

CICLESONIDE

MATERIAL SAFETY DATA SHEET

In accordance with Regulation (CE) 1907/2006, (CE) 1272/2008 and (EU) 453/2010 (Annex I)
Revision no.4 - Revision date: June 27, 2012

SECTION 1. IDENTIFICATION OF THE SUBSTANCE AND OF THE COMPANY

1.1. Substance identifier

Substance name:	CICLESONIDE
Other names (if available): Name in Annex VI-CLP: Name reported in the inventory of harmonized classification and labelling:	[11 β - 16 α (R)] - 16,17- [[R- cyclohexylmethylene)-bis(oxy)] -11- hydroxy-21-(2-methyl-1-oxopropoxy) pregna-1,4-diene-3,20-dione unlisted not available
CAS number	126544-47-6
REACH registration number	Exempt of registration

1.2. Relevant identified uses of the substance and uses advised against

Relevant use(s)	Corticosteroid - API (Active Pharmaceutical Ingredient)
Uses advised against	none

1.3. Details of the supplier of the safety data sheet

Manufacturer/Distributor:

Company name: **STERLING S.r.l**

Address : **Via della Carboneria, 30 Solomeo
06073 Corciano (PG) – Italy**

Phone number : 075/5294001

Fax number: 075/5294000

Competent person responsible for the safety data sheet:

Aragona Anna Alessandra
e-mail: aragona@sterling.it

1.4. Emergency telephone number

02 66101029 (Centro Antiveleni Niguarda Ca' Granda – Milano)

SECTION 2 HAZARDS IDENTIFICATION

2.1 Classification of the substance

Classification of the substance in accordance with Regulation (CE) n. 1272/2008:

Hazard class	Class code and hazard category	Hazard statement	Hazard warning
-	Not classified	None	None

Classification in accordance with Directive 67/548/CEE : Not classified

Classification	Risk phrases
Not classified	None

Main adverse effects

Physico-chemical effects

Health effects

No adverse effects known.

The incidence of adverse effects increases with dose and duration of exposure.

Symptoms may include muscular pain, lassitude, and depression. Rarely, immediate hypersensitivity reactions or contact dermatitis may occur.

Possible allergic reaction to material if inhaled, ingested or in contact with skin.

A bioaccumulation potential may be expected.

Environmental effects

See also sections from 9 to 12

2.2 Label elements

Labelling in accordance with regulation n. 1272/2008/EC

Pictograms	None
Signal Word	None
Hazard indication (H)) ^[1]	None
Safety statements (P) ^[1]	
- <i>Prevention</i>	-
- <i>Reaction</i>	-
- <i>Storage</i>	-
- <i>Disposal</i>	-

^[1] For the explanation of H and P statements: see Section 16

2.3 Other hazards (which do not results in the classification)

The substance satisfies the PBT criteria

- PBT

- vPvB

YES	NO
	X
	X

- Health hazards

May be harmful if ingested, inhaled or in contact with skin. May be irritant or sensitizer.

The incidence of adverse effects increases with dose and duration of exposure.

- Environmental hazards

Not known

- Physico-chemical hazards

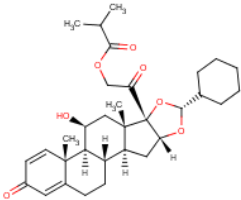
Not known

- Specific effects

unknown

SECTION 3 COMPOSITION/INFORMATION ON INGREDIENTS

Description: Active Pharmaceutical Principle; anti-inflammatory corticosteroid

Name of the component	Ciclesonide
Concentration	Pure substance
Structural formula	
Chemical formula	C ₃₂ H ₄₄ O ₇
Molecular weight	540.69 g/mol
Substance with Community OEL	No
CAS name	Pregna-1,4-diene-3,20-dione, 16,17-[[[(R)-cyclohexylmethylene]bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-, (11β.,16α.)-
CAS number	126544-47-6
IUPAC name	Pregna-1,4-diene-3,20-dione, 16,17-(((R)-cyclohexylmethylene)bis(oxy))-11-hydroxy-21-(2-methyl-1-oxopropoxy)-, (11β,16α)-
EC number	not assigned
Index number	not assigned
Impurity/ies (if classified)	-
Additive/ies (if classified)	-

<p align="center">SECTION 4</p> <p align="center">FIRST AID MEASURES</p>	
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4.1 Description of the first aid measures

