EXEMESTANE

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: April 5, 2012

SECTION 1.
IDENTIFICATION OF THE SUBSTANCE AND OF THE COMPANY

1.1. Substance identifier

Substance name:	**EXEMESTANE**
Other names (if available): Name in Annex VI-CLP: Name reported in the inventory of harmonized classification and labelling:	6-Methyleneandrosta-1,4-diene-3,17-dione unlisted not available
CAS number	107868-30-4
REACH registration number	Exempt of registration

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

Relevant use(s)	Antineoplastic Agent - 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
Reproductive toxicity	**Repr. Cat. 1B**	**H360FD**	**May damage fertility or the unborn child**

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

Classification	**Risk phrases**	
Repr. Cat 2, R60, R61	**R60**	**May impair fertility**
	R61	**May cause harm to the unborn child.**

Main adverse effects

Physico-chemical effects No adverse effects known.

Health effects May damage fertility or the unborn child.
Adverse effect may include chest pain, hypoesthesia, confusion, dyspepsia, arthralgia, back pain, skeletal pain, infection, infections, pharyngitis, rhinitis, alopecia, headache, insomnia, dizziness, weakness, fever.

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	Danger
Hazard indication (H))[1]	H360FD
Safety statements (P)[1]	P201, P202, P281 P308+313 P405 P501
- *Prevention*	
- *Reaction*	
- *Storage*	
- *Disposal*	

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

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

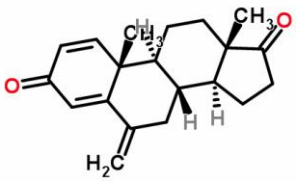
The substance satisfies the PBT criteria	YES	NO
- PBT		X
- vPvB		X

- 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 none
- Specific effects unknown

SECTION 3
COMPOSITION/INFORMATION ON INGREDIENTS

Description: active pharmaceutical principle

Name of the component	EXEMESTANE
Concentration	Pure substance
Structural formula	
Chemical formula	$C_{26}H_{38}O_4$
Molecular weight	296.41 g/mol
Substance with Community OEL	No
CAS name	Androsta-1,4-diene-3,17-dione, 6-methylene-
CAS number	107868-30-4
IUPAC name	(8R,9S,10R,13S,14S)-10,13-dimethyl-6-methylidene-7,8,9,11,12,14,15,16-octahydrocyclopenta[a]phenanthrene-3,17-dione
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*	Adverse effect may include chest pain, hypoesthesia, confusion, dyspepsia, arthralgia, back pain, skeletal pain, infection, infections, pharyngitis, rhinitis, alopecia, headache, insomnia, dizziness, weakness, fever.
- *Delayed effects:*	May damage fertility or the unborn child.

4.3 Indication of any immediate medical attention and special treatment needed

- *Medical monitoring:*	none
- *Antidotes, if known*	none
- *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.
- *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 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
- *Recommandation for personal hygiene:*	Do not absolutely 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

	Store at controlled room temperature
	Store in the original package
- *Ventilation requirements*	Use in a well ventilated place at room temperature
- *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. 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.
- *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. 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 to ivory white solid (Crystalline powder)
Odor:	odourless
Odour threshold:	-
pH:	Data not available in the literature search carried out
Melting point/freezing point:	192 ÷ 198 °C
Boiling point:	453.7 °C at 760 mmHg (predicted) (1)
Flash point:	169 °C (predicted) (1)
Auto-ignition temperature:	Data not available in the literature search carried out
Surface tension:	42.9 dyne/cm (predicted) (1)
Vapour pressure:	2.02x 10^{-8} mmHg at 25°C (predicted) (1)
Relative density:	1,13 ± 1 g/cm³ (predicted) (1)
Water solubility:	Insoluble
Organic solvent solubility:	soluble in dichloromethane
Partition coefficient Octonol/water (Log Kow):	2.95 (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

-

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.

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: May be damage fertility or the unborn child.
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)

Absorption**:** Following oral administration, exemestane is rapidly absorbed; at least 42% was absorbed from the gastrointestinal tract. Exemestane plasma levels increased by approximately 40% after a high-fat breakfast.

Distribution**:** distributed extensively into tissues. It's 90% bound to plasma proteins and the fraction bound is independent of the total concentration. Albumin and α -acid glycoprotein both contribute to the binding. The distribution of exemestane and its metabolites into blood cells is negligible.

