.

- UNI EN 1232:1999 Workplace atmospheres - Pumps for personal sampling of chemical agents. Requirements and test methods.

• UNI EN 1540:2001 Workplace Atmosphere. Terminology.

### 8.2 Exposure controls

**Appropriate engineering control**

Charge/discharge equipment under nitrogen purging, using local exhaust ventilation next to equipment openings, proper ventilation and conveying emissions to abatement systems.

**Individual protection measures**

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| Eye/face protection: | Full mask. |
| Skin protection: | Professional disposable overall with hood for use with chemicals. |
| Hand protection: | Natural rubber gloves. |
| Respiratory protection: | Full mask with P3 filter. |
| Thermal hazards: | Not determined. |

**Environmental exposure control**

Not available.

## SECTION 9: PHYSICAL AND CHEMICAL PROPERTIES

### 9.1 Information on basic physical and chemical properties

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| Appearance: | Undiluted isosorbide dinitrate is a fine, white or almost white, crystalline powder.<br>Lactose is a white or almost white powder. |
| Odour: | Odourless. |
| Odour threshold: | Not available. |
| pH: | Lactose: Acidity: max 0.4 ml NaOH 0.1 N / 6 g |
| Melting/freezing point: | Isosorbide dinitrate: 69.0 ± 72.0 °C<br>Lactose: 201 ± 202 °C, decomposes at 203.5 °C |
| Initial boiling point: | Isosorbide dinitrate: 303.79 °C<br>Lactose: decomposes |
| Boiling range: | Not available. |
| Flash point: | Isosorbide dinitrate: see explosive properties.<br>Lactose: Not relevant information because the substance is a solid with a relatively high melting point. |
| Evaporation rate: | Not available. |
| Flammability (solid/gas): | Isosorbide dinitrate: see explosive properties.<br>Lactose: Dust explosion hazard. Class: ST1<br>According to special provisions of the regulations of the international carriage of dangerous good, isosorbide dinitrate mixture with not less than 60% lactose, mannose, starch, or calcium hydrogen phosphate is subject to the provisions of these codes as flammable solid (class 4.1) in packing group II (according to Method N.1 as described in 33.2.1 of the UN RTDG, Manual of Tests and Criteria: wetted zone does not stop fire).<br>The mixture contains not less than 60% of lactose and therefore available data are regarded as conclusive to classify as Flam. Sol. 1, H228 (Flammable solid). |

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| Upper/lower flammability or explosive limits: | Isosorbide dinitrate: see explosive properties.<br>Lactose: Lower explosive limit: 30 – 125 g/m$^3$, upper explosive limit: not determined. |
| Vapour pressure: | Isosorbide dinitrate: 0.000601 mmHg (25°C )<br>Lactose: 3.42x10$^{-16}$ mm Hg at 25°C (estimated) |
| Vapour density: | Not relevant information because the substance is a solid with a very low vapour pressure. |
| Relative density: | Isosorbide dinitrate: Bulk density: 0.5 ÷ 0.6 kg/l<br>Lactose: 1.525 |
| Solubility: | Undiluted isosorbide dinitrate is very soluble in acetone, sparingly soluble in ethanol (96 per cent). The solubility of the diluted product depends on the diluent and its concentration.<br>Lactose is practically insoluble in alcohol. |
| Solubility in water: | Undiluted isosorbide dinitrate is very slightly soluble in water.<br>Lactose is freely but slowly soluble in water. |
| Partition coefficient (n-octanol/water): | Isosorbide dinitrate: 1.31<br>Lactose: -5.03 |
| Auto-ignition temperature: | Not available. |
| Decomposition temperature: | Isosorbide dinitrate: See explosive properties.<br>Lactose: See boiling point. |
| Viscosity: | Isosorbide dinitrate: Not available.<br>Lactose: Not relevant information because the substance is a solid with a relatively high melting point. |
| Explosive properties: | Isosorbide dinitrate: The pure substance is a strong explosive. |

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| Oxygen balance | -54.2 % |
| Nitrogen percentage | 11.87 % |
| Melting point | ca. 70°C (decomposition) |
| Lead block test | 311 cm$^3$/10 g |
| Detonation velocity, confined | 5300 m/s at ρ = 1.08 g/cm$^3$ |
| Deflagration point | 173 °C |
| Impact sensitivity | 1.5 kp·m = 15 N·m |
| Friction sensitivity | over 16 kp = 160 N pistil load crackling |

Lactose: Dust explosion hazard. Class: ST1

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|---|---|
| Oxidising properties: | Isosorbide dinitrate: See explosive properties.<br>Lactose: The classification procedure for this class shall not apply because the substance contains oxygen and this element is chemically bonded only to carbon and/or to hydrogen. |

**9.2 Other information**

Molecular weight

ISDN: 236.136 g/mol

LACTOSE: 360.311 g/mol (monhydrate)

Chirality

Isosorbide dinitrate presents four stereo centres.

