FULVESTRANT

MATERIAL SAFETY DATA SHEET

According to Regulation (EC) No. 1907/2006
Revision: 05 – Revision date: April 24, 2014

SECTION 1 IDENTIFICATION OF THE SUBSTANCE AND OF THE COMPANY

1.1 Product identifier

Product name:	FULVESTRANT
CAS Number:	129453-61-8
EC Number:	Not applicable
INDEX Number:	Not applicable
Registration Number:	Exempt from registration
Molecular Weight:	606.77
Molecular Formula:	$C_{32}\,H_{47}\,F_5\,O_3\,S$

1.2 Relevant identified uses of the substance

Common use:	Chemical intermediate for the preparation of pharmaceutical products

1.3 Details of the supplier of the safety data sheet

Company name:	STERLING S.p.A.
Address:	Via della Carboneria, 30 06073 Solomeo di Corciano (PG) – Italy
E-mail address:	Canali Claudia ccanali@sterling.it
Telephone:	075/5294001
Fax:	075/5294000

1.4 Emergency telephone number

Italy:	+39 02 66101029 (Poison Information Centre Niguarda Ca' Granda – Milano)
Foreign countries:	Contact the closest Poisons Information Centre.

SECTION 2 HAZARDS IDENTIFICATION

2.1 Classification of the substance

2.1.1 Classification according to Regulation (EC) N. 1272/2008 (CLP/GHS)

Repr. 1B	H360Df
Lact.	H362
Aquatic acute 1	H400 (M-Factor (self-classification) = 1)
Aquatic chronic 1	H410

2.1.2 Classification of the substance according to Directive 67/548/EEC

Repr. Cat. 2	R61
Repr. Cat. 3	R62
N	R50/53
	R64

Full text of R and H-phrases: see section 16

2.2 Label elements

GHS 08 GHS 09

Signal Word: **DANGER**

Hazard Statement

H360Df : May damage the unborn child. Suspected of damaging fertility

H362 : May cause harm to breast-fed children

H410 : Very toxic to aquatic life with long lasting effects

Precautionary Statement

Prevention

P202 : Do not handle until all safety precautions have been read and understood

P260 : Do not breathe dust/fume/gas/mist/vapours/spray

P263 : Avoid contact during pregnancy/while nursing

P281 : Use personal protective equipment as required

Response

P308 + P313 : IF exposed or concerned: Get medical advice/attention

P391 : Collect spillage

Disposal

P501 : Dispose of contents/container in accordance with local/regional/national/international

2.3 Other hazards

This substance does not meet the criteria for classification as PBT or vPvB according to Annex XIII of Regulation (EC) n. 1907/2006.

Health effects : Risk of harm to the fetus and fertility.

Physico-chemical effects : No adverse effects known.

Environmental effects : The substance is toxic for the environment. M-Factor = 1 according to Regulation (EC) No 1272/2008.

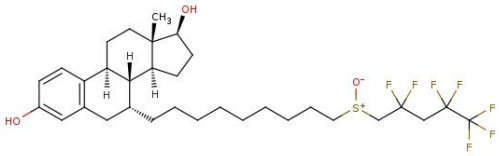
See also sections from 9 to 12.

SECTION 3 COMPOSITION/INFORMATION ON INGREDIENTS

3.1 Substance

Product name : FULVESTRANT

Structural formula :



Chemical name : 7*α*-(9-((4,4,5,5,5-Pentafluoropentyl)sulfinyl)nonyl)estra-1,3,5(10)-triene-3,17*β*-diol
Molecular Weight : 606.77
Molecular formula : $C_{32}H_{47}F_5O_3S$
CAS No. : 129453-61-8
EC No. : Not applicable
Concentration : 97.0%-102.0%

3.2 Mixture

Not applicable

SECTION 4 FIRST AID MEASURES

4.1 Description of first aid measures

General advice: In case of contact with the substances immediately change contaminated clothing.

Ingestion: In case of ingestion, if conscious, rinse mouth with water. If the casualty is unconscious, place in the recovery position. Gastric lavage is not necessary after small to moderate ingestions if activated charcoal can be given promptly.

Inhalation: Remove casualty to fresh air as quickly as possible. Keep warm and at rest. Maintain an open airway. If breathing is difficult, give oxygen if possible, or assisted ventilation.

