Bayer HealthCare
Bayer Schering Pharma

SAFETY DATA SHEET (EC) 1907/2006

NORETHISTERONE ACETATE (NORETHINDRONE ACETATE)

Version: 8.0 - 2008.12.14

1. Identification of the substance/preparation and of the company/undertaking

1.1	Trade name:	NORETHISTERONE ACETATE (NORETHINDRONE ACETATE)
1.2	Use:	pharmaceutical drug substance
1.3	Company:	Bayer Schering Pharma AG 13342 Berlin, Germany Telephone: +49 (0) 202 36 7738 E-mail: msds@bayerhealthcare.com
1.4	Emergency telephone number:	Sicherheitszentrale Bayer Telephone: +49 (0) 214 30 99300

2. Hazards identification

2.1

R60	May impair fertility.
R61	May cause harm to the unborn child.
R40	Limited evidence of a carcinogenic effect.
R50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
R64	May cause harm to breastfed babies.

2.2 May cause dust explosions in fine crystalline form.

3. Composition/information on ingredients

Chemical characterization

17beta-Acetoxy-17alpha-ethynyl-4-estren-3-one

Formula:	C22 H28 O3
CAS-No.:	51-98-9
EC-No.:	200-131-5

4. First-aid measures

General advice:	Take off contaminated clothing and shoes immediately. Call a physician immediately.

Skin contact:	In case of skin contact with powders or solution immediately rinse the areas affected continuously with water and then wash with soap and water. Do NOT use solvents or thinners.
Eye contact:	Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes.
Ingestion:	Rinse mouth.

Notes to physician

Risks:	Liver injury may occur.

5. Fire-fighting measures

5.1	Suitable extinguishing media:	Water spray jet foam dry powder carbon dioxide (CO2)
	Unsuitable extinguishing agents:	high volume water jet
5.2	Thermal decomposition:	carbon dioxide (CO2) carbon monoxide
5.3	Special protective equipment for fire-fighters:	In the event of fire, wear self-contained breathing apparatus.

6. Accidental release measures

Methods for cleaning up:	Use mechanical handling equipment. Avoid dust formation. Pack separately and send back to manufacturer. Flush with plenty of water. Dispose of wastewater according to paragraph 13.
Additional advice:	No conditions to be specially mentioned.

7. Handling and storage

7.1 Handling

Hygiene measures:	Wash hands and face before breaks and immediately after handling the product. Use protective skin cream before handling the product. Take off contaminated clothing and shoes immediately. Smoking, eating and drinking should be prohibited in the application area.
Advice on safe handling:	Avoid contact with skin, eyes and clothing. Measures must be taken to prevent dust explosion when processing in fine crystalline form.

7.2 Storage

Requirements for storage areas and containers:	Protect from light. Keep container tightly closed in a dry and well-ventilated place. Keep away from heat.

8. Exposure controls/personal protection

8.1 Exposure limit(s)

Control parameters	Basis
0,012 mg/m3	SOEL (Schering Occupational Exposure Limit)

8.2 Personal protective equipment

Respiratory protection:	respirator with P3 filter
Eye protection:	safety glasses with side-shields
Hand protection:	During the handling of the substance according to the intended use protection gloves from nitrile rubber have been proved. During the handling of pure solid substances or powder mixtures a permeation of the rubber material is not to be expected. In case of doubt, especially during handling of the substance together with organic solvents, the stability of the protection gloves has to be clarified with the manufacturer.
Skin and body protection:	Choose body protection according to the amount and concentration of the dangerous substance at the work place.

9. Physical and chemical properties

9.1	Form:	crystalline
9.2	Colour:	off-white
9.3	Odour:	odourless
9.4	Change in physical state	
	Melting point/range :	158,0 - 164,0 °C
9.5	Density / Bulk density	
		no data available
9.6	Vapour pressure:	< 0,001 Pa at 25 °C
9.7	Viscosity	
		no data available
9.8	Solubility / Miscibility	
	Water solubility:	4,4 mg/l at 20 °C
9.9	log Pow:	3,67
9.10	pH:	no data available
9.11	Flash point:	no data available
9.12	Ignition temperature:	no data available
9.13	Explosion limits	
		no data available
9.14	Dust explosion class:	3 (2 µm)
9.15	Minimum ignition energy:	< 3 mJ (10 µm)
9.16	Hygroscopicity:	no data available

10. Stability and reactivity

10.1	Conditions to avoid:	no data available
10.2	Materials to avoid:	no data available

10.3 Hazardous decomposition products

Thermal decomposition:	carbon dioxide (CO_2) carbon monoxide
Hydrolytic decomposition:	none reasonably foreseeable

11. Toxicological information

Acute oral toxicity:	LD50 rat Dose: > 2.800 mg/kg Remarks: Solution in sesame oil
Acute oral toxicity:	LD50 mouse Dose: 1.400 mg/kg
Acute oral toxicity:	LD50 rat Dose: 4.000 mg/kg Remarks: Microcrystalline suspension
Cancerogenic:	3
Toxic to reproduction (RE) :	2
Toxic to reproduction (RF) :	1

Toxicological assessment

Mode of action:

On oral administration of the norethisterone acetate ester and intramuscular administration of the norethisterone enanthate ester, norethisterone is released by ester cleavage and this is the actual active substance. Norethisterone is an orally very potent progestogen. The substance has been used for many years in the treatment of menstrual disorders and endometriosis as well as for hormonal contraception.