Isosorbide dinitrate molecule belongs to the $C_1$ symmetry group, so it has optical activity.

Specific optical rotation

ISDN: $[\alpha]_D^{20}$ = +140° (dissolved 1% in absolute alcohol)

LACTOSE: +54.4°÷+55.9

Polymorphism

ISDN: Differential Scanning Calorimetry shows an unchanging melting point, so it is demonstrated that ISDN cannot have polymorphism problems.

## SECTION 10: STABILITY AND REACTIVITY

### 10.1 Reactivity

There are no particular risks of reaction with other substances in normal conditions of use.

### 10.2 Chemical stability

The mixture is stable in normal condition of use and storage. Based on stability studies, the retest date is 5 years.

Lactose: Stable in air.

### 10.3 Possibility of hazardous reactions

Airborne particles may fuel fires/explosion in presence of source of ignition.

### 10.4 Conditions to avoid

As a precautionary measure, avoid dust generation and keep away from source of ignition like heat sources or electrostatic discharges.

### 10.5 Incompatible materials

Keep the mixture away from acids, alkalis, strong oxidizing agents.

### 10.6 Hazardous decomposition products

In the event of thermal decomposition or fire, vapours potentially dangerous to health may be released.

Possible combustion products: carbon oxides ($CO_x$), nitrogen oxides ($NO_x$).

## SECTION 11: TOXICOLOGICAL INFORMATION

Pharmacodynamic properties

Isosorbide dinitrate is a vasodilator, anti-anginal drug. It reduces the number, duration and severity of episodes of angina pectoris. It is used in acute myocardial infarction in control of ischemic pain, reduction of elevated blood pressure and in the treatment of pulmonary oedema and congestive cardiac failure. It is also useful in the treatment of severe hypertension.

Pharmacokinetic properties

Absorption: Isosorbide dinitrate is readily absorbed from the oral mucosa and has a short duration of action. Following oral administration, it is well absorbed from the gastrointestinal tract. In view of its first pass effect and short plasma half life, slow release formulations are available. Sublingual administration produces maximal concentration of the drug in plasma within 6 minutes. Isosorbide dinitrate is also absorbed through the skin from an ointment base. The bioavailability of isosorbide dinitrate is about 29% following oral or sublingual dosing.

Distribution: The volume of distribution of isosorbide dinitrate into human body is ranged from 48 to 473 litres; the distribution half-life is 4.7 minutes.

Biotransformation: Isosorbide dinitrate is metabolized in man by enzymatic denitration followed by formation of glucuronides. The primary initial metabolites, isosorbide-2-mononitrate and isosorbide-5-mononitrate, have longer half-lives (2-5 hours) and are presumed to be responsible, at least in part, for the therapeutic efficacy of isosorbide dinitrate.

Elimination: Isosorbide dinitrate is eliminated through renal excretion (80-90%) and feces (limited). The majority is excreted as conjugated isosorbide dinitrate within 24 hours and as metabolites during either acute or chronic therapy. The total body clearance is 2.3 - 3.4 litres/minutes. During chronic administration of 15, 30, 60, and 120 mg doses of isosorbide dinitrate four times a day to angina patients, clearance decreased with increasing dose. The same effect was not seen following single doses. Clearance following intravenous administration exceeds hepatic blood flow.

The half-life of isosorbide dinitrate appears to be dependent upon the route of administration: intravenous 20 minutes, sublingual 1 hour. The metabolites 5-mononitrate and 2-mononitrate have longer half-lives: 4.3 to 5 hours and 1.8 to 3.17 hours respectively. By contrast, the mean half-life of isosorbide dinitrate is about 7.7 hours after chronic dose of 60 mg.

Undesirable effects: The following table shows the adverse reactions reported for Isosorbide dinitrate.

