

# Safety Data Sheet ISOTRETINOIN



Safety Data Sheet dated 3/23/2011, version 2

## 1. IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/UNDERTAKING

### 1.1 Product Identifier

Identification of the substance

Trade name: ISOTRETINOIN

Trade code: SOLGA112

CAS number: 4759-48-2

The transition time according to REACH Regulation, Article 23 is still not expired.

1.2 Relevant identified uses of the substance/mixture and uses advised against: See paragraph 3

Recommended use:

active pharmaceutical ingredient

1.3 Details of the supplier of the safety data sheet

Company:

FIDIA FARMACEUTICI SPA - Division Solmag

via Ponte della Fabbrica, 3 / A

35031 Abano Terme (Padova) Italy

Competent person responsible for the safety data sheet:

msds@solmag.it

## 2. HAZARDS IDENTIFICATION

2.1 Classification of the substance or mixture

Directive criteria, 67/548/CE, 99/45/EC and following amendments thereof:

Properties / Symbols:

Carcinogenic category 3

Toxic for reproduction category 1

Xi Irritant

R Phrases:

R36/37/38 Irritating to eyes, respiratory system and skin.

R40 Limited evidence of a carcinogenic effect.

R61 May cause harm to the unborn child.

EC regulation criteria 1272/2008 (CLP)

⚠ Warning, Skin Irrit. 2, Causes skin irritation.

⚠ Warning, Eye Irrit. 2, Causes serious eye irritation.

⚠ Warning, Carc. 2, Suspected of causing cancer.

⚠ Danger, Repr. 1A, May damage the unborn child.

⚠ Warning, STOT SE 3, May cause respiratory irritation.

Adverse physicochemical, human health and environmental effects:

No other hazards

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#### 2.2 Label elements



Symbols:

T Toxic

R Phrases:

R36/37/38 Irritating to eyes, respiratory system and skin.

R40 Limited evidence of a carcinogenic effect.

R61 May cause harm to the unborn child.

S Phrases:

S20 When using do not eat or drink.

S26 In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.

S36/37 Wear suitable protective clothing and gloves.

S45 In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

S53 Avoid exposure - obtain special instructions before use.

S60 This material and its container must be disposed of as hazardous waste.

Symbols:



Danger

Hazard statements:

H315 Causes skin irritation.

H319 Causes serious eye irritation.

H351 Suspected of causing cancer.

H360D May damage the unborn child.

H335 May cause respiratory irritation.

Precautionary statements:

P261 P261.2

P280 Wear protective gloves/protective clothing/eye protection/face protection.

P305+P351+P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

P321 Specific treatment (see supplementary instructions on this label)

P405 Store locked up.

P501 Dispose of contents/container in accordance with all local/Regional/national/international regulations.

Special Provisions:

Not classified

#### 2.3 Other hazards

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The product can support combustion. The ignition of dust in certain conditions can cause an explosion. Dust may be sensitive to electrostatic ignition sources. In case of fire, may emit toxic fumes (oxides of nitrogen, carbon).

vPvB Substances: - PBT Substances: Not classified

Other Hazards:

No other hazards

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### 3. COMPOSITION/INFORMATION ON INGREDIENTS

#### 3.1 Substances

Identification of the substance

Chemical characterization: ISOTRETINOIN


Trade code: SOLGA112

CAS number: 4759-48-2

100 % Retinoic acid, 13-cis-

CAS: 4759-48-2

Carc. Cat. 3, Repr. Cat. 1, Xi; R40-61-36/37/38

 3.2/2 Skin Irrit. 2 H315

 3.3/2 Eye Irrit. 2 H319

 3.6/2 Carc. 2 H351

 3.7/1A Repr. 1A H360D

 3.8/3 STOT SE 3 H335

#### 3.2 Mixtures

N.A.

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### 4. FIRST AID MEASURES

#### 4.1 Description of first aid measures

In case of skin contact:

Immediately take off all contaminated clothing.

Wash immediately with running water and soap if areas of the body that have come in contact with the product, even if only suspected.