- | | |
|----------------|---|
| - Eye contact | Wash immediately with large amounts of water or normal saline. Keep eyelid open during the washing. Get medical advice if adverse symptoms will appear. |
| - Skin contact | Remove contaminated clothes (eventually shoes). Wash affected area with soap or mild detergent and large amount of water until no evidence of substance remains. Get medical advice if adverse symptoms will appear. |
| - Ingestion | If swallowed wash mouth with large amounts of water provided person is conscious. If victim is conscious and alert, give milk or water. Get medical advice if adverse symptoms will appear. |
| - Inhalation | Remove the person from the exposed area to fresh air immediately. If breathing has stopped perform artificial respiration, keep person warm and at rest. Get medical advice if the exposure was significant in terms of quantity or time. |

4.2 Most important symptoms and effects (acute and delayed)

- | | |
|---------------------------|--|
| - <i>Acute effects</i> | Symptoms may include muscular pain, lassitude, and depression. Rarely, immediate hypersensitivity reactions or contact dermatitis may occur. |
| - <i>Delayed effects:</i> | Possible allergic reaction to material if inhaled, ingested or in contact with skin. |

4.3 Indication of any immediate medical attention and special treatment needed

- | | |
|---|-----------|
| - <i>Medical monitoring:</i> | none |
| - <i>Antidotes, if known</i> | unknow |
| - <i>Contraindications</i> | unknow |
| - <i>Immediate treatment at workplace</i> | not known |

SECTION 5 FIREFIGHTING MEASURES

5.1 Extinguishing media

- | | |
|---|---|
| - <i>Suitable extinguishing media</i> | Water spray or chemical foam, dry foam, CO ₂ . |
| - <i>Unsuitable extinguishing media</i> | not known |

5.2 Special hazards arising from the substance

- | | |
|--|----------------------------------|
| - <i>Hazardous combustion products</i> | May generate toxic fumes of Cox. |
| - <i>Other special hazards</i> | not known |

5.3 Advice fo firefighters

- | | |
|--|---|
| - <i>Technical actions for protection</i> | Keep containers cool with water. |
| - <i>Special protective equipment for firefighters</i> | Wear boots, overalls, gloves, eye and face protection and breathing apparatus. Equipment must be conformed with EN criteria and used in highest condition of protection on the basis of the information reported in the previous sub-sections |

SECTION 6 ACCIDENTAL RELEASE MEASURES

6.1 Personal precautions, protective equipment and emergency procedures

- For non-emergency personnel

Wear appropriate protective equipment (see Section 8) to prevent contamination of the skin, eyes and personal clothing. In case of fire and/or and explosions avoid breathing fumes and vapors. Use a self-contained breathing apparatus (SCBA) and appropriate protective clothing. The fumes can be eliminated by spraying with water.
See also section 8

- For emergency responders

See section 8.

6.2 Environmental precautions

In case of accidental release in the environment avoid that the substance can reach drains, surface water and ground water. Contact local authorities in case of environmental release.

6.3 Methods and material for containment and clearing up

- *Containment procedures:* Coverage of the discharges
- *Cleaning up procedures:* Recover the substance for suction or other mechanical means and wash the area with plenty of water and detergents. Store the material into a company that specializes pending disposal. Containers must be cleaned up and disposed of as waste remediation above.

6.4 Reference to other sections

See also section 8 and 13.

SECTION 7 HANDLING AND STORAGE

7.1. Precautions for safe handling

- *Recommendation for handling:*
 - Handle away from sparkles and flames - sources of ignition
 - Handle in a well ventilated place
 - Avoid contact with incompatible materials
 - Wear suitable Personal Protection Equipment (see section 8)
 - Keep the substance away from drains, surface or ground waters
- *Recommendation for personal hygiene:*
 - Do not eat, drink and smoke in the working areas
 - Wash hands after handling the substance
 - Remove contaminated clothing and protective equipment before entering eating areas

7.2. Condition for safe storage including any incompatibilities

The substance is not classified for any physical and chemical properties and no risk management is foreseen.