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| Cardiovascular | In patients receiving isosorbide dinitrate, the most common cardiovascular adverse effects include heart block, hypotension, light-headedness, myocardial ischemia, peripheral oedema, rebound hypertension, syncope. |
| Endocrine/Metabolic | In patients receiving isosorbide dinitrate, the most common endocrine/metabolic adverse effects include pituitary apoplexy. |
| Hematologic | In patients receiving Isosorbide dinitrate, the most common hematologic adverse effects include glucose-6-phosphate dehydrogenase deficiency anaemia, methemoglobinemia (rare). |
| Neurologic | In patients receiving isosorbide dinitrate, the most common neurologic adverse effects include headache (common). |

## 11.1 Information on toxicological effects

Acute toxicity:

Acute toxicity - oral

ISOSORBIDE DINITRATE:

Oral $LD_{50}$ (rat): 747 mg/kg

Oral $LD_{50}$ (mouse): 1050 mg/kg

LACTOSE:

Oral $LD_{50}$ (rat): > 10 000 mg/kg

The classification of the mixture is based on its ingredients (the lowest $LD_{50}$ values in animals (747 mg/kg in rats) for ISDN while LACTOSE (LD50 >10 g/kg) is not acutely toxic) and the ATEMIX calculated according to the formula LD50(ISDN): mixture concentration (ISDN) x 100 gives the result of 1867.5 mg/kg.

Overall, available data are regarded as conclusive to classify the mixture as Acute Tox. 4; H302, harmful if swallowed.

Acute toxicity- dermal

ISOSORBIDE DINITRATE: Skin $LD_{50}$ (rat): > 3 000 mg/kg

LACTOSE: No data on this property were found in literature. Therefore, the substance is not classified for this hazard because of data lacking.

ISDN has an acute dermal toxicity not reaching the limits for their classification while no data on this property were found in literature for LACTOSE, therefore the mixture is not classified for this hazard because of data lacking.

Acute toxicity – inhalation

ISOSORBIDE DINITRATE: Not available.

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| | LACTOSE: The purpose of this work was to investigate the safety of lactose and chitosan to the pulmonary tissue when delivered by inhalation to Wistar rats. Lactose and chitosan administered by inhalation failed to show toxic effects to the pulmonary tissue. A protective effect against oxidative stress might even be attributed to chitosan, since some biomarkers had values significantly lower than those observed in the control group when this product was inhaled. Nevertheless, caution must be taken regarding chemical composition and technological processes applied to incorporate these products during drug formulation, in particular for dry powder inhalators.<br>Available data are regarded as inconclusive to determine the classification of the mixture for this hazard. |
| Skin corrosion/irritation: | ISDN: Standard Draize test, rabbit, skin: 500 mg/24 hours, reaction: mild<br>LACTOSE: No data on this property were found in literature. Therefore, the substance is not classified for this hazard because of data lacking.<br>Available data for ISDN are regarded as inconclusive to determine the classification of the substance for this hazard. No data on this property were found in literature for LACTOSE. Overall, available data are regarded as inconclusive to determine the classification of the mixture for this hazard. |
| Serious eye damage/irritation: | The mixture is not classified for this hazard because of data lacking. |
| Respiratory/skin sensitisation: | The mixture is not classified for this hazard because of data lacking. |
| Germ cell mutagenicity: | ISDN: Isosorbide mononitrate did not produce gene mutations (Ames test, mouse lymphoma test) or chromosome aberrations (human lymphocyte and mouse micronucleus tests) at biologically relevant concentration. These data may apply to isosorbide dinitrate due to similarities in mode of action and chemical structure.<br>LACTOSE No data on this property were found in literature. Therefore, the substance is not classified for this hazard because of data lacking.<br>The mixture is not classified for this hazard because of data lacking for LACTOSE. |
| Carcinogenicity: | ISDN: The carcinogenicity of isosorbide mononitrate was assessed in a study performed in rats. No evidence of carcinogenicity was observed in rats exposed to isosorbide mononitrate in their diets at doses of up to 900 mg/kg/day for the first 6 months and 500 mg/kg/day for the remaining duration of a study in which males were dosed for up to 121 wks and females were dosed for up to 137 weeks. These data may apply to isosorbide dinitrate due to similarities in mode of action and chemical structure.<br>LACTOSE: In a 130-week study of rats fed diets containing 20% anhydrous lactose, female rats showed no evidence of carcinogenicity and male rats had an increase in medullary and Leydig cell tumours.<br>Overall, available data are regarded as inconclusive in order to exclude the classification of the mixture for this hazard. |
| Reproductive toxicity: | Available data are regarded as conclusive to exclude the classification of the mixture for this hazard. |
| Summary of evaluation of the CMR properties: | Not available. |
| STOT-single exposure: | ISDN:<br>Oral $TDL_0$ (man): 1 714 µg/kg 3 days intermittent |