Wash thoroughly the body (shower or bath).

In case of eyes contact:

After contact with the eyes, rinse with water with the eyelids open for a sufficient length of time, then consult an ophthalmologist immediately.

Protect uninjured eye.

In case of Ingestion:

Do not under any circumstances induce vomiting. OBTAIN A MEDICAL EXAMINATION IMMEDIATELY.

In case of Inhalation:

In case of inhalation, consult a doctor immediately and show him packing or label.

After contact with skin, wash immediately with soap and plenty of water.

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

None

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

In case of accident or unwellness, seek medical advice immediately (show directions for use or safety data sheet if possible).

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Treatment:  
None

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### 5. FIRE-FIGHTING MEASURES

#### 5.1 Extinguishing media

Suitable extinguishing media:

Water.

Carbon dioxide (CO<sub>2</sub>).

Extinguishing media which must not be used for safety reasons:

avoid water jets to disperse the product.

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

Do not inhale explosion and combustion gases.

Burning produces heavy smoke.

Substance that can sustain combustion when exposed to heat and ignition sources. Thermal decomposition produces toxic fumes of oxides of nitrogen and carbon. In the absence of oxygen may generate other toxic gases. Like most organic powders, may cause an explosion if the powder is dispersed into the air and set off.

#### 5.3 Advice for fire-fighters

Use suitable breathing apparatus .

Wear respirator, gloves, protective footwear. CAUTION: Pressurized containers may explode when exposed to fire. And 'recommended the use of breathing apparatus and full protection for fire fighting, since the combustion of this substance may generate toxic fumes, corrosive and flammable. If possible contain water used for fire fighting and collect for later disposal Collect contaminated fire extinguishing water separately. This must not be discharged into drains.

Move undamaged containers from immediate hazard area if it can be done safely.

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### 6. ACCIDENTAL RELEASE MEASURES

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

Wear personal protection equipment.

Wear breathing apparatus if exposed to vapours/dusts/aerosols.

Provide adequate ventilation.

Use appropriate respiratory protection.

See protective measures under point 7 and 8.

#### 6.2 Environmental precautions

Circumscribe the area of the spill and prevent the staff will come into contact if not properly protected. Avoid flames, sparks and prevent static buildup. Avoid generation of dust.

Do not allow to enter into soil/subsoil. Do not allow to enter into surface water or drains.

Retain contaminated washing water and dispose it.

In case of gas escape or of entry into waterways, soil or drains, inform the responsible authorities.

Suitable material for taking up: absorbing material, organic, sand

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

Wash with plenty of water.

#### 6.4 Reference to other sections

See also section 8 and 13

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### 7. HANDLING AND STORAGE

#### 7.1 Precautions for safe handling:

Avoid contact with skin and eyes, inhalation of vapours and mists.

Use localized ventilation system.

Don't use empty container before they have been cleaned.

Before making transfer operations, assure that there aren't any incompatible material residuals in the containers.

Contaminated clothing should be changed before entering eating areas.



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Do not eat or drink while working.

See also section 8 for recommended protective equipment.

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

Always keep the containers tightly closed.

Keep away from food, drink and feed.

Incompatible materials:

None in particular.

Instructions as regards storage premises:

Adequately ventilated premises.

#### 7.3 Specific end use(s)

None in particular

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## 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

### 8.1 Control parameters

Retinoic acid, 13-cis- - Index: NA, CAS: 4759-48-2, EC No: NA

TLV TWA - TLV STEL- OEL 8h- OEL short: None.

### 8.2 Exposure controls

Eye protection:

Use close fitting safety goggles, don't use eye lens.

Protection for skin:

Use clothing that provides comprehensive protection to the skin, e.g. cotton, rubber, PVC or viton.

Protection for hands:

Use protective gloves that provides comprehensive protection, e.g. P.V.C., neoprene or rubber.

Respiratory protection:

Provide exhaust systems in the workplace. Avoid inhalation of vapors and dust. Adequate ventilation to the premises where the product is stored and / or manipulated, however, avoid excessive ventilation and dust dispersed generation. Change clothes at the end of shift.