Other advice

- *Ventilation requirements* Store at controlled room temperature
- *Containers* Store in the original package
- *Specific design of storage rooms* Use in a well ventilated place at room temperature
- *Quantity limits for storage* Keep containers tightly closed and correctly labelled
- *Packaging compatibilities* Not requested on the base of the classification
- See also section 10.5

7.3. Specific end use(s)

- Recommendation for specific final use(s): Active Pharmaceutical Principle

	YES	NO
- Exposure scenario attached		X
- Chemical Safety Assessment (CSA) attached		X
- Industry or sector specific guidance available and attached		X

SECTION 8 EXPOSURE CONTROLS/PERSONAL PROTECTION

8.1. Control parameters

- National/European Occupational Exposure Limits	unknown
- Other National/European Occupational Exposure Limits	unknown
- Recommended monitoring procedures	The measurement of substances in the workplace must be carried out with standardized methods (eg EN 689:1997: Workplace atmospheres - Guide for assessment of exposure by inhalation to chemical agents for comparison with limit values and measurement strategy; UNI EN 482:2006: atmospheres in the workplace - General requirements for the provision of procedures for the measurement of chemical agents) or, failing that, with appropriate methods.
- DNEL values (components)	unknown
- PNEC values (components)	unknown

8.2. Exposure controls

	YES	NO
- Exposure scenario attached		X
- Chemical Safety Assessment (CSA) attached		X

8.2.1. Appropriate engineering controls

The adoption of the most appropriate technical controls is also based on the local Risk Assessment done by the employer in its workplace conditions (use of the substance) when a unique and standardized exposure scenario described in a dossier registered REACH is not available.

8.2.2. Individual protection measures, such as Personal Protective Equipment (PPE)

a) Eye and Face protection	Safety goggles as for EN 166; facial shield
b) Skin protection	
- <i>hands protection</i>	Wear protective gloves. Gloves resistant to chemical agents as for the EN 374, parts 1, 2 e 3 and the European Directive 89/89/CEE. The glove material has to be made of rubber or polyethylene impermeable and resistant to the substance. Make the choice of the glove material on consideration of the penetration times, rates of diffusion and degradation. The selection of suitable gloves not only depends on the material, but also on further marks of quality and varies from manufacturer to manufacturer.
- <i>other, body protection</i>	Select the suitable protective equipment based on the activity of use and possible exposure. Wear gauntlets, boots, bodysuit and other devices in accordance with EN 13982.
c) Respiratory protection	Dust mask with approved dust filter. Use only devices approved by the Competent Authorities such as NIOSH (USA) and CEN (EU) In the case of brief exposure or minimal exposure use respiratory filter; in case of intensive and sustained exposition wear self-contained breathing. Where risk assessment shows air-purifying respirators are appropriate use a dust mask type P3 (EN 143) respirator
d) Thermal hazards	Not foreseen in the standard use. Assess possible Personal Protection Equipment on the

basis of specific uses of the substance.

8.2.3 Environmental exposure controls

	YES	NO
- Exposure scenario attached		X
- Chemical Safety Assessment (CSA) attached		X

SECTION 9 PHYSICAL AND CHEMICAL PROPERTIES

9.1. Information on basic physical and chemical properties

Appearance:	white or whitish solid (powder)
Odor:	Odourless
Odour threshold:	-
pH:	Data not available in the literature search carried out
Melting point:	203 – 213 °C
Boiling point:	665 °C (predicted) ⁽¹⁾
Flash point:	210 °C (predicted) ⁽¹⁾
Auto-ignition temperature:	Data not available in the literature search carried out
Surface tension:	51.8 dyne/cm (predicted) ⁽¹⁾
Vapour pressure:	1.61x 10 ⁻²⁰ mmHg at 25°C (predicted) ⁽¹⁾
Density:	1,23 g/cm ³ (predicted) ⁽¹⁾
Water solubility:	practically insoluble in water
Organic solvent solubility:	Data not available in the literature search carried out
Partition coefficient Octanol/water (Log Kow):	6.13 (predicted by ACS/Lab) ⁽¹⁾
Explosive properties:	Data not available in the literature search carried out
Oxidising properties:	Data not available in the literature search carried out

9.2. Other information

Data not available in the literature search carried out

SECTION 10 STABILITY AND REACTIVITY

10.1. Reactivity

Stable in normal conditions of storage.

10.2. Chemical stability

The substance is stable at the normal condition of temperature and pressure and if stored in closed containers in well ventilated and cool place.

- Stabilisers:
- Change in physical appearance

NO	YES	Used stabiliser
X	-	
X	-	

10.3. Possibility of hazardous reactions

- Possibility of an exothermic reaction:
- Possibility of a reaction releasing excessive pressure
- Possible degradation with instable product formation

NO	YES
X	-
X	-
X	-

10.4. Condition to avoid

Keep protected from light, humidity and high temperatures.

10.5. Incompatible materials

Strong oxidizing agents

10.6. hazardous decomposition products

If heated at high temperatures, decomposes releasing fumes and toxic gases of Cox.

