


## Safety Data Sheet



Bristol-Myers Squibb Company

<b>1. PRODUCT AND COMPANY IDENTIFICATION</b>	
<i>Product Information</i>	
Product name	Hydrea Capsules, 500 mg.
Version	1.0, 17.05.2012
Jurisdiction	This Safety Data Sheet was prepared for the European Union (EU).
Synonyms	SQ 1089; Hydrea
Intended Uses	This material is a finished drug product for patient use. It is used in the treatment of cancer. It is used to treat certain blood disorders.
Registration Number:	Not available
<i>Company/Undertaking Identification</i>	
Address	<b>Swords Laboratories</b> Swords Laboratories, Watery Lane Swords Ireland 353-1813-9456
E-mail:	MG-GBS-MSDS-Request@bms.com
Emergency Phone Number	In the EU, call 353-1813-9456.

<b>2. HAZARDS IDENTIFICATION</b>	
<i>Emergency Overview</i>	
<b>EU Globally Harmonized System (GHS)</b>	
Classification	Serious Eye Damage/Eye Irritation - Category 2 Germ Cell Mutagenicity - Category 2 Toxic To Reproduction - Male Reproductive Toxicity - Category 1B Toxic To Reproduction - Developmental Toxicity - Category 1B Effects on or via lactation Specific Target Organ Systemic Toxicity (Repeated Exposure) - Category 1
Symbol	
Signal Word	Danger
Hazard Statements	Causes serious eye irritation. Suspected of causing genetic defects. May damage fertility. (male reproductive toxicity) . May damage the unborn child. (developmental toxicity) . May cause harm to breast-fed children. Causes damage to organs (bone marrow, male reproductive organs, gastrointestinal tract, liver, skin, pancreas, kidney, lungs, peripheral nervous system, central nervous system, cardiovascular system) through prolonged or repeated exposure.
Precautionary	Do not breathe dust/fume/gas/mist/vapours/spray.

**2. HAZARDS IDENTIFICATION**

Statements      Use personal protective equipment as required.  
                       Wash thoroughly after handling.  
                       Do not eat, drink or smoke when using this product.  
                       Obtain special instructions before use.  
                       Avoid contact during pregnancy/while nursing.

**EU Directive 1999/45/EC**

Regulatory Status

BULK                      Classified as a dangerous preparation.MATERIALDRUG                      Not regulatedPRODUCT**3. COMPOSITION/INFORMATION ON INGREDIENTS**

Components	Concentration	CAS-No.	EINECS/ELINCS/ Registration Number	Symbol(s)	R-phrase(s)
<i>Hazardous components</i>					
Hydroxyurea	83.33 %	127-07-1	204-821-7	T	R48/25, R60, R61, R64, R68
Citric Acid Anhydrous	< 5 %	77-92-9	201-069-1	--	--
Magnesium Stearate	< 5 %	557-04-0	209-150-3	--	--
<i>Other ingredients</i>					
Non-Hazardous Ingredients	< 10 %	Not available	--	--	--
See section 16 for R-Phrase text.					

**4. FIRST AID MEASURES**

Eye contact	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. If eye irritation persists, get medical advice/attention.
Skin contact	Take off contaminated clothing and shoes immediately. Wash off immediately with plenty of water for at least 15 minutes. If skin irritation persists, call a physician.
Inhalation	Move to fresh air. Oxygen or artificial respiration if needed. If exposed or concerned: Get medical attention/advice.
Ingestion	Do NOT induce vomiting. Never give anything by mouth to an unconscious person. If exposed or concerned: Get medical attention/advice.
Notes to Physician	This product has been reported to interact with the following medications: cytotoxic and cytostatic medicines, Didanosine, Stavudine. Refer to Section 11.
Medical Surveillance	A pre-placement physical examination and history for employees with potential exposure to this compound is recommended. Baseline testing would include: a complete blood count with differential, a blood test for kidney function, a urine analysis, a blood test for liver function, lung function test. Based on opportunity for exposure and duration of exposure a periodic follow-up examination may be considered. This exam should be overseen by a physician thoroughly knowledgeable about both the toxicity of this compound and the extent of work place exposure. It is recommended that the content be similar to the pre-placement exam.  Employees who are pregnant, are breast-feeding, or who are concerned with other reproductive issues should be encouraged to consult with the occupational health physician monitoring worker's health.

**4. FIRST AID MEASURES**

Other information	Precautionary risk management may be different from the exposure categories in the annex.
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**5. FIRE-FIGHTING MEASURES**

Flammable Properties	Not available
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Extinguishing Media	Suitable extinguishing media: Dry chemical, Water spray, Foam Unsuitable extinguishing media: Do NOT use water jet.
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Protection of Firefighters	Specific hazards: Not available Protective equipment: Use personal protective equipment. In the event of fire, wear self-contained breathing apparatus. Hazardous Combustion Products: carbon oxides (COx), nitrogen oxides (NOx)
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Other information	Decontaminate protective clothing and equipment before reuse.
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**6. ACCIDENTAL RELEASE MEASURES**

Personal precautions	Refer to protective measures listed in sections 7 and 8. Use personal protective equipment. Examples include tightly fitting safety goggles, lab coat and impervious gloves. Wear respiratory protection. Depending on the nature of the spill (quantity and extent of spill) additional protective clothing and equipment such as a self-contained breathing apparatus may be needed.
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Environmental precautions	Prevent release to drains and waterways. Prevent release to the environment.
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Containment Methods	Wet down any dust to prevent generation of aerosols, if appropriate. Cover with suitable material.
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Cleanup Methods	Contain and collect spillage and place in container for disposal according to local regulations (see Section 13). Handle waste materials, including gloves, protective clothing, contaminated spill cleanup material, etc., as appropriate for chemically and pharmacologically similar materials.
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**7. HANDLING AND STORAGE**

Handling Precautions	Avoid exposure - obtain special instructions before use. Avoid formation of dust and aerosols. Keep away from heat and sources of ignition. Prevent release to drains and waterways.
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Container Requirements	Store in sturdy containers appropriate to maintain the integrity of this material for its intended use. Keep tightly closed.
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Storage Conditions	Store at room temperature. Protect against light. Keep away from heat, sparks and flames.
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Specific use(s)	Refer to Section 1
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**8. EXPOSURE CONTROLS / PERSONAL PROTECTION****COMPONENT EXPOSURE LIMIT(S)**

Exposure limit(s)	Company Guideline	ACGIH	Germany OEL	UK MEL
Hydroxyurea	100 µg/m <sup>3</sup> TWA	--	--	--
Citric Acid Anhydrous	--	--	--	--

**8. EXPOSURE CONTROLS / PERSONAL PROTECTION**

Magnesium Stearate	--	10 mg/m <sup>3</sup> TWA	--	--
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Magnesium Stearate