Use respiratory protection where ventilation is insufficient or exposure is prolonged, e.g. CEN/FFP-2(S) or CEN/FFP-3(S).

Thermal Hazards:

None

Environmental exposure controls:

None

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## 9. PHYSICAL AND CHEMICAL PROPERTIES

### 9.1 Information on basic physical and chemical properties

Appearance and colour:	solid
Odour:	N.D.
Odour threshold:	N.D.
pH:	N.D.
Melting point / freezing point:	171-173 °C (1)
Initial boiling point and boiling range:	462.8+/-14.0 °C (2)
Solid/gas flammability:	N.D.
Upper/lower flammability or explosive limits:	N.D.
Vapour density:	N.D.
Flash point:	350.6+/-6.0 °C (2)
Evaporation rate:	N.D.
Vapour pressure:	1.006584 e -007 Pa a 25 °C (2)
Relative density:	1.011+/-0.06 g/cm3

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Solubility in water:	0.0063 g/l (2)
Lipid solubility:	N.D.
Partition coefficient (n-octanol/water):	Log Pow 6.263+/-0.358 a 25°C (2)
Auto-ignition temperature:	N.D.
Decomposition temperature:	N.D.
Viscosity:	N.D.
Explosive properties:	N.D.
Oxidizing properties:	N.D.
9.2 Other information	
Miscibility:	N.D.
Fat Solubility:	N.D.
Conductivity:	N.D.
(1) Ref.:	Mineeva, I. V.; Russian Journal of Organic Chemistry 2008 V44(9)
P1261-1266 CAPLUS	
(2) Ref.:	Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 ((C) 1994-2010 ACD/Labs)

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## 10. STABILITY AND REACTIVITY

- 10.1 Reactivity
  - Stable under normal conditions
- 10.2 Chemical stability
  - Stable under normal conditions
- 10.3 Possibility of hazardous reactions
  - N.D.
- 10.4 Conditions to avoid:
  - Stable under normal conditions.
- 10.5 Incompatible materials:
  - N.D.
- 10.6 Hazardous decomposition products:
  - N.D.

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## 11. TOXICOLOGICAL INFORMATION

### 11.1 Information on toxicological effects

There is no toxicological information on the substance. We do, however, refer to section 2.

#### ACUTE TOXICITY:

Acute toxicity: oral

mouse LD50 Mg/kg 3389

Ref.: "The Retinoids, Vol.2," Sporn, M.B., et al., eds., New York, Academic Press, Inc., 1984 Vol. 2, Pg. 287, 1984

rat LD50 Mg/kg 4000

Ref.: Journal of the American Academy of Dermatology.

Vol. 6, Pg. 652, 1982. Link to PubMed

rabbit LD50 Mg/kg 1960

Acute toxicity: other routes

mouse LD50 intraperitoneal Mg/kg 138

Ref.: "The Retinoids, Vol.2," Sporn, M.B., et al., eds., New York, Academic Press, Inc., 1984 Vol. 2, Pg. 287, 1984.

rat LD50 intraperitoneal Mg/kg 901

Ref.: Journal of the American Academy of Dermatology.

Vol. 6, Pg. 652, 1982. Link to PubMed

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#### REPEATED DOSE TOXICITY:

Repeated dose toxicity: oral

Cheilitis and hypertriglyceridemia are usually dose related. Most adverse reactions reported in clinical trials were

reversible when therapy was discontinued; however, some persisted after cessation of therapy

Repeated dose toxicity: dermal

allergic reactions, including vasculitis, systemic hypersensitivity edema, fatigue, lymphadenopathy, weight loss

Repeated dose toxicity: inhalation

bronchospasms (with or without a history of asthma), respiratory infection, voice alteration.