SECTION 11 INFORMATION ON TOXICOLOGICAL EFFECTS

- Exposure routes:

- Inhalation:
- Ingestion:
- Skin contact:
- Eye contact:

YES	NO
X	
X	
X	
X	

- Effects (acute, delayed, chronic) following the exposure (short and/or prolonged):

- Inhalation: May be harmful or sensitizing by inhalation
- Ingestion: May be harmful if swallowed
- Skin contact: May be irritant or sensitizing.
- Eye contact: May be irritant

-Toxico-kinetics information (ADME=Adsorption,Distribution,Metabolism,Excretion): ⁽²⁾

Adsorption: Ciclesonide and des-ciclesonide have negligible oral bioavailability (both less than 1%) due to low gastrointestinal absorption and high first-pass metabolism. The intranasal administration of ciclesonide at recommended doses results in negligible serum concentrations of ciclesonide. However, the known active metabolite (des-ciclesonide) is detected in the serum of some patients after nasal inhalation of ciclesonide. The bioanalytical assay used has a lower limit of quantification of 25 pg/mL and 10 pg/mL, for ciclesonide and des-ciclesonide, respectively.

Distribution: Following intravenous administration The percentage of ciclesonide and des-ciclesonide bound to human plasma proteins averaged $\geq 99\%$ each, with $\leq 1\%$ of unbound drug detected in the systemic circulation. Des-ciclesonide is not significantly bound to human transcortin.

Metabolism: Intranasal ciclesonide is hydrolyzed to a biologically active metabolite, des-ciclesonide, by esterases in the nasal mucosa. Des-ciclesonide undergoes further metabolism in the liver to additional metabolites. The full range of potentially active

metabolites of ciclesonide has not been characterized. After intravenous administration of C-ciclesonide, 19.3% of the resulting radioactivity in the plasma is accounted for by ciclesonide or des-ciclesonide; the remainder may be a result of other, as yet, unidentified multiple metabolites.

Excretion: following intravenous administration Ciclesonide is predominantly excreted via the feces after intravenous administration (66%) indicating that excretion through bile is the major route of elimination. Approximately 20% or less of drug related radioactivity was excreted in the urine.

- Acute toxicity effects:

- *Oral:* Data not available in the literature search carried out
- *Dermal:* Data not available in the literature search carried out
- *Inhalation:* Data not available in the literature search carried out
- *Other effects:* Data not available in the literature search carried out

- Corrosion/Irritation effects: Data not available in the literature search carried out

- Severe ocular lesion : Data not available in the literature search carried out

- Sensitisation: Data not available in the literature search carried out

- Repeated dose toxicity (experimental.): Data not available in the literature search carried out

- CMR effects:

- Germinal cell mutagenicity ⁽²⁾: Ciclesonide was not mutagenic in an Ames test or in a forward mutation assay and was not clastogenic in a human lymphocyte assay or in an in vitro micronucleus test. However, ciclesonide was clastogenic in the in vivo mouse micronucleus test.

- Carcinogenicity ⁽²⁾:

Ciclesonide demonstrated no carcinogenic potential in a study of oral doses up to 900 mcg/kg (approximately 20 and 10 times the maximum human daily intranasal dose in adults and children, respectively, based on mcg/m) in mice for 104 weeks and in a study of inhalation doses up to 193 mcg/kg (approximately 8 and 5 times the maximum human daily intranasal dose in adults and children, respectively, based on mcg/m) in rats for 104 weeks.

- Reproductive toxicity ⁽²⁾

Oral administration of ciclesonide in rats up to 900 mcg/kg (approximately 35 times the maximum human daily intranasal dose in adults based on mcg/m) produced no evidence of impairment of fertility, no teratogenicity or other fetal effects. However, subcutaneous administration of ciclesonide in rabbits at 5 mcg/kg (less than the maximum human daily intranasal dose in adults based on mcg/m) or greater produced fetal toxicity. This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects. No toxicity was observed at 1 mcg/kg (less than the maximum human daily intranasal dose based on mcg/m).

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Pregnancy category C – There are no adequate and well-controlled studies in pregnant women.

