DROSPIRENONE

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:	DROSPIRENONE
Other names (if available): Name in Annex VI-CLP: Name reported in the inventory of harmonized classification and labelling:	1,2-Diydrospirorenone unlisted not available
CAS number	67392-87-4
REACH registration number	Exempt of registration

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

Relevant use(s)	Synthetic hormone - API (Active Pharmaceutical Ingredient)
Uses advised against	none

1.3. Details of the supplier of the safety data sheet

Manufacturer/Distributor:
Company name: **STERLING S.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
Acute toxicity	**Acute Tox. 4**	**H302**	**Harmful if swallowed**
Carcinogenicity	**Carc. Cat. 2**	**H351**	**Suspected of causing cancer**
Reproductive toxicity	**Repr. Cat. 2**	**H361fd**	**Suspected of damaging fertility. Suspected of damaging the unborn child.**

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

Classification	Risk phrases
Xn; R22	**Harmful if swallowed.**
Carc. Cat. 3; R40	**Limited evidence of a carcinogenic effect.**
Repr. Cat. 3; R62, R63	**Possible risk of impaired fertility.** **Possible risk of harm to the unborn child.**

Main adverse effects

Physico-chemical effects — No adverse effects known.

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

Environmental effects — May be harmful to aquatic life with long lasting effects.

See also sections from 9 to 12

2.2 Label elements

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

Pictograms			
Signal Word	Warning		
Hazard indication (H))[1]	H302	H351	H361fd
Safety statements (P)[1]	P202, P281 P301 + P312, P308+313		
- Prevention			
- Reaction			

- *Storage*	P405
- *Disposal*	P501

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

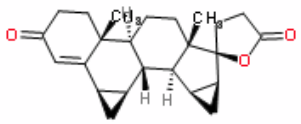
2.3 Other hazards (which do not results in the classification)

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

- Health hazards: May be irritant or sensitizing.
- Environmental hazards: unknown.
- Physico-chemical hazards: none
- Specific effects: unknown

SECTION 3
COMPOSITION/INFORMATION ON INGREDIENTS

Description: active pharmaceutical ingredient - progestins

Name of the component	Drospirenone
Concentration	Pure substance
Structural formula	$C_{24}H_{30}O_3$
Chemical formula	
Molecular weight	366.54 g/mol
Substance with Community OEL	No
CAS name	Spiro[17H-dicyclopropa[6,7:15,16]cyclopenta[a]phenanthrene-17,2'(5'H)-furan]-3,5'(2H)-dione, 1,3',4',6,7,8,9,10,11,12,13,14,15,16,20,21-hexadecahydro-10,13-dimethyl-, [6R-(6α,7α,8β,9α,10β,13β,14α,15α,16α,17b
CAS number	67392-87-4
IUPAC name	(6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11,12,13,14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17H-dicyclopropa-6,715,16]cyclopenta[a]phenanthrene-17,2'(5H)-furan]-3,5'(2H)-dione)
EC number	266-679-2
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 and shown it the container/label.
- *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*	Possible eye, skin, gastrointestinal and/or respiratory tract irritation
- Delayed effects:	Possible hypersensitization, headache, dizziness, depression, changes in menstrual cycle, jaundice, hepatitis, porphyria, blood clots, and cancer. Suspected of damaging fertility and the unborn child.

4.3 Indication of any immediate medical attention and special treatment needed

- *Medical monitoring:*	In case of ingestion and prolonged exposure.
- *Antidotes, if known*	unknown
- *Contraindications*	unknown
- *Immediate treatment at workplace*	not known

SECTION 5
FIREFIGHTING MEASURES

5.1 Extinguishing media

- *Suitable estinguishing media*	Carbon Dioxide (CO_2), foam, dry powder, water spray jet.
- *Unsuitable estinguishing media*	not known

5.2 Special hazards arising from the substance

- *Hazardous combustion products*	May generate toxic fumes of carbon monoxide, carbon dioxide..
- *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 temparature
- *Ventilation requirements*	Use in a well ventilated place at room temperature (not more than 25 °C)
- *Containers*	Keep containers tightly closed and correctly labeled
- *Specific design of storage rooms*	Not requested on the base of the classification
- *Quantity limits for storage*	Not requested on the base of the classification
- *Packaging compatibilities*	See also section 10.5

7.3. Specific end use(s)

- Recommendation for specific final use(s): Active Pharmaceutical Principle

	YES	NO
- Exposure scenario attached		X
- Chemical Safety Assessment (CSA) attached		X
- Industry or sector specific guidance available and attached		X

SECTION 8
EXPOSURE CONTROLS/PERSONAL PROTECTION

8.1. Control parameters

- National/European Occupational Exposure Limits	unknow
- Other National/European Occupational Exposure Limits	unknow
- Recommended monitoring procedures	The measurement of substances in the workplace must be carried out with standardized methods (eg EN 689:1997: Workplace atmospheres - Guide for assessment of exposure by inhalation to chemical agents for comparison with limit values and measurement strategy; UNI EN 482:2006: atmospheres in the workplace - General requirements for the provision of procedures for the measurement of chemical agents) or, failing that, with appropriate methods.
- DNEL values (components)	unknow
- PNEC values (components)	unknow

8.2. Exposure controls

	SI	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.
d) Thermal hazards	Not foreseen in the standard use. Assess possible Personal Protection Equipment on the basis of specific uses of the substance.

