

ABIRATERONE ACETATE

MATERIAL SAFETY DATA SHEET

According to Regulation (EC) No. 1907/2006
Revision: 04 – Revision date: April 24, 2014

SECTION 1 IDENTIFICATION OF THE SUBSTANCE AND OF THE COMPANY

1.1 Product identifier

<i>Product name:</i>	ABIRATERONE ACETATE
<i>Chemical name:</i>	(3β)-17-(pyridin-3-yl)androsta-5,16-dien-3-yl acetate
<i>CAS Number:</i>	154229-18-2
<i>EC Number:</i>	No data available
<i>INDEX Number:</i>	No data available
<i>Registration Number:</i>	Exempt from registration
<i>Molecular Formula:</i>	C ₂₆ H ₃₃ N O ₂
<i>Molecular Weight:</i>	391.55

1.2 Relevant identified uses of the substance

Common use: Steroidal inhibitor API (Active Pharmaceutical Ingredient)

1.3 Details of the supplier of the safety data sheet

<i>Company name:</i>	STERLING S.p.A.
<i>Address:</i>	Via della Carboneria, 30 06073 Solomeo di Corciano (PG) – Italy
<i>E-mail address:</i>	Canali Claudia ccanali@sterling.it
<i>Telephone:</i>	075/5294001
<i>Fax:</i>	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. 2	H361
Aquatic chronic 1	H410

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

Repr. Cat. 3	R62
Repr. Cat. 3	R63
	R53

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

2.2 Label elements



Signal Word: **WARNING**

Hazard Statement

H361 : Suspected of damaging fertility or the unborn child.
 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
 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: The most common adverse reactions seen are peripheral oedema, hypokalaemia, hypertension and urinary tract infection. Other important adverse reactions include, cardiac disorders, hepatotoxicity, and fractures. Possible allergic reaction to material if inhaled, ingested or in contact with skin.

Physico-chemical effects: No adverse effects known.

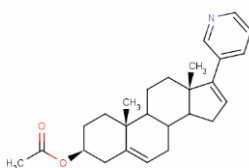
Environmental effects: The substance have safety concern for the aquatic environment. A bioaccumulation potential may be expected.

See also sections from 9 to 12.

SECTION 3 COMPOSITION/INFORMATION ON INGREDIENTS

3.1. Substance

Product name : ABIRATERONE ACETATE
 Structural formula :



Chemical name : (3 β)-17-(pyridin-3-yl)androsta-5,16-dien-3-yl acetate
 Molecular Weight : 391.55
 Molecular formula : C₂₆ H₃₃ N O₂
 CAS No. : 154229-18-2
 EC No. : No data available
 Concentration : Pure substance

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 change immediately contaminated clothing.
Ingestion:	In case of ingestion, if conscious, rinse mouth with plenty of water. If the casualty is unconscious, place in the recovery position. Induce vomiting only if indicated by the doctor. Get medical advice if adverse symptoms will appear.
Inhalation:	Move casualty to fresh air as quickly as possible. Keep warm and at rest. If breathing is difficult, give oxygen if possible, or assisted ventilation. Get medical advice if the exposure was significant in terms of quantity or time.
Skin contact:	Take off contaminated clothing and shoes. In case of contact with dust or solutions, wash immediately and thoroughly with soap or mild detergent and large amounts of water until no evidence of residues of the substance. Get medical advice if the exposure was significant in terms of quantity or time.
Eye contact:	Irrigate eyes with copious amounts of water for at least 10-15 min, holding eyelids apart to ensure thorough rinsing. Get medical advice if the exposure was significant in terms of quantity or time.

4.2 Most important symptoms and effects, both acute and delayed

Abiraterone acetate is a prodrug of abiraterone, which blocks androgen production. Thus, related to the pharmacological activity of abiraterone, abiraterone acetate decreased the growth of androgen dependent organs and suppressed plasma testosterone levels. The most common adverse reactions seen are peripheral oedema, hypokalaemia, hypertension and urinary tract infection. Other important adverse reactions include, cardiac disorders, hepatotoxicity, and fractures.

4.3 Indication of any immediate medical attention and special treatment needed

Immediately call a POISON CENTER or doctor/physician for all cases of contact. 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 (CO₂), foam, dry chemical powder, water spray, and water jet, unless otherwise stated.

Unsuitable extinguishing media: None

NOTE:

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

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) and nitrogen oxides (NO_x).

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. The equipment must comply to the standard EN and used in conditions of maximum protection on the basis of the information given in the previous sub-sections.

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.

In case of fire and/or 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.

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

6.3 Methods and material for containment and cleaning up

Collect free product with suitable mechanical means. Avoid creating dust by spraying the product with water, if there is no contraindication. Ventilate area and wash spill site after material pickup is complete. 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.