Ref.: Label su Drugs-FDA

#### GENETIC TOXICITY: Res. NEGATIVE

Genetic toxicity in vitro

oms-hmn-emb umol/L 25

Ref.: Teratogenesis, Carcinogenesis, and Mutagenesis. (Alan R. Liss, Inc., 41 E. 11th St., New York, NY 10003) V.1- 1980-

11,297,1991 (TCMUD8);

sce-hmn-lym umol/L 50

Ref.: Basic Life Sciences. (Plenum Pub. Corp., 223 Spring St., New York, NY 10003) V.1- 1973- 29A,333,1984 (BLFSBY)

#### CARCINOGENICITY: Res. POSITIVE

oral: Effect level

In rats male and female

dosages of 8 or 32 mg/kg/day (1.3 to 5.3 times the

recommended clinical dose of 1.0 mg/kg/day, respectively, after normalization for total body surface area)

there was a dose-related increased incidence of pheochromocytoma relative to controls.

The incidence of adrenal medullary hyperplasia was also increased at the higher dosage in both sexes. The relatively high level of spontaneous pheochromocytomas occurring in the male Fischer 344 rat makes it an

equivocal model for study of this tumor; therefore, the relevance of this tumor to the human population is uncertain.

Ref.: Label su Drugs-FDA

#### MOUSE

Strain/Sex: B6C3F1/MALE 200 MG/KG FEED FOR 60 WK (STUDY DURATION: 60 WK)

Type of Lesion: LIVER: HEPATOCELLULAR CARCINOMA

Ref.: DI BISCEGLIE, AM OSMACK, P AND BRUNT, EM; CHEMOPREVENTION OF HEPATOCELLULAR

CARCINOMA: USE OF TAMOXIFEN IN AN ANIMAL MODEL OF

HEPATOCARCINOGENESIS; J. LAB.

CLIN. MED. 145(3):134-138, 2005

#### HAMSTER SYRIAN/FEMALE ORAL

0.4 MMOL/KG/D

Type of

Lesion: PANCREAS: DUCTULAR CARCINOMA

Ref.: BIRT, DF, DAVIES, MH, POUR, PM AND SALMASI, S; LACK OF INHIBITION BY RETINOID OF BIS(2-OXOPROPYL)NITROSAMINE-INDUCED

CARCINOGENESIS IN SYRIAN HAMSTERS;

CARCINOGENESIS 4(10):1215-1220, 1983



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#### TOXICITY TO REPRODUCTION / DEVELOPMENT:

Reproductive toxicity Res. NEGATIVE

In rats, oral

at doses of 2, 8, or 32 mg / kg / day (0.3, 1.3 or 5.3 times the recommended dose of 1.0 mg / kg / day).

not have adverse effects on gonadal function, fertility, conception rate, pregnancy or childbirth.

Developmental toxicity / teratogenicity Res. POSITIVE

should not be used by female patients who are or may become pregnant. There is a great high risk of serious birth defects while taking in any amount even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. birth defects that have been documented following exposure include abnormalities of face, eyes, ears, skull, central nervous system, cardiovascular system and the thymus and parathyroid glands.

Ref: Label on Drugs-FDA

Toxicity to reproduction: other studies

It is not known whether this drug is excreted in human milk. Because of the potential for adverse effects, nursing mothers should not receive the product.

May cause harm to the unborn child.

Carcinogenic category 3

Toxic for reproduction category 1

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## 12. ECOLOGICAL INFORMATION

### 12.1 Toxicity

Adopt good working practices, so that the product is not released into the environment.

#### BIOACCUMULATION:

aquatic / sediment: BCF (aquatic species)

33839.67

Ref.: Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 ((C) 1994-2010 ACD/Labs

#### TRANSPORT AND DISTRIBUTION:

Adsorption / desorption: Koc at 20 °C 60775.11

Ref.: Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 ((C) 1994-2010 ACD/Labs

### 12.2 Persistence and degradability

See above

### 12.3 Bioaccumulative potential

Bioaccumulative:

see above See above

### 12.4 Mobility in soil

See above

### 12.5 Results of PBT and vPvB assessment

vPvB Substances: - PBT Substances:Not classified

### 12.6 Other adverse effects

See above

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## 13. DISPOSAL CONSIDERATIONS

### 13.1 Waste treatment methods



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Recover, if possible. Send to authorised disposal plants or for incineration under controlled conditions. In so doing, comply with the local and national regulations currently in force.