Skin contact: In case of skin contact with powders or solutions immediately rinse affected area with copious amount of water and then wash with soap and water. Remove contaminated clothing and shoes.

Eye contact: Irrigate eyes with copious amounts of water for at least 10-15 min, holding eyelids apart to ensure thorough rinsing.

4.2 Most important symptoms and effects, both acute and delayed

Fulvestrant has a low potential for toxicity, both acute and chronic. Acute adverse effects may occur with respect to the pharmacological activity of the active ingredient. Swelling of extremities. Swelling of face. Constipation. Nausea. Vomiting. Headache. Diarrhea. Fatigue. Fainting. Fever. Body aches. Flu symptoms. Sore throat. Skin rash. Itching. Anxiety. Numbness or tingling of skin. Swollen glands. Bleeding or bruising. Sweating. Depression. Insomnia. Loss of appetite. Cough. Urine discoloration. Difficulty swallowing. Painful or difficult urination.

4.3 Indication of any immediate medical attention and special treatment needed

Get medical attention if breathing is difficult and if there is irritation or blistering of the skin. Induce vomiting only if indicated by your doctor.

SECTION 5 FIRE-FIGHTING MEASURES

5.1 Extinguishing media

The product is combustible and, like organic dusts in general, can ignite and give explosive mixtures with air at high temperatures or the presence of ignition sources.

Suitable extinguishing media*:*	Carbon Dioxide (CO_2), foam, dry chemical powder, and water spray, unless otherwise stated.
Unsuitable extinguishing media:	Heavy water stream.

NOTE:

Cool containers that are not involved in the fire but exposed to fire with water to prevent possible explosion and fire propagation.

5.2 Special hazards arising from the substance

Specific hazard(s):	The product is combustible and, like the dust in general, can make an explosive mixture with air. When heated or in the event of a fire, vapors may be harmful to health: carbon oxides (CO_x), sulfur oxides and hydrogen fluoride (HF).

5.3 Advice for firefighters

Special fire fighting procedures:	Protective Equipment: Wear full fire resistant self-contained breathing apparatus and protective clothing to prevent contact with skin and eyes.

SECTION 6 ACCIDENTAL RELEASE MEASURES

6.1 Personal precautions, protective equipment and emergency procedures

6.1.1 For non-emergency personnel

Keep non-involved personnel away from the area of spillage.

Avoid the generation and spreading of dust.

Wear appropriate protective equipment (see Section 8) to prevent contamination of the skin, eyes and personal clothing.

Ventilate area.

Eliminate sources of ignition.

In case of fire and/or and explosions avoid breathing fumes and vapors.

Use a self-contained breathing apparatus (SCBA) and appropriate protective clothing.

Avoid contact with skin, eyes and inhalation of dust.

6.1.2 For emergency personnel

See also sections 8 (protective equipment)

6.2 Environmental precautions

Prevent product from entering sewers, rivers or other bodies of water or into the environment.

If required, notify relevant authorities according to all applicable regulations.

6.3 Methods and material for containment and cleaning up

Collect solid product with suitable mechanical means. Avoid creating dust by spraying the product with water, if there is no contraindication. Wash spill site after material pickup is complete with plenty of water. Transfer the gathered product and the washings to suitable tanks or containers and store/dispose according to relevant regulations.

6.4 Reference to other sections

See also sections 8 (protective equipment) and 13 (disposal).

SECTION 7 HANDLING AND STORAGE

7.1 Precautions for safe handling

Use of personal protective equipment must be consistent with good occupational hygiene practices.

Handling recommendations:

Handle away from ignition sources, sparks and open flame.

Handle in a well ventilated place.

Do not breathe mist, and/or vapors associated with the material.

Do not breathe dust.

Wear suitable Personal Protection Equipment (see section 8).

Keep the substance away from drains, surface or ground waters.

Recommendation for personal hygiene:

Avoid direct contact with skin, eyes and clothing.

Do not eat, drink or smoke in the working areas.

Do not reuse contaminated clothing. Remove contaminated clothing and protective equipment before entering common areas.

Wash hands thoroughly with soap and water before meals and after work shift.

7.2 Conditions for safe storage

Store refrigerated at 2 to 8°C. Store in the original package. Store away from all heat sources, including direct sunlight. Open flame. Sources of ignition. Sparks. Incompatible materials.