8.2.3 Environmental exposure controls

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

SECTION 9
PHYSICAL AND CHEMICAL PROPERTIES

9.1. Information on basic physical and chemical properties

Appearance:	White or whitish solid (crystallin powder)
Odor:	Odourless
Odour threshold:	-
pH:	Data not available in the literature search carried out
Melting point/freezing point:	199 - 200 °C
Boiling point:	552.2 °C at 760 mmHg (predicted) (1)
Flash point:	241.6 °C (predicted) (1)
Auto-ignition temperature:	Data not available in the literature search carried out
Surface tension:	51.2 dyne/cm (predicted) (1)
Density:	1.26 g/cm^3 (predicted) (1)
Vapour pressure:	3.07E-12 mmHg at 25°C (predicted) (1)
Water solubility:	Slightly soluble
Organic solvent solubility:	Soluble in ethanol, slightly soluble in dichloromethane
Partition coefficient Octonol/water (Log Kow):	4.71 (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

Data not available in the literature search carried out

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	SI
- 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 carbon monoxide, carbon dioxide.

SECTION 11
INFORMATION ON TOXICOLOGICAL EFFECTS

	SI	NO
- **Exposure routes:**		
- Inhalation:	X	
- Ingestion:	X	
- Skin contact:	X	

- Eye contact:	X	

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

- Inhalation:	May be irritant.
- Ingestion:	Harmful if swallowed
- Skin contact:	May be irritant or sensitizer.
- Eye contact:	May be irritant.

-Toxico-kinetics information (ADME=Adsorption,**D**istribution,**M**etabolism,**E**xcretion**):** [2]

Adsorption: The absolute bioavailability of drospirenone (DRSP) from a single entity tablet is about 76%. Serum concentrations of reached peak levels within 1-2 hours after administration. The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1-10 mg.

Distribution: The apparent volume of distribution of DRSP is approximately 4 L/kg. DRSP does not bind to sex hormone binding globulin (SHBG) or corticosteroid binding globulin (CBG) but binds about 97% to other serum proteins. Multiple dosing over 3 cycles resulted in no change in the free fraction (as measured at trough levels).

Metabolism: The two main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydrodrospirenone-3-sulfate. These metabolites were shown not to be pharmacologically active. In in vitro studies with human liver microsomes, DRSP was metabolized only to a minor extent mainly by Cytochrome P450 3A4 (CYP3A4).

Excretion: DRSP serum levels are characterized by a terminal disposition phase half-life of approximately 30 hours after both single and multiple dose regimens. Excretion of DRSP was nearly complete after ten days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38-47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17-20% of the metabolites were excreted as glucuronides and sulfates.

- Acute toxicity effects:

- Oral: [3]	LD_{50} (rat) = 500 - 1250 mg/kg
	LD_{50} (mouse) = 500 - 2500 mg/kg
- Dermal:	Data not available in the literature search carried out
- Inhalation:	Data not available in the literature search carried out
- Other effects:	-
RTECS no.	**WH1299000**

- 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**:

Drospirenone was not mutagenic in a number of in vitro (Ames/Salmonella, Chinese Hamster Lung gene mutation and chromosomal damage in human lymphocytes) and in vivo (mouse micronucleus) genotoxicity tests. Drospirenone increased unscheduled DNA synthesis in rat hepatocytes and formed adducts with rodent liver DNA but not with human liver DNA. [2]

- **Carcinogenicity**:

In a 24 month oral carcinogenicity study in mice, there was an increase in carcinomas of the harderian gland in the group that received 10 mg/kg/day dose of drospirenone. In a similar study in rats given 10 mg/kg/day drospirenone, there was an increased

incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas. [2]
Drospirenone is a progestin, hormonal contraceptive.
Progestins are considered by IARC to be possibly carcinogenic to humans (Group 2B). There is inadequate evidence in humans for the carcinogenicity, but there is sufficient evidence in experimental animals for the carcinogenicity of progestogen-only contraceptives .
- **Reproductive toxicity**:
Estrogens and progestins should not be used during pregnancy A teratology study in pregnant rats given drospirenone orally at doses of 5, 15 and 45 mg/kg/day resulted in an increased number of fetuses with delayed ossification of bones of the feet in the two higher doses. A similar study in rabbits dosed orally with 1, 30 and 100 mg/kg/day drospirenone resulted in an increase in fetal loss and retardation of fetal development (delayed ossification of small bones, multiple fusions of ribs) at the high dose only. When drospirenone was administered with ethinyl estradiol (100:1) during late pregnancy (the period of genital development) at doses of 5, 15 and 45 mg/kg, there was a dose dependent increase in feminization of male rat fetuses. In a study in 36 cynomolgous monkeys, no teratogenic or feminization effects were observed with orally administered drospirenone and ethinyl estradiol (100:1) at doses up to 10 mg/kg/day drospirenone. [2]

- 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:
Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. [2]

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 : 147.18 (predicted by ACS/Lab) [1]
LogPow = 4.71 [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		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 Drospirenone.

(2) DailyMed, Current Medication Information - YAZ (drospirenone and ethinyl estradiol) kit

(3) PRODUCT MONOGRAPH PrYASMIN® 21 PrYASMIN® 28, 2007, Bayer Inc.

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

H302	**Harmful if swallowed**
H351	**Suspected of causing cancer**
H361fd	**Suspected of damaging fertility. Suspected of damaging the unborn child.**

List of P statements

Prevention

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.**
P301 + P312	**IF SWALLOWED: Call a POISON CENTER or doctor/physician if you feel unwell.**
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	
R22	Harmful if swallowed.
R40	Limited evidence of a carcinogenic effect.
R62	Possible risk of impaired fertility.
R63	Possible risk of 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

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