# NORGESTIMATE

MATERIAL SAFETY DATA SHEET

**In accordance with Regulation (EC) 1907/2006, (EC) 1272/2008 and (EU) 453/2010 (Annex I)**

**Revision no. 4 - Revision date: October 1, 2012**

## SECTION 1.
## IDENTIFICATION OF THE SUBSTANCE AND OF THE COMPANY

### 1.1. Substance identifier

| | |
|---|---|
| Substance name: | **NORGESTIMATE** |
| Other names (if available):<br>Name in Annex VI-CLP:<br>Name reported in the inventory of harmonized classification and labelling: | (17α)17-(acetyloxy)-13-ethyl-18,19-dinorpregn-4-en-20-yn-3-one oxime<br>unlisted<br><br>not available |
| CAS number | 35189-28-7 |
| REACH registration number | Exempt of registration |

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

| | |
|---|---|
| Relevant use(s) | Synthetic hormone 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.p.A.**
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 |
|---|---|---|---|
| **Carcinogenicity** | **Carc. Cat. 2** | **H351** | **Suspected of causing cancer** |

- **Classification in accordance with Directive 67/548/CEE :**

| Classification | Risk phrases |
|---|---|
| **Carc. Cat 3, R40** | **Limited evidence of a carcinogenic effect** |

Main adverse effects

*Physico-chemical effects* — No adverse effects known.

*Health effects* — Adverse effects of progestins may include abnormal uterine bleeding; dry mouth or cough; frequent urination, loss of appetite, unusual thirst, unexplained flow of breast milk, mental depression, skin rash, abdominal or joint pain, nausea, diarrhea, vomiting, cramping, constipation, dizziness, swelling in hands, ankles, or feet, headache, mood changes, nervousness, unusual tiredness or weakness, unusual or rapid weight gain, acne, breast pain or tenderness, vaginal dryness, hot flashes, trouble sleeping, loss of sexual desire, loss or gain of hair, brown spots on skin, vision changes, slurred speech, trembling and seizures. Possible allergic reaction to material if inhaled, ingested, or in contact with skin. Suspected of causing cancer.

*Environmental effects* — No adverse effects known.

See also sections from 9 to 12

### 2.2 Label elements

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

| | |
|---|---|
| Warning |  |
| Signal Word | Warning |
| Hazard indication (H))[1] | H351 |
| Safety statements (P)[1] | |
| - *Prevention* | P201, P202, P281 |
| - *Reaction* | P308+313 |
| - *Storage* | P405 |
| - *Disposal* | P501 |

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

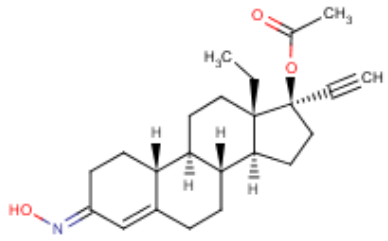
### 2.3 Other hazards (which do not results in the classification)

| The substance satisfies the PBT criteria | YES | NO |
|---|---|---|
| - PBT | | X |
| - vPvB | | X |

| | |
|---|---|
| - Health hazards | May be harmful if ingested, inhaled or in contact with skin. May be irritant or sensitizer. |
| - Environmental hazards | not known |
| - Physico-chemical hazards | not known |
| - Specific effects | unknown |

## SECTION 3
## COMPOSITION/INFORMATION ON INGREDIENTS

**Description:** active pharmaceutical principle - Progestinic

| | |
|---|---|
| *Name of the component* | Norgestimate |
| *Concentration* | Pure substance |
| *Structural formula* |  |
| *Chemical formula* | $C_{23}H_{31}NO_3$ |
| *Molecular weight* | 369.5 g/mol |
| *Substance with Community OEL* | No |
| *CAS name* | (17α)-17-(Acetyloxy)-13-ethyl-18,19-dinorpregn-4-en-20-yn-3-one, 3-oxime |
| *CAS number* | 35189-28-7 |
| *IUPAC name* | 13-Ethyl-17-hydroxy-18,19-dinor-17α -pregn-4-en-20-yn-3-one oxime acetate (ester) |
| *EC number* | not assigned |
| *Index number* | not assigned |
| *Impurity/ies (if classified)* | - |
| *Additive/ies (if classified)* | - |

## SECTION 4
## FIRST AID MEASURES

### 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)

| | |
|---|---|
| - *Acute effects* | Eye, skin, gastrointestinal and/or respiratory tract irritation |
| - *Delayed effects:* | Possible hypersensitization, reproductive disorder, changes in menstrual cycle, jaundice, hepatitis, porphyria, blood clots, and cancer. |

