

CHLORMADINONE ACETATE

MATERIAL SAFETY DATA SHEET

In accordance with Regulation (CE) 1907/2006, (CE) 1272/2008 and (EU) 453/2010 (Annex I)
Revision no. 5 - Revision date: October 1, 2012

SECTION 1. IDENTIFICATION OF THE SUBSTANCE AND OF THE COMPANY

1.1. Substance identifier

Substance name:	CHLORMADINONE ACETATE
Other names (if available): Name in Annex VI-CLP: Name reported in the inventory of harmonized classification and labelling:	Pregna-4,6-diene-3,20-dione, 6-chloro-17-hydroxy-, acetate unlisted not available
CAS number	302-22-7
REACH registration number	Exempt of registration

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

Relevant use(s)	Contraceptive 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
Germ cell mutagenicity	Mut. Cat. 2	H341	Suspected of causing genetic defects
Carcinogenicity	Carc. Cat. 2	H351	Suspected of causing cancer
Reproductive toxicity	Repr. Cat. 1B	H360FD	May damage fertility or the unborn child

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

Classification	Risk phrases
Mut. Cat.3, R68	Possible risk of irreversible effects
Carc. Cat 3, R40	Limited evidence of a carcinogenic effect
Repr. Cat 2, R60, R61	May impair fertility May cause harm to the unborn child.

Main adverse effects
Physico-chemical effects
Health effects

No adverse effects known.


Suspected of causing genetic defects and cancer. May damage fertility or the unborn child. Adverse reactions following acute exposition may be gastrointestinal disturbance, headache .

Environmental effects
See also sections from 9 to 12

No adverse effects known.

2.2 Label elements

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

Warning			
Signal Word			
Hazard indication (H) ^[1]	H341	H351	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
- vPvB
- Health hazards
- Environmental hazards
- Physico-chemical hazards

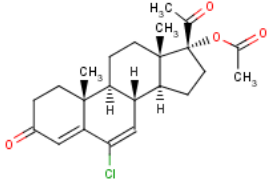
	X
	X

May be harmful if ingested, inhaled or in contact with skin. May be irritant or sensitizer.
not known
not known

- Specific effects
- unknown

SECTION 3 COMPOSITION/INFORMATION ON INGREDIENTS

Description: active pharmaceutical principle - Contraceptive

<i>Name of the component</i>	Chlormadinone acetate
<i>Concentration</i>	Pure substance
<i>Structural formula</i>	
<i>Chemical formula</i>	C ₂₃ H ₂₉ ClO ₄
<i>Molecular weight</i>	404,9 g/mol
<i>Substance with Community OEL</i>	No
<i>CAS name</i>	Pregna-4,6-diene-3,20-dione, 17-(acetyloxy)-6-chloro-
<i>CAS number</i>	302-22-7
<i>IUPAC name</i>	[(8R,9S,10R,13S,14S,17R)-17-acetyl-6-chloro-10,13-dimethyl-3-oxo-2,8,9,11,12,14,15,16-octahydro-1H-cyclopenta[a]phenanthren-17-yl] acetate
<i>EC number</i>	206-118-0
<i>Index number</i>	not assigned
<i>Impurity/ies (if classified)</i>	-
<i>Additive/ies (if classified)</i>	-

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 reactions following acute exposition may be gastrointestinal disturbance, headache. |
| - Delayed effects: | Suspected of causing genetic defects and cancer. May damage fertility or the unborn child. Possible allergic reaction to material if inhaled, ingested or in contact with skin. |

4.3 Indication of any immediate medical attention and special treatment needed

- | | |
|------------------------------------|-----------------------------|
| - Medical monitoring: | In case of pronged exposure |
| - Antidotes, if known | unknown |
| - Contraindications | unknown |
| - Immediate treatment at workplace | not known |

SECTION 5 FIREFIGHTING MEASURES

5.1 Extinguishing media

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

5.2 Special hazards arising from the substance

- | | |
|---------------------------------|--|
| - Hazardous combustion products | May generate toxic fumes of CO _x and compounds containing chlorine. |
| - 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

- | | |
|--|--|
| <ul style="list-style-type: none"> - <i>Containment procedures:</i> - <i>Cleaning up procedures:</i> | <p>Coverage of the discharges</p> <p>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.</p> |
|--|--|

6.4 Reference to other sections

See also section 8 and 13.