Metabolism and Elimination**:** the amounts of exemestane excreted in urine and feces is similar (about 42% over a 1-week collection period). The amount of drug excreted unchanged in urine was less than 1% of the dose. Exemestane is extensively metabolized, with levels of the unchanged drug in plasma accounting for less than 10% of the total radioactivity.

- Acute toxicity effects:

- Oral: DL50 Orale - ratto - > 5.000 mg/kg (3)

DL50 Orale - topo - > 3.000 mg/kg [3]

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

- Corrosion/Irritation effects: Skin (rabbit): No irritation [3]
Eye (rabbit) : Slight irritation [3]

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

- Sensitisation: No sensitiser [3]

- **Repeated dose toxicity** (experimental.): [3]
4 Week(s) Rat Oral 150 mg/kg/day NOAEL None identified
4 Week(s) Rat Oral 1000 mg/kg/day LOAEL Liver, Thymus, Spleen, Reproductive system
4 Week(s) Dog Oral 30 mg/kg/day LOAEL Reproductive system
13 Week(s) Mouse Oral 30 mg/kg/day LOAEL Reproductive system
26 Week(s) Rat Oral 30 mg/kg/day LOAEL Female reproductive system

- CMR effects:

- **Germinal cell mutagenicity**[2]:
Ames test: negative
Mammalian cells (V79 Chinese hamster lung cells): negative
Human lymphocytes in vitro without metabolic activation: positive
Micronucleus test: negative
Exemestane did not increase unscheduled DNA synthesis in rat hepatocytes when tested in vitro.

- **Carcinogenicity**[2]:
  - A 2-year carcinogenicity study in mice at doses of 50, 150 and 450 mg/kg/day by gavage, resulted in an increased incidence of hepatocellular adenomas and/or carcinomas in both genders at the high dose level. An increased incidence of renal tubular adenomas was observed in male mice at the high dose. Since the doses tested in mice did not achieve an MTD, neoplastic findings in organs other than liver and kidneys remain unknown.
  - A carcinogenicity study in rats at the doses of 30, 100 and 315 mg/kg/day by gavage for 92 weeks in males and 2 years in females showed no evidence of carcinogenic activity in females up to the highest dose. The male rat study was inconclusive.
  -

- **Reproductive toxicity**[2]:
  - In a pilot reproductive study in rats, male rats were treated with doses of 125–1000 mg/kg/day exemestane, beginning 63 days prior to and during cohabitation. Untreated female rats showed reduced fertility when mated to males treated with ≥500 mg/kg/day exemestane.
  - In a separate study, exemestane was given to female rats at 4–100 mg/kg/day beginning 14 days prior to mating and through day 15 or 20 of gestation. Exemestane increased the placental weights; showed no effects on ovarian function, mating behavior and conception rate in rats given doses up to 20 mg/kg/day, but decreases in mean litter size and fetal body weight, along with delayed ossification were evidenced at ≥20 mg/kg/day.
  - In general toxicology studies, changes in the ovary, including hyperplasia, an increase in the incidence of ovarian cysts and a decrease in corpora lutea were observed with variable frequency in mice, rats and dogs at doses that ranged from 3–20 times the human dose on a mg/m basis.

Pregnancy category D: Positive evidence of risk.

- 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: (2)
It is not known whether exemestane is excreted in human milk.
There are no studies in pregnant women. The API is indicated for postmenopausal women.

SECTION 12
ECOLOGICAL INFORMATION

12.1. Toxicity

Green Algae OECD EC-50 72 Hours 7.1 mg/L (4)

12.2. Persistence and degradability

Data not available in the literature search carried out

12.3. Bioaccumulative potential

Log Pow = 2.95 (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 value of logPow a low bioaccumulation potential is expected; on the basis of ecotoxicological studies the substance is not classified dangerous for the environment

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

Bibliographic sources:

(1) Chemspider data base, search for Exemestane
(2) Daily Med, Current Medication Information, AROMASIN (exemestane) tablet
(3) Product Monograph AROMASIN, exemesane of Pfizer Canada Inc., January 7, 2009
(4) Sigma-Aldrich MSDS (PZ0006) Version 3, 27/01/2010

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

H360FD:	**May damage fertility or the unborn child**

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.**

List of P statements

Prevention

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

R phrases

R60:	**May impair fertility.**
R61:	**May cause harm to the unborn child.**

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

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.

Safety data sheet prepared by : Chemsafe Srl, Colleretto Giacosa (TO) Italia.
Tel. 0039 0125 538888, fax 0039 0125 538475, email chemsafe@chemsafe-consulting.com