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

| | |
|---|---|
| - *Medical monitoring:* | In case of prolonged exposure |
| - *Antidotes, if known* | In chronic toxicity, obtain a baseline CBC, hepatic and renal function tests, and treat symptomatically.(2) |
| - *Contraindications* | unknow |
| - *Immediate treatment at workplace* | not known |

## SECTION 5
## FIREFIGHTING MEASURES

### 5.1 Extinguishing media

| | |
|---|---|
| - *Suitable estinguishing media* | Water spray or chemical foam, dry foam, $CO_2$. |
| - *Unsuitable estinguishing media* | not known |

### 5.2 Special hazards arising from the substance

| | |
|---|---|
| - *Hazardous combustion products* | May generate toxic fumes of Cox, NOx. |
| - *Other special hazards* | not known |

### 5.3 Advice fo firefighters

| | |
|---|---|
| - *Technical actions for protection* | Keep containers cool with water. |
| - *Special protective equipment for firefighters* | 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

| | |
|---|---|
| - *Recommandation for handling:* | Handle away from sparkles and flames - sources of ignition<br>Handle in a well ventilated place<br>Avoid contact with incompatible materials<br>Wear suitable Personal Protection Equipment (see section 8)<br>Keep the substance away from drains, surface or ground waters |
| - *Recommandation for personal hygiene:* | Do not absolutely eat, drink and smoke in the working areas<br>Wash hands after handling the substance<br>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

| | |
|---|---|
| | The API does not require any special storage conditions |
| - *Ventilation requirements* | Use in a well ventilated place at room temperature (not more than 25 °C) |
| - *Containers* | Keep containers tightly closed and correctly labeled |
| - *Specific design of storage rooms* | Not requested on the base of the classification |
| - *Quantity limits for storage* | Not requested on the base of the classification |
| - *Packaging compatibilities* | 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 | unknow |
| - Other National/European Occupational Exposure Limits | unknow |
| - 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) | unknow |
| - PNEC values (components) | unknow |

### 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 | |
| - *hands protection* | Wear protective gloves.<br>Gloves resistant to chemical agents as for the EN 374, parts 1, 2 e 3 and the European Directive 89/89/CEE.<br>The glove material has to be made of rubber or polyethylene impermeable and resistant to the substance.<br>Make the choice of the glove material on consideration of the penetration times, rates of diffusion and degradation.<br>The selection of suitable gloves not only depends on the material, but also on further |

| | |
|---|---|
| | marks of quality and varies from manufacturer to manufacturer. |
| *- other, body protection* | 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.<br>Use only devices approved by the Competent Authorities such as NIOSH (USA) and CEN (EU)<br>In the case of brief exposure or minimal exposure use respiratory filter; in case of intensive and sustained exposition wear self-contained breathing. |
| 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 (crystalline powder) |
| Odor: | odourless |
| Odour threshold: | - |
| pH: | Data not available in the literature search carried out |
| Melting point/freezing point: | 213 - 218°C |
| Boiling point: | 497.9 °C at 760 mmHg (predicted) (1) |
| Flash point: | 254.9 °C (predicted) (1) |
| Auto-ignition temperature: | Data not available in the literature search carried out |
| Surface tension: | 44.3 dyne/cm (predicted) (1) |
| Density: | 1.22 g/cm$^3$(predicted) (1) |
| Vapour pressure: | 5.32 x $10^{-12}$ mmHg at 25°C (predicted) (1) |
| Water solubility: | Insoluble; 0.2615 mg/l (predicted) (1) |
| Organic solvent solubility: | sparingly soluble in acetonitrile; freely to very soluble in dichloromethane |
| Partition coefficient Octonol/water (Log Kow): | 4.98 (predicted) (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**

| | |
|---|---|
| Henrys Law Constant (25 deg C): | 1.48 x $10^{-8}$ atm-m$^3$/mole (predicted) (1) |
| Specific rotation: | +110°; [<]D, +40° to +46° (in chloroform) |

## 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.

| | NO | YES | Used stabiliser |
|---|---|---|---|
| - Stabilisers: | X | - | |
| - Change in physical appearance | X | - | |

## 10.3. Possibility of hazardous reactions

| | NO | YES |
|---|---|---|
| - Possibility of an exothermic reaction: | X | - |
| - Possibility of a reaction releasing excessive pressure | X | - |
| - Possible degradation with instable product formation | 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 re leasing fumes and toxic gases of Cox, NOx.