- Specific Target Organ Toxicity (STOT)-single exposure: Data not available in the literature search carried out

- Specific Target Organ Toxicity (STOT)- repeated exposure : Data not available in the literature search carried out

- Aspiration hazards: Data not available in the literature search carried out

- Epidemiological information: ⁽³⁾

Ciclesonide, like other corticosteroids, is secreted in human milk. The amounts of inhaled corticosteroids excreted into breastmilk are minute and infant exposure is negligible.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients ⁽²⁾

SECTION 12 ECOLOGICAL INFORMATION

12.1. Toxicity

Data not available in the literature search carried out

12.2. Persistence and degradability

Data not available in the literature search carried out

12.3. Bioaccumulative potential

BCF = 26845.69 (predicted) ⁽¹⁾

Log Pow = 6.13 (predicted by ACS/Lab)⁽¹⁾

12.4. Mobility in soil

Data not available in the literature search carried out

12.5. Results of PBT e vPvB assessment

Assessment is not available - in relation to the value of logPow and BCF a bioaccumulation potential is expected.

12.6. Other adverse effects

Not known

SECTION 13 DISPOSAL CONSIDERATION

13.1. Waste treatment methods

- Mixture wastes:
- Contaminated packaging:

Incineration	Recycling	Landfilling
X		
	X	

Should never be disposed through wastewater.

Refers to Community/National/Local requirements concerning the waste disposal.

SECTION 14 TRANSPORT INFORMATION

The substance is not classified for transport.

SECTION 15 REGULATORY INFORMATION

15.1 Safety, Health and Environmental regulation/legislation specific for the mixture or its ingredients

Council Directive 89/391/EEC of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work and following amendment and National reinforcements..

Council Directive 89/686/EEC of 21 December 1989 on the approximation of the laws of the Member States relating to the personal protective equipment

Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC) Official Journal L 131 , 05/05/1998 P. 0011 – 0023

Regulation (EC) no 689/2008 of the european parliament and of the council of 17 June 2008 concerning the export and import of dangerous chemicals.

15.2. Chemical Safety Assessment

- Exposure scenario attached
- Chemical Safety Assessment (CSA) attached

YES	NO
	X
	X

SECTION 16 OTHER INFORMATION

Revisions:

- **Revision n. 03 dated** January 2011 (regarding all sections in according to Regulation no. 453/2010).

Bibliographic sources:

- ⁽¹⁾ Chempider data base, search for CAS 126544-47-6
- ⁽²⁾ Daily Med, Current Medication Information, OMNARIS (ciclesonide) spray
- ⁽³⁾ Ciclesonide - National Library of Medicine LactMed Database

Acronyms

- ACGIH: American Conference of Governmental Industrial Hygienists
- ADR: Agreement concerning the carriage of dangerous goods by Road
- BCF: Bioaccumulative factor
- BEI : Biological Exposure Indices (Indici di esposizione biologica)
- CAS: Chemical Abstract Service (division of the American Chemical Society)
- CLP: Classification, Labelling and Packaging
- CMR: Carcinogens, Mutagens, Toxic for reproduction substances
- EINECS: European Inventory of existing Commercial Substances
- EPA: US Environmental Protection Agency
- GHS: Globally Harmonised System
- IARC: International Agency for Research on Cancer
- IATA: International Air Transport Association Code
- IMDG: International Maritime Dangerous Goods Code
- IUPAC: International Union of Pure and Applied Chemistry
- LOEL: Lowest Observed Effect Level
- NOAEL: No Observed Adverse Effect Level)
- NTP: National Toxicology Program
- OEL: Occupational Exposure Limit
- OSHA: Occupational Safety and Health Administration
- PPE : Personal protective Equipment
- PBT: Persistent, Bioaccumulative and Toxic substances

- RID: Regulation concerning the International carriage of Dangerous goods by rail
- TLV/TWA: Threshold Limit Value/Threshold Weighted Average
- vPvB: very Persistent, very Bioaccumulative

Information related to the regulation CE/1272/2008

List of hazards statements -

List of P statements

Prevention -

Reaction -

Storage -

Disposal -

Information related to the Directive 67/ 548/ CEE, Directive 1999/45/CE and Regulation (CE) n. 1907/2006

R phrases -

Information on workers training

Follow criteria of Directive 98/24/CE, its amendments and National reinforcements

Restriction of use : None

Substance under authorisation : no

DISCLAIMER

This document aims to provide guidance for appropriate handling and precaution of this product by qualified personnel or operating under the supervision of personnel trained in handling chemicals. The product should not be used for purposes other than those mentioned in section 1, unless they are given adequate written information received on how to handle the material. The provider of this document can not provide any warnings about the dangers of ' use or interaction with other chemicals or materials. And 'the user's safe use of the product, the product suitability for the purpose for which it is applied and proper disposal. The information below should not be considered a declaration or guarantee, either expressed or implied, of merchantability, fitness for a particular purpose, quality, or any other. The information contained in this SDS are in accordance with Annex I of Regulation No 453/2010/EU.

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