7.3 Specific end use(s)

Chemical intermediate for the preparation of pharmaceutical products

SECTION 8 EXPOSURE CONTROLS/PERSONAL PROTECTION

8.1 Control Parameter

Exposure limit values (ACGIH 2013):

- TLV TWA: No data available

- TLV STEL: No data available

Other exposure limit values in literature:

- TLV TWA: 0.001 mg/m^3 (U. S. Pharmacopeia SDS)
- TLV STEL: No data available

Monitoring procedures:

Refer to Dir. 96/82/EC.

The measurement of substances in the workplace must be carried out with standardized methods (e.g. 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.

8.2 Exposure Controls

8.2.1 Appropriate engineering controls

When feasible, use closed loop systems or with local exhaust.

When inside buildings or confined spaces, ensure adequate ventilation.

The lyophilized powder should be used in biological safety cabinets or in systems with equivalent content.

Provide eyewash fountains at the workplace.

8.2.2 Personal protection measures, such as personal protective equipment

Personal Protective Equipment:	The personal protective equipment should be chosen in the configuration according to the concentration and quantity of hazardous substances specifically for the workplace.
a) Eye / Face Protection:	Wear safety goggles (EN 166).
b) Skin and body Protection:	Protective clothing global. Use rubber or synthetic gloves (EN 374).
c) Respiratory Protection:	Avoid inhalation of dust, respiratory protection: dust mask with filter type P3 (EN 143). Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).
d) Heat Dangers:	The product is not handled hot.

8.2.3 Environmental Exposure Controls

Take all the technical precautions necessary to prevent the spread of the product into the surrounding.

SECTION 9 PHYSICAL AND CHEMICAL PROPERTIES

9.1 Information on basic physical and chemical properties

a) Appearance	White crystalline powder
b) Odor	-
c) Odor threshold	No data available
d) pH	No data available
e) Melting point/freezing point	109-112°C
f) Initial boiling point and boiling range	No data available
g) Flash point	No data available
h) Evaporation rate	No data available
i) Flammability (solid, gas)	No data available
j) Upper/lower flammability or explosive limits	No data available
k) Vapor pressure	$1.56x10^{-16}$ mm Hg @ 25°C.(1
l) Vapor density	Not applicable
m) Relative density	1.201 g/cm^3
n) Solubility(ies)	Very slightly soluble in water, $1.0x10^{-6}$ mg/L @ 25°C. Very soluble in ethanol and soluble in glycols.
o) Partition coefficient: *n*-octanol/water	Log Pow 7.848
p) Auto-ignition temperature	No data available
q) Decomposition temperature	No data available
r) Viscosity	Not applicable
s) Explosive properties	Not applicable
t) Oxidising properties	No data available

9.2 Other information

No data available

SECTION 10 STABILITY AND REACTIVITY

10.1 Reactivity

The substance does not present additional dangers of reactivity than those reported in the next subtitles.

10.2 Chemical stability

Store refrigerated at 2 to 8°C. Store away from all heat sources, including direct sunlight, open flame, sources of ignition, sparks, and incompatible materials.

10.3 Possibility of hazardous reactions

Product does not polymerise.

10.4 Conditions to avoid

Heat. Static Electricity.

10.5 Incompatible materials

Store separately from oxidizing agents.

10.6 Hazardous decomposition products

When heated or in case of fire vapors may be harmful to health: carbon oxides (CO_x), sulfur oxides and hydrogen fluoride (HF).

SECTION 11 TOXICOLOGICAL INFORMATION

11.1 Information on toxicological effects

Signs and Symptoms of Exposure: Fulvestrant has a low potential for toxicity, both acute and chronic. Acute adverse effects may occur with respect to the pharmacological activity of the active ingredient. Swelling of extremities. Swelling of face. Constipation. Nausea. Vomiting. Headache. Diarrhea. Fatigue. Fainting. Fever. Body aches. Flu symptoms. Sore throat. Skin rash. Itching. Anxiety. Numbness or tingling of skin. Swollen glands. Bleeding or bruising. Sweating. Depression. Insomnia. Loss of appetite. Cough. Urine discoloration. Difficulty swallowing. Painful or difficult urination.