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:

Avoid direct contact with skin, eyes and clothing.

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

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

The API does not require any special storage conditions.

Store in the original package.

Store away from all heat sources, including direct sunlight, open flame, sources of ignition, sparks, incompatible materials.

Abiraterone acetate is not intended for long-term storage. Keep container tightly closed in a cool, well ventilated place.

7.3 Specific end use(s)

Active Pharmaceutical Ingredient (API)

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

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

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 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).

Wear gauntlets, boots, bodysuit and other devices in accordance with standard EN 13982.

c) *Respiratory Protection:* Avoid inhalation of dust, respiratory protection: dust mask with filter type P3 (EN 143).

In case of intense and sustained exposure wear self-contained breathing.

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

Use according to good manufacturing practices avoiding litter.

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	-
d) pH	Data not available in the literature search carried out
e) Melting point/freezing point	127-130°C (decomposes)
f) Initial boiling point and boiling range	Not applicable
g) Flash point	Not applicable
h) Evaporation rate	Not applicable
i) Flammability (solid, gas)	Data not available in the literature search carried out
j) Upper/lower flammability or explosive limits	Data not available in the literature search carried out
k) Vapor pressure	Data not available in the literature search carried out
l) Vapor density	Not applicable
m) Relative density	1.14 g/cm ³
n) Solubility(ies) ⁽¹⁾	Practically insoluble in water, very slightly soluble in 0.1N HCl solution and soluble to freely soluble in organic solvents (chloroform and methanol).
o) Partition coefficient: <i>n</i> -octanol/water	Log Pow 5.12 ⁽²⁾
p) Auto-ignition temperature	Data not available in the literature search carried out
q) Decomposition temperature	Data not available in the literature search carried out
r) Viscosity	Not applicable
s) Explosive properties	Data not available in the literature search carried out
t) Oxidising properties	Data not available in the literature search carried out

9.2. Other information

pKa 5.19 ⁽²⁾

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 at controlled room temperature. Store away from all heat sources, including direct sunlight, open flame, sources of ignition and sparks.

Abiraterone acetate is not intended for long-term storage. Keep container tightly closed in a cool, well ventilated place.

10.3 Possibility of hazardous reactions

Product does not polymerize.

10.4 Conditions to avoid

Keep protected from direct sunlight, humidity, high temperatures, and static electricity.

10.5 Incompatible materials

Avoid contact with strong oxidizing agents.

10.6 Hazardous decomposition products

When heated or in the event of a fire, vapors may be harmful to health: Carbon oxides (CO_x), nitrogen oxides (NO_x).

SECTION 11 TOXICOLOGICAL INFORMATION

11.1 Information on toxicological effects

Signs and Symptoms of Exposure: Abiraterone acetate is a prodrug of abiraterone, which blocks androgen production. Thus, related to the pharmacological activity of abiraterone, abiraterone acetate decreased the growth of androgen dependent organs and suppressed plasma testosterone levels. The most common adverse reactions seen are peripheral oedema, hypokalaemia, hypertension and urinary tract infection. Other important adverse reactions include, cardiac disorders, hepatotoxicity, and fractures.

CLASS OF RELEVANT RISK FOR SUBSTANCE:

a) *Acute toxicity:* ^(1, 3)

Route	Specie	Results	Note	Reference
Oral	Rat	> 2000 mg/kg	No test article-related findings	(1)
Oral	Mice (male, female)	> 2000 mg/kg	No test article-related findings	(1)
Oral	Human - man	TDLo 2.86 mg/kg	Endocrine - androgenic	On (3): BJCAAI 90,2317,2004