SECTION 7 HANDLING AND STORAGE

7.1. Precautions for safe handling

- | | |
|--|---|
| <ul style="list-style-type: none"> - <i>Recommendation for handling:</i> - <i>Recommendation for personal hygiene:</i> | <p>Handle away from sparkles and flames - sources of ignition</p> <p>Handle in a well ventilated place</p> <p>Avoid contact with incompatible materials</p> <p>Wear suitable Personal Protection Equipment (see section 8)</p> <p>Keep the substance away from drains, surface or ground waters</p> <p>Do not absolutely eat, drink and smoke in the working areas</p> <p>Wash hands after handling the substance</p> <p>Remove contaminated clothing and protective equipment before entering eating areas</p> |
|--|---|

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

- | | |
|---|--|
| <ul style="list-style-type: none"> - <i>Ventilation requirements</i> - <i>Containers</i> - <i>Specific design of storage rooms</i> - <i>Quantity limits for storage</i> - <i>Packaging compatibilities</i> | <p>The API does not require any special storage conditions</p> <p>Store in the original package</p> <p>Use in a well ventilated place at room temperature (not more than 25 °C)</p> <p>Keep containers tightly closed and correctly labeled</p> <p>Not requested on the base of the classification</p> <p>Not requested on the base of the classification</p> <p>See also section 10.5</p> |
|---|--|

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

- 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.
- 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 solid (powder)
Odor:	odourless
Odour threshold:	-
pH:	Data not available in the literature search carried out
Melting point/freezing point:	213°C ⁽¹⁾
Boiling point:	512.5 °C at 760 mmHg (predicted) ⁽¹⁾
Flash point:	172.5 °C (predicted) ⁽¹⁾
Auto-ignition temperature:	Data not available in the literature search carried out
Surface tension:	469.6 dyne/cm (predicted) ⁽¹⁾
Density:	1.23 g/cm ³ (predicted) ⁽¹⁾
Vapour pressure:	1.28 x 10 ⁻¹⁰ mmHg at 25°C (predicted) ⁽¹⁾
Water solubility:	Insoluble; 1.216 mg/l (predicted) ⁽¹⁾
Organic solvent solubility:	Soluble in chloroform and acetonitril. Slightly soluble in ethanol and diethyl ether.
Partition coefficient Octonol/water (Log Kow):	3.95 (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

Optical rotation:	-10.0° to -14.0° ⁽⁴⁾
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SECTION 10 STABILITY AND REACTIVITY

10.1. Reactivity

Stable in normal conditions of storage.

10.2. Chemical stability

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

- Stabilisers:

- Change in physical appearance

NO	YES	Used stabiliser
X	-	
X	-	

10.3. Possibility of hazardous reactions

- Possibility of an exothermic reaction:

- Possibility of a reaction releasing excessive pressure

- Possible degradation with instable product formation

NO	YES
X	-
X	-
X	-

10.4. Condition to avoid

Keep protected from light, humidity and high temperatures.

10.5. Incompatible materials

Strong oxidizing agents

10.6. hazardous decomposition products

If heated at high temperatures, decomposes releasing fumes and toxic gases of COx, NOx and compounds containing chlorine.

SECTION 11
INFORMATION ON TOXICOLOGICAL EFFECTS

- **Exposure routes:**

- *Inhalation:*

- *Ingestion:*

- *Skin contact:*

- *Eye contact:*

YES	NO
X	
X	
X	
X	

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

- *Inhalation:* Suspected of causing genetic defects and cancer. May 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):**

Data not available in the literature search carried out

- **Acute toxicity effects:**

- Oral: ⁽²⁾	LD50 rat > 10 g/kg Note: Behavioral - somnolence (general depressed activity) Endocrine - adrenal cortex hypoplasia
	LD50 mouse > 15 g/kg Note: Behavioral - somnolence (general depressed activity) Endocrine - adrenal cortex hypoplasia
- Dermal:	Data not available in the literature search carried out
- Inhalation:	Data not available in the literature search carried out
- Other effects: ⁽²⁾	LD50 intraperitoneal. rat = 5 g/kg Behavioral -somnolence (general depressed activity)
	LD50 subcutaneous rat > 10 g/kg Behavioral -somnolence (general depressed activity)
	Endocrine - adrenal cortex hypoplasia
	LD50 intraperitoneal mouse = 3 g/kg Behavioral -somnolence (general depressed activity)
	Endocrine - adrenal cortex hypoplasia
	LD50 subcutaneous mouse >10 g/kg Behavioral -somnolence (general depressed activity)
	Endocrine - adrenal cortex hypoplasia
	LD50 intravenous mouse > 2 g/kg Sense Organs and Special Senses (Eye) -effect, not otherwise specified
	Behavioral - ataxia
	Skin and Appendages - hair

RTECS no. **TU3750000**

- **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:** ⁽³⁾ ⁽⁵⁾ Chromosomal aberration: positive
Micronucleus test: positive
UDS rat hepatocytes: positive
- **Carcinogenicity**⁽⁴⁾ ⁽⁵⁾:

This material has not been classified by OSHA, ACGIH, EPA, or NTP as to its carcinogenicity, however, some studies have shown that this material may induce certain types of cancers.