Acute toxicity:

Because of the low acute toxicity of norethisterone acetate as demonstrated in animal experiments no risk of toxicity is to be expected after a single dose.

Effects following repeated contact:

A number of studies involving intramuscular administration of norethisterone enanthate can be called upon in assessment of long-term tolerance and/or tumorigenicity. These studies were conducted in mice, rats, dogs and monkeys over a treatment period of up to a maximum of 10 years (monkeys). Here, in monkeys for example, no effects indicative of an organotoxic effect were observed in 10 years even after administration of the largest dose tested (50 times the human doses on the basis of the body weight). On the other hand, typical species-specific progestogenic effects were observed in all studies (e.g. endometrial hyperplasia in dogs). Adverse effects such as headache, gastrointestinal disorders, increased weight and disturbed liver function which are familiar with progestogens in humans may also reckoned with after repeated oral, inhalatory or skin contact with norethisterone acetate.

Mutagenic effect:

Neither in vitro nor in vivo genotoxicity testing with norethisterone, norethisterone acetate and norethisterone enanthate has provided any indication of a genotoxic or mutagenic potential.

Tumorigenic effect:

Tumorigenicity studies were carried out on norethisterone enanthate with rodents, dogs and monkeys. On the basis of the results obtained, norethisterone acetate is not expected to have any tumorigenic potential relevant to humans in the doses intended for its therapeutic use (up to 20 mg/woman/day p.o.). However, in handling norethisterone acetate, it should be borne in mind that sex steroids can stimulate the growth of certain hormone dependent tissues and tumors.

Reproduction toxicology:

In humans a dose of appr. 350 µg norethisterone/woman/day (administered alone without estrogens) is an effective dose for oral contraception. Thus, reversible fertility disorders are to be reckoned with in women after administration such doses. Embryotoxicity studies were carried out with the esters, norethisterone acetate and norethisterone enanthate, in mice, rats, rabbits and monkeys. There was no indication of a teratogenic potential with the exception of signs of masculinization in female monkey fetuses after high doses of norethisterone acetate (from 60 mg/kg/day), which were sufficient to cause embryo-lethal effects. Treatment of pregnant rats during the sensitive phase of differentiation of the fetal sex organs also led to masculinization of female fetuses following relatively high subcutaneous doses (>1 mg/kg BW/day). Signs of masculinization of female embryos have been also described in humans after treatment with high doses of norethisterone or norethisterone acetate (10 to 40 mg/woman/day) during the sensitive phase of fetal sexual differentiation (from day 45 following conception). On the basis of available data, 10 mg/woman/day p.o. can be taken as the threshold dose for the occurence of these anomalies in humans. The production of milk can be inhibited in nursing mothers. At uptake by nursing mothers, norethisterone acetate may pass into the milk and affect the development of the child.

12. Ecological information

Ecotoxicity effects

Toxicity to algae:	static test EC50 Species: desmodesmus subspicatus Dose: 0,5 - 0,7 mg/l Exposure time: 72 h Method: OECD Test Guideline 201, Paris, 1981

13. Disposal considerations

Product:	Dissolve or suspend cautiously in a flammable solvent and incinerate in a combustion plant for chemical waste.
Waste code:	07 05 08

14. Transport information

14.1 Land transport - ADR

Class:	9
Risk No.:	90
UN-No:	3077
ADR/RID-Labels:	9
Packaging group:	III
Description of the goods:	ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S. (NORETHISTERONE ACETATE)

14.2 Sea transport - IMDG

IMDG-Code:	9
EmS:	
UN-No:	3077
Packaging group:	III
Marine pollutant:	no data available
Description of the goods:	ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S. (NORETHISTERONE ACETATE)

14.3 Air transport - ICAO/IATA

IATA-DGR:	9
UN/ID No.:	3077
Packaging group:	III
Description of the goods:	ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S. (NORETHISTERONE ACETATE)

15. Regulatory information

15.1 Labelling according to EEC Directive

Symbol(s):	T	Toxic
	N	Dangerous for the environment
R-phrase(s):	R60	May impair fertility.
	R61	May cause harm to the unborn child.
	R40	Limited evidence of a carcinogenic effect.
	R50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
	R64	May cause harm to breastfed babies.

S-phrase(s):	S53	Avoid exposure - obtain special instructions before use.
	S45	In case of accident or if you feel unwell, seek medical advice immediately (show label where possible).
	S60	This material and its container must be disposed of as hazardous waste.

15.2 National legislation

Germany

Water contaminating class (Germany):	3 Self classification VWVWS 5/99
German storage class:	6.1A - Combustible substances, toxic
Pharmaceutical substance class:	G3 Determination from doses for humans (SOEL)

16. Other information

Further information

Changes made since the last version are highlighted in the margin. This version replaces the previous version.
The above information is based on our present knowledge and experience and is intended as a description of the safety requirements for our product. It is not intended as an assurance that the product in question has certain properties.