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| | Toxic effects: Lung, thorax, or respiration – cyanosis Blood – methemoglobinemia - carboxyhemoglobin |
| | Oral $TDL_0$ (woman): 100 µg/kg |
| | Toxic effects : Behavioural – coma, cardiac - pulse rate, cardiac - other changes |
| | Oral $TDL_0$ (rat): 1 000 mg/kg |
| | Toxic effects: Cardiac - change in pulse rate, vascular - BP lowering not characterized in autonomic section |
| | Oral $TDL_0$ (mouse): 2.5 mg/kg |
| | Toxic effects : Behavioural – analgesia |
| | LACTOSE: No data on this property were found in literature. Therefore, the substance is not classified for this hazard because of data lacking. |
| | Available data are regarded as inconclusive to determine the classification of the mixture for this hazard. |
| STOT-repeated exposure: | ISDN: Adverse reactions to isosorbide dinitrate are generally dose related, and almost, all of these reactions are the result of isosorbide dinitrate's activity as vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients. Methemoglobinemia is infrequent at these doses (Physicial Desk Reference - Isosorbide dinitrate - 2012). |
| | LACTOSE: In animal toxicity studies, lactose has been administered primarily by the inhalation and dietary routes to the rat, dog and/or primate. Adverse findings, such as abdominal distension and diarrhoea, have been demonstrated in rodent feeding studies. However, these changes are considered to be due to nonspecific effects associated with high dietary doses of lactose, with a subsequent production of a dietary imbalance which results in physiological disturbances and an overload in the metabolic processes particularly involving calcium. These changes at high dietary intakes of lactose are considered to be of little relevance for man under the normal conditions of use of the material as an excipient in pharmaceutical formulations. No adverse local effects to the lung have been demonstrated in the animal studies using the inhalation route. Although the inhalation dose of lactose in the animal studies, of which most is subsequently swallowed, is markedly higher than the clinical dose, it is considerably less than consumed in animal studies using the dietary route. Consequently, it is not surprising that lactose is well tolerated by the inhalation route. |
| | Overall, available data are regarded as inconclusive to determine the classification of the mixture for this hazard. |
| Aspiration Hazard: | Based on available data, the classification criteria are not met. |
| Other: | Not available. |
| **11.2 Additional information on potential adverse human health effects and symptoms** | |
| Eye contact: | Not available. |
| Skin contact: | Not available. |
| Inhalation: | Not available. |
| Ingestion: | Harmful if swallowed. |
| Aspiration: | Not available. |

## SECTION 12: ECOLOGICAL INFORMATION

### 12.1 Toxicity

No data on this property were found in literature neither for the mixture nor for its components. Therefore, the mixture is not classified for this hazard because of data lacking.

### 12.2 Persistence and degradability

Not available.

### 12.3 Bioaccumulative potential

There are no available data on this property neither for the mixture nor for its components except for ISDN.

According to the value of the n-octanol/water partition coefficient of both ISDN (1.31) and LACTOSE (-5.03), the mixture is unlikely to have a real potential to bioconcentrate.

### 12.4 Mobility in soil

Not available.

### 12.5 Results of PBT and vPvB assessment

A chemical safety report is not required neither for the mixture nor for its components, therefore PBT and vPvB assessments were not performed.

### 12.6 Other adverse effects

Not available.

## SECTION 13: DISPOSAL CONSIDERATIONS

### 13.1 Waste treatment methods

Burn the mixture, moistened with a flammable liquid, in small amounts at a time, in open air, in suitable areas, keeping a safe distance. Due to the explosive characteristics of isosorbide dinitrate (ISDN), it is appropriate that disposal of its mixtures is done according to the attentions of the detailed rules for explosives: destruction by burning, moistened with flammable substances, in small quantities at a time, in suitable areas, keeping a safe distance.

Product / Packaging disposal

Product residues, previously burned, should be considered special hazardous waste. Disposal must be performed through an authorized waste management firm, in compliance with national and local regulations. Contaminated packaging, previously burned, must be disposed of in compliance with national waste management regulations.