CLASS OF RELEVANT RISK FOR SUBSTANCE:

a) Acute toxicity:	The acute toxicity of fulvestrant is low. In rodents, the median lethal dose was greater than 70 mg/kg after intramuscular administration (more than 400 times the therapeutic dose), exceeding 50 mg/kg after intravenous administration, and greater than 2000 mg/kg after oral administration.
b) Skin corrosion / irritation:	Not reported evidence concerning this effect
c) Serious eye damage / serious eye irritation:	Not reported evidence concerning this effect
d) Respiratory / skin sensitization:	Not reported evidence concerning this effect
e) Germ cell mutagenicity:	Fulvestrant has been evaluated for genotoxic activity in the Ames assay, mouse lymphoma assay, *in vitro* chromosome aberration assay with human lymphocytes and the micronucleus test in rats after a single oral dose of 2000 mg / kg. All tests were negative for genotoxic potential.
f) Carcinogenicity:	Fulvestrant did not induce liver tumors in rats.
g) Reproductive toxicity:	FDA Pregnancy Risk Category: D. Studies on humans or experimental data or post-marketing experience, have demonstrated fetal risk. However, the potential benefits of using the drug may outweigh the potential risks. Fulvestrant has been shown to cross the placenta after single intramuscular doses in rat and rabbit.

	In female rats a dosage of 0.01 mg/kg bw/day caused a reduction of fertility and embryonic survival. At higher doses, fulvestrant caused a higher incidence of fetal abnormalities in rats at 2 mg/kg bw/day and no tubercle ossification of the tooth and ventral to the first cervical vertebra at doses of 0.1 mg/kg bw/day IM when administered during the period of organogenesis. Rabbits was unable to maintain pregnancy, when treated with 1 mg/kg bw/day IM during the period of organogenesis. The potential effects of fulvestrant on the fertility of male animals have not been studied, but in a 6-month toxicological study, male rats treated with intramuscular doses of 15 mg/rat/30 days, 10 mg/rat/30 days, or 10 mg/rat/15 days fulvestrant showed a loss of sperm from the seminiferous tubules, seminiferous tubular atrophy, and degenerative changes of the epididymis. Changes in the testes and epididymides were not recovered 20 weeks after cessation of administration. It is not known if fulvestrant is excreted in human milk. Fulvestrant is found in rat milk at levels significantly higher (approximately 12-fold) than plasma after administration.
h) Specific target organ toxicity (STOT)-Single exposure-:	The product may cause mild irritation of the mucous membranes and upper respiratory tract
h) Specific target organ toxicity (STOT)-Repeated exposure- :	Not reported evidence concerning this effect
j) Aspiration hazard:	Not applicable
k) Toxic-kinetics information (ADME):	Fulvestrant has a low oral bioavailability. After intramuscular injection, fulvestrant is slowly absorbed and maximum plasma concentrations (Cmax) are reached after days. Is subject to extensive and rapid distribution and is highly (>98%) bound to plasma proteins. The metabolism of fulvestrant has not been fully evaluated, but involves combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids. Is eliminated mainly in metabolised form. The major route of excretion is via the faeces, with less than 1% being excreted in the urine. The terminal half-life (t1/2) after intramuscular administration is governed by the absorption rate and was estimated to be 50 days.
Other information	RTECS N. KG7623000

SECTION 12 ECOLOGICAL INFORMATION

Ecological Information: Use according to good manufacturing practices, avoid dispersion into the environment.

Notify relevant authorities according to all applicable regulations if the product can reach waterways or sewers or contaminate soil or vegetation.

12.1 Toxicity

Endpoint	Value	Reference
LC_{50} Daphnia magna 96h	129.39 µg/L	USEPA ECOTOX database (Clubbs,R.L.,

		and B.W. Brooks, 2007)

The effects and mechanism of action of fulvestrant were studied in an *in vivo* test of teleost fish and sea bream (Sparus auratus). Were measured calcium levels in plasma, liver and testicular gene expression of three subtypes of estrogen receptors (ER), ERα, ERβa, and ERβb; the genes sensitive to estrogen, vitellogenin II and choriogenin L, are were analyzed by semi-quantitative RT-PCR. These results demonstrated that fulvestrant has agonist effects on several typical responses to estrogen in fish, but its actions are tissue-specific.

12.2 Persistence and degradability

Minimally biodegradable (2

12.3 Bioaccumulative potential

Log Pow 7.848

12.4 Mobility in soil

Not reported evidence concerning this outcome

12.5 Results of PBT and vPvB assessment

Assessment is not available. However, the log K ow of fulvestrant indicates that its potential to bioaccumulate is expected to be high.