b) *Skin corrosion / irritation:*

May cause skin irritation

c) *Serious eye damage / serious eye irritation:*

May cause eye irritation

d) *Respiratory / skin sensitization:*

Not reported evidence concerning this effect

e) Germ cell mutagenicity: ⁽²⁾	Not mutagenic or clastogenic in the in vitro assays in the <i>in vivo</i> rat micronucleus assay at the highest dose tested, 2000 mg/kg.
f) Carcinogenicity:	Not reported evidence concerning this effect
g) Reproductive toxicity: ⁽²⁾	<p>Pregnancy category X. Also if there are no studies on human fertility and embryo fetal development, studies with rats and monkeys show a significant amount of toxicities in the reproductive organs at all doses.</p> <p>In fertility studies in both male and female rats (4-and 3-weeks), abiraterone acetate reduced fertility, which was completely reversible in 4 to 16 weeks after abiraterone acetate was stopped. In an embryofetal developmental study in the rat, abiraterone acetate at ≥ 10 mg/kg/day affected pregnancy including reduced fetal weight and survival, delayed ossification, and increases in late resorptions and post implantation loss with a subsequent reduction in live fetuses.</p> <p>Administration of the drug, therefore, may affect fertility in humans. This was the result of the anti-androgen pharmacology of abiraterone acetate and the longer duration of treatment. Shorter term treatment of abiraterone acetate did not have a major effect on reproductive organs with the exception of the ovaries.</p>
h) Specific target organ toxicity (STOT)-Single exposure-	Not reported evidence concerning this effect
h) Specific target organ toxicity (STOT)-Repeated exposure-	Not reported evidence concerning this effect
j) Aspiration hazard:	Not applicable
k) Toxic-kinetics information (ADME): ⁽²⁾	<p><u>Adsorption</u>: Following oral administration the bioavailability is like 37%. Abiraterone acetate is rapidly converted to the metabolite, abiraterone.</p> <p><u>Distribution</u>: Binding of abiraterone acetate to human plasma proteins is greater than 99.8%. The apparent volume of distribution is approximately 5,630 l, suggesting that abiraterone extensively distributes to peripheral tissues. No relevant species differences were observed. The liver was one of the major organs affected when abiraterone acetate was given for a long duration.</p> <p><u>Metabolism</u>: Abiraterone acetate is a prodrug for abiraterone. Abiraterone acetate is rapidly converted to abiraterone in vivo by esterases.</p> <p><u>Excretion</u>: Abiraterone acetate and its metabolite abiraterone are eliminated primarily in the feces, while excretion in urine is limited (less than 2% of the administered dose). There was no difference in routes and rates of excretion between male and female rats. The mean half-life of abiraterone in plasma is approximately 15 hours based on data from healthy subjects.</p>
Other information	No data available

SECTION 12

ECOLOGICAL INFORMATION

Ecological Information:	<p>Abiraterone acetate is classified hazardous for the aquatic environment, chronic, category 1 (H410) based on the NOEC value. Based on Log Pow and low degradability is classified as R53.</p> <p>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.</p>
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12.1 Toxicity⁽³⁾

NOEC (Fathead minnow partial life cycle) = 0.013 µg/L (OECD 229)

NOEC (Daphnia sp. Reproduction Test) = 0.47 µg/L (OECD 211)

No data on acute toxicity.

12.2 Persistence and degradability⁽⁴⁾

No significant degradation is observed after exposure to different stress tests such as simulated sunlight, elevated temperature, humid conditions and oxygen from air.

12.3 Bioaccumulative potential⁽³⁾

BCF = 625 (for low conc, 0.13 µg /L)

576 (for high conc, 1.3 µg /L)

Log Pow = 5.12

12.4 Mobility in soil

Not reported evidence concerning this outcome

12.5 Results of PBT and vPvB assessment

The Environmental Risk of Abiraterone acetate has been assessed and it is concluded that abiraterone acetate is not a PB substance but it is T substance.

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. (ABIRATERONE ACETATE)

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 not dangerous under the Seveso Regulation (Dir. 96/82/CE and f.a.)

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

H361 Suspected of damaging fertility or the unborn child

H410 Very toxic to aquatic life with long lasting effects

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

R53 May cause long-term adverse effects in the aquatic environment

R62 Possible risk of impaired fertility

R63 Possible risk of harm to the unborn child

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° 00 (January 2011) Emission of the SDS according to Annex I of Regulation UE453/2010 which amended Annex II of EC Regulation 1907/2006 (REACH).

Revision n° 01 (April 2012) Revision of the conditions of storage of the substance (section 7.2).

Revision n° 02 (October 2012) Change of company name.

Revision n° 03 (April 2013) General update of the safety data sheet. Change in classification (sec. 2) and update of toxicological data (sec. 11).

Bibliography

THE MERCK INDEX-XI Ed.(1989)- Merck & Co. Inc.-Rahway, N.J.- USA

⁽¹⁾ EMA/CHMP/542871/2011 - Committee for Medicinal Products for Human Use (CHMP)

⁽²⁾ 202, 379 - Abiraterone acetate - PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

⁽³⁾ EMA/CHMP/755312/2012 - Committee for Medicinal Products for Human Use (CHMP)

⁽⁴⁾ Data from (WO2014009437) OXIDATION STABILITY OF ABIRATERONE ACETATE

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

Change in classification (sec. 2), update of physical and chemical properties (sec. 9), update of toxicological data (sec. 11), eco-toxicological data (sec. 12) and transport (sec. 14).

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The contained information is based upon our current understanding. It is applicable only to the indicated product and does not constitute any guarantee of the properties of the product. The user is responsible to ensure his or her own fitness and completeness of such information in relation to the specific use. The contained information is intended for the use of the product exclusively by appropriately qualified personnel. STERLING S.p.A. shall not be held liable for any damages caused from handling or from contact with the substance.

STERLING S.p.A.