## SECTION 11
## INFORMATION ON TOXICOLOGICAL EFFECTS

| - **Exposure routes:** | YES | NO |
|---|---|---|
| *- Inhalation:* | X | |
| *- Ingestion:* | X | |
| *- Skin contact:* | X | |
| *- Eye contact:* | X | |

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

- *Inhalation:* Suspected of causing cancer.
  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=A**dsorption,**D**istribution,**M**etabolism,**E**xcretion**):**

Very little is known about the pharmacokinetics of orally administered norgestimate except that it is a relatively complex pro-drug. After its oral administration, the acetate group at carbon 17 is rapidly removed during hepatic first-pass metabolism. The product Formed, norelgestromin, has progestational activity. Mean peak serum levels of norelgestromin were approximately 4 ng/mL and were attained after about 1.4 h; the levels remained elevated up to 36 h after treatment. In contrast, peak levels of norgestimate were only <100 pg/mL 1 h after treatment; the concentration declined rapidly thereafter and none was detectable 5 h after treatment. Norgestimate is converted to levonorgestrel. On average, about 22% of the administered dose of norgestimate became systemically available as levonorgestrel.

**- Acute toxicity effects:**

| | |
|---|---|
| *- Oral:* | LD50 > 2000 mg/kg |
| *- 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 |
| *RTECS no.* | JF7976000 |

**- 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:**

| | |
|---|---|
| *- Dermal:* | Data not available in the literature search carried out |
| *- Respiratory:* | 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**:

Data not available in the literature search carried out

- **Carcinogenicity**: (3)

No carcinogenicity studies were conducted with norgestimate.

Norgestimate is a progestin, hormonal contraceptive.

Progestins are considered by IARC to be possibly carcinogenic to humans (Group 2B). There is inadequate evidence in humans for the carcinogenicity, but there is sufficient evidence in experimental animals for the carcinogenicity of progestogen-only contraceptives .

- **Reproductive toxicity**:

Therapeutic use of progestins during pregnancy may be associated with malformations in the fetus, although some studies suggest that progestin doses used for contraception do not pose a risk.

TYPE OF TEST : TDLo - Lowest published toxic dose
ROUTE OF EXPOSURE : Oral
SPECIES OBSERVED : Rodent - rat
DOSE : 1 mg/kg
SEX/DURATION : female 2 day(s) pre-mating
TOXIC EFFECTS :
Reproductive - Fertility - other measures of fertility (4)

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

## 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 : 3725.43 (predicted) (1)
LogPow = 4.98 (predicted) (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 logPow and BCF predicted values a bioaccumulation potential is expected.

### 12.6. Other adverse effects

Not known

## SECTION 13
## DISPOSAL CONSIDERATION

### 13.1. Waste treatment methods

| | Incineration | Recycling | Landfilling |
|---|---|---|---|
| - Mixture wastes: | X | | |
| - Contaminated packaging: | | 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

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

## SECTION 16
## OTHER INFORMATION

**Revisions:**

- **Revision n. 04** dated October 2012 (regarding all sections in according to Regulation no. 453/2010).

**Bibliographic sources:**

(1) Chemspider data base, search for CAS 35189-28-7
(2) USP Safety data sheet NORGESTIMATE Catalog Number: 1471914
(3) International Agency for Research on Cancer (IARC), VOL.: 72 (1999) (p. 339)
(4) CCPTAY Contraception. (Geron-X, Inc., POB 1108, Los Altos, CA 94022) V.1-1970- Volume(issue)/page/year: 16,541,1977

**Acronyms**

- ACGIH: American Conference of Governmental Industrial Hygienists
- ADR: Agreement concerning the carriage of dangerous goods by Road
- BCF: Bioaccumulative factor
- BEI : Biological Esposure 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 re production 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***

| | |
|---|---|
| **H351:** | **Suspected of causing cancer** |

***List of P statements***

| | |
|---|---|
| *Prevention* | |
| **P201** | **Obtain special instructions before use.** |
| **P202** | **Do not handle until all safety precautions havebeen read and understood.** |
| **P281** | **Use personal protective equipment as required.** |
| *Reaction* | |
| **P308+P313:** | **IF exposed or concerned: Get medical advice/attention.** |
| *Storage* | |
| **P405** | **Store locked up.** |
| *Disposal* | |
| **P501:** | **Dispose of contents/container in accordance with local/regional/national/ international regulation.** |

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

*R phrases*

| | |
|---|---|
| **R40**: | **Limited evidence of a carcinogenic effect.** |

**Information on workers training**
Follow criteria of Directive 98/24/CE, its amendments and National reinforcements
**Restriction of use :** None
**Substance under authorisation** : no

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