Waste treatment-relevant information

The hazard level of waste containing this product should be evaluated according to applicable regulations.

Sewage disposal-relevant information

Waste should not be disposed of by release to sewers.

Other disposal recommendations

To ensure that risks are adequately controlled at the waste stage, disposal must be in accordance with current applicable laws and regulations and material characteristics at the time of disposal. Final decisions on the appropriate waste management method, in line with regional, national and European legislation, and possible adaptation to local conditions, remains the responsibility of the waste treatment operator.

## SECTION 14: TRANSPORT INFORMATION

**Transport information according to ADR/RID/IMDG/ICAO/IATA**

### 14.1 UN Number

| | |
|---|---|
| ADR/ RID(Land),IMDG(Sea), IATA/ICAO (Air) : | 2907 |

| | |
|---|---|
| **14.2 UN proper shipping name** | |
| ADR/ RID(Land),IMDG(Sea), IATA/ICAO (Air) : | ISOSORBIDE DINITRATE MIXTURE |
| **14.3 Transport hazard class(es)** | |
| ADR/ RID(Land),IMDG(Sea), IATA/ICAO (Air) : | 4.1 |
| **14.4 Packing group** | |
| ADR/ RID(Land),IMDG(Sea), IATA/ICAO (Air) : | II<br>Furthermore, this mixture must be packed in packaging made of materials compatible with the relevant ICH short-term and long-term stability studies. |
| **14.5 Environmental hazards** | |
| ADR/ RID(Land),IMDG(Sea), IATA/ICAO (Air) : | The mixture is not environmentally hazardous according to the criteria of Regulations (as mentioned in IMDG Code, ADR, RID and ADN) and, therefore, is not a marine pollutant according to the IMDG Code. |
| **14.6 Special precautions for user** | |
| None in particular. | |
| **14.7 Transport in bulk according to annex II of Marpol and the IBC Code** | |
| The mixture is not intended being transported in bulk. | |
| **14.8 Additional transport information** | |
| Not available. | |

## SECTION 15: REGULATORY INFORMATION

**15.1 Safety, health and environmental regulations/legislation specific for the substance/mixture**

Not applicable.

**15.2 Chemical safety assessment**

A chemical safety assessment has not been carried out.

## SECTION 16: OTHER INFORMATION

**16.1 Changes since the previous version**

Not applicable.

**16.2 Abbreviations and acronyms used**

| | |
|---|---|
| ADR: | European Agreement concerning the International Carriage of Dangerous Goods by Road |
| CAS: | Chemical Abstracts Service (division of the American Chemical Society) |
| EC (number): | European Community (number) |
| IATA: | International Air Transport Association |
| ICAO: | International Civil Aviation Organization |
| IMDG: | International Maritime Code for Dangerous Goods |
| IUPAC: | International Union of Pure and Applied Chemistry |
| PBT: | Persistent, Bioaccumulative and Toxic substance |

| | |
|---|---|
| RID: | Regulations Concerning the International Transport of Dangerous Goods by Rail |
| STOT: | Specific Target Organ Toxicity |
| UN (number): | United Nations (number) |
| vPvB: | very Persistent and very Bioaccumalative |

**16.3 Key literature references/sources for data**

European Chemicals Agency.
https://www.echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database/

**16.4 Method of classification in case of mixture**

Classification based on the main component.

**16.5 Relevant Hazard statements and/or precautionary statements**

For information on hazard and/or precautionary statements refer to section 2 up to and including section 15.

**16.6 Training advisement**

Not available

**16.7 Notice for user(s)**

The information provided in this MSDS has been established in accordance with Commission Regulation (EU) 2015/830 of 28 May 2015, amending Regulation (EC) No 1907/2006 of the European Parliament and of the Council, on the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH), establishing the European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94, as well as Council Directive 76/769/EEC and Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC of the Commission.

This MSDS is intended to provide a brief summary of our knowledge and guidance regarding the use of this material. The information has been compiled from sources considered to be dependable and is accurate to the best of the FSA NV's knowledge. However, the information is provided without any representation or warranty, expressed or implied regarding its accuracy or correctness. FSA NV cannot assume responsibility for adverse events which may occur in the use and/or misuse of this product and expressly disclaims liability for loss, damage and/or expense arising out of or in any way connected with the handling, storage, use and/or disposal of this product.

**16.8 Department issuing MSDS**

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