In a 14-days study 8–12 male Sprague-Dawley Crl:CD(SD)Br rats were castrated and injected immediately thereafter twice daily with one of a number of synthetic progestogens, including chlormadinone acetate. The prostatic content of ornithine carboxylase was measured, as it is considered to be a highly specific, sensitive marker of androgenic activity in the prostate. Chlormadinone acetate caused significant increases in prostate weight; it has weak but significant androgenic activity in the rat ventral prostate. The incidences of pituitary and liver adenoma, benign and malignant mammary tumours in male and female mice were increased.

IARC: Group 2B - Possibly carcinogenic to humans (Chlormadinone acetate). There is limited evidence in experimental animals for the carcinogenicity of chlormadinone acetate.

TDLo Oral dog
Dose/duration : 182 mg/kg/2Y-C
Toxic effects : Tumorigenic - equivocal tumorigenic agent
Skin and Appendages - tumors

TD Oral dog
Dose/duration: 639 mg/kg/7Y-C

Toxic effects: Tumorigenic - equivocal tumorigenic agent
 Skin and Appendages - tumors
 Endocrine - diabetes mellitus

- Reproductive toxicity ^{(4) (5)}:

Chlormadinone acetate given orally at doses of 1–50 mg/kg bw on days 8–15 of pregnancy to Japanese ddS and CF1 mice caused a significant increase in the incidence of cleft palate. A dose of 10 mg/kg bw, but not of 1 or 3 mg/kg bw, given orally on days 8–20 of gestation to Japanese albino rabbits increased the incidence of cleft palate, abdominal wall defects and wrist contractures.

Effects observed in studies in woman: Effects on uterus, cervix, vagina ovaries, fallopian tubes; menstrual cycle changes or disorders; effects on fertility.

Effects observed in studies in rat: effects on urogenital system, fetotoxicity, Specific Developmental Abnormalities (musculoskeletal and urogenital system), Paternal Effects (prostate, seminal vesicle, Cowper's gland, accessory glands).

Effects observed in studies in mouse: effects on Fertility (pre and post-implantation mortality), Maternal Effects (uterus, cervix, vagina, menstrual cycle changes or disorders), Specific Developmental Abnormalities (craniofacial including nose and tongue), fetal death, fetotoxicity.

- 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: No increase in the incidence of malformations was reported in 305 infants whose mothers had been exposed to chlormadinone and oestrogens during pregnancy. ⁽⁴⁾

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 : 235.55 (predicted by ACS/Lab) ⁽¹⁾
 LogPow = 3.95 (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 logPow and BCF predicted values a low 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
- Chemical Safety Assessment (CSA) attached

	X
	X

SECTION 16 OTHER INFORMATION

Revisions:

- **Revision n. 05** dated October 2012 (regarding all sections in according to Regulation no. 453/2010).

Bibliographic sources:

- (1) Chempider data base, search for CAS no. 302-22-7 (lutoral)
- (2) ChemIDplus Lite data base, search for CAS no. 302-22-7
- (3) CHLORMADINONE ACETATE - National Library of Medicine CCRIS Database
- (4) IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS, Volume 72 Hormonal contraception and post-menopausal hormonal therapy (1999)
- (5) RTECS NUMBER-TU3750000-Chemical Toxicity Database

Acronyms

- ACGIH: American Conference of Governmental Industrial Hygienists
- ADR: Agreement concerning the carriage of dangerous goods by Road
- BCF: Bioaccumulative factor
- BEI : Biological Exposure Indices (Indici di esposizione biologica)
- CAS: Chemical Abstract Service (division of the American Chemical Society)
- CLP: Classification, Labelling and Packaging
- CMR: Carcinogens, Mutagens, Toxic for 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

- H341: Suspected of causing genetic defects
H351: Suspected of causing cancer
H360FD: May damage fertility or the unborn child

List of P statementsPrevention**P201****Obtain special instructions before use.****P202****Do not handle until all safety precautions have been 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***R68:****Possible risk of irreversible effects****R40:****Limited evidence of a carcinogenic effect.****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**DISCLAIMER**

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