12.6 Other adverse effects

No data available

SECTION 13 DISPOSAL CONSIDERATIONS

13.1 Waste treatment methods

Do not discharge on the ground or in sewers, tunnels or water courses.
Dispose of waste or used sacks/containers according to Community/National/Local regulations.

SECTION 14 TRANSPORT INFORMATION

14.1 ONU Number

3077

14.2 UN Shipping Name

ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S. (FULVESTRANT)

14.3 CLASS OF RISK RELATED TO THE TRANSPORTATION

Road / rail transport (ADR/RID)

Class :	9
Label :	9 + Environmentally hazardous
Kemler N. :	90
Tunnel restriction code:	(E)

Sea Transport (IMDG)

Class :	9
EMS :	F-A, S-F
Label :	9 + Marine pollutant

Air transport (IATA)

Class :	9
Label :	9 + Environmentally hazardous

14.4 Packaging group

III

14.5 Environmental hazards

Marine pollutant

14.6 Special precautions for users

None

14.7 Transport of bulk cargo in accordance with Annex II of MARPOL 73/78 and the IBC Code

None

SECTION 15 REGULATORY INFORMATION

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

Authorizations according to REACH Regulation: the substance is not subjected

Restrictions according to REACH Regulation: the substance is not subjected

Other UE:

The substance is dangerous under the Seveso Regulation (Dir. 96/82/CE and f.a.): Annex I, part 2, group 9i.

15.2 Chemical Safety Assessment

A chemical safety assessment has not been carried out for this product.

SECTION 16 OTHER INFORMATION

List of relevant phrases

Classification according to Regulation (EC) No 1272/2008 (CLP/GHS) as amended

H360Df	May damage the unborn child. Suspected of damaging fertility.
H362	May cause harm to breast-fed children
H400	Very toxic to aquatic life
H410	Very toxic to aquatic life with long lasting effects

Classification according to European Directive 67/548/CEE as amended

R61	May cause harm to the unborn child
R62	Possible risk of impaired fertility
R64	May cause harm to breast-fed babies
R51/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

Guidelines for the formation

Workers potentially exposed to this substance must be trained adequately on the basis of the contents of this MSDS.

More information

Revision n° 01 (March 2012) Revision of the SDS according to Annex I of Regulation UE453/2010 which amended Annex II of EC Regulation 1907/2006 (REACH).
Revision n° 02 (April 2012) Revision of the conditions of storage of the substance (section 7.2).
Revision n° 03 (October 2012) Change of company name.

Revision n° 04 (May 2013) Revision of classification, ecological data and transportation. The following sections 2, 3, 9, 10, 12, and 14, have been updated.

Bibliography

[1)] Estimated value by EPI Suite v. 4.10
[2)] EDQM SDS - Y0001413 version 2.0 of 27/06/2013
NCBI – PUBCHEM Compound Database
BANCA DATI SOSTANZE CHIMICHE - ICARO S.R.L. - CORTONA (AR)
RTECS Database
HSDB – Toxnet Database
Documents of EMEA (EMA) on fulvestrant
U. S. Pharmacopeia SDS – 5298 Version 02 of 28/06/2013

Acronyms:

ACGIH	= *American Conference of Governmental Industrial Hygienists*
ADR/RID	= *European Agreement of Dangerous Goods by Road/Rail*
CSR	= *Chemical Safety Report*
DNEL	= *Derived No effect Level*
DMEL	= *Derived Minimal Effect Level*
IARC	= *International Agency for Research on Cancer*
ICAO	= *International Civil Aviation Organization*
IMDG	= *International Maritime Code for Dangerous Goods*
IMO	= *International Maritime Organization*
IATA	= *International Air Transport Association*
OSHA	= *Occupational Safety and Health Administration*
PNEC	= *Predicted No Effect Concentration*
PBT	= *Persistent, Bioaccumulative and Toxic substance*
STOT	= *Specific Target Organ Toxicity*
(STOT) RE	= *Repeated Exposure*
(STOT) SE	= *Single Exposure*
TLV	= *Threshold Limit Value*
TWA	= *Time-Weighted Average*
STEL	= *Short Term Exposure Limit*
vPvB	= *very Persistent and very Bioaccumulative*

Update Reason

General revision of the SDS. The following sections 8, and 11, have been updated.

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Update Num. 05

STERLING S.p.A.