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#### 14. TRANSPORT INFORMATION

- 14.1 UN number:  
Not classified as dangerous in the meaning of transport regulations.
- 14.2 UN proper shipping name:  
N.A.
- 14.3 Transport hazard class(es):  
N.A.
- 14.4 Packing Group:  
N.A.
- 14.5 Environmental hazards  
N.A.
- 14.6 Special Precautions for User  
N.A.
- 14.7 Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code  
Environmental Pollutant:  
No

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#### 15. REGULATORY INFORMATION

- 15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture  
Dir. 67/548/EEC (Classification, packaging and labelling of dangerous substances). Dir. 99/45/EEC (Classification, packaging and labelling of dangerous preparations). Dir. 98/24/EC (Risks related to chemical agents at work). Dir. 2000/39/EC (Occupational exposure limit values); Dir. 2006/8/CE. Regulation (CE) n. 1907/2006 (REACH), Regulation (CE) n. 1272/2008 (CLP), Regulation (CE) n. 790/2009 (1° ATP CLP), Regulation (EU) n. 453/2010 (Annex I).  
Where applicable, refer to the following regulatory provisions :  
Directive 2003/105/CE ('Activities linked to risks of serious accidents') and subsequent amendments.  
Regulation (EC) nr 648/2004 (detergents).  
1999/13/EC (VOC directive)
- 15.2 Chemical Safety Assessment  
No

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#### 16. OTHER INFORMATION

- Full text of phrases referred to in Section 3:  
R36/37/38 Irritating to eyes, respiratory system and skin.  
R40 Limited evidence of a carcinogenic effect.  
R61 May cause harm to the unborn child.

H315 Causes skin irritation.  
H319 Causes serious eye irritation.  
H351 Suspected of causing cancer.  
H360D May damage the unborn child.  
H335 May cause respiratory irritation.

This document was prepared by a competent person who has received appropriate training.

Main bibliographic sources: Abbreviations and Acronyms:

ADR: European Agreement concerning the International Carriage of Dangerous Goods by Road.  
CAS: Chemical Abstracts Service (division of the American Chemical Society).

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CLP:	Classification, Labeling, Packaging.
DNEL:	Derived No Effect Level.
EINECS:	European Inventory of Existing Commercial Chemical Substances.
GefStoffVO:	Ordinance on Hazardous Substances, Germany.
GHS:	Globally Harmonized System of Classification and Labeling of Chemicals.
IATA:	International Air Transport Association.
IATA-DGR:	Dangerous Goods Regulation by the "International Air Transport Association" (IATA).
ICAO:	International Civil Aviation Organization.
ICAO-TI:	Technical Instructions by the "International Civil Aviation Organization" (ICAO).
IMDG:	International Maritime Code for Dangerous Goods.
INCI:	International Nomenclature of Cosmetic Ingredients.
KSt:	Explosion coefficient.
LC50:	Lethal concentration, for 50 percent of test population.
LD50:	Lethal dose, for 50 percent of test population.
PNEC:	Predicted No Effect Concentration.
RID:	Regulation Concerning the International Transport of Dangerous Goods by Rail.
STEL:	Short Term Exposure limit.
STOT:	Specific Target Organ Toxicity.
TLV:	Threshold Limiting Value.
TWATLV:	Threshold Limit Value for the Time Weighted Average 8 hour day. (ACGIH Standard).
WGK:	German Water Hazard Class.
N.D. / N.A.:	non disponibile / not available

### SOURCES CONSULTED:

ECDIN - Environmental Chemicals Data and Information Network - Joint Research Centre,  
Commission of the European Communities  
SAX's DANGEROUS PROPERTIES OF INDUSTRIAL MATERIALS - Eight Edition - Van  
Nostrand Reinold  
CCNL - Appendix 1  
Insert further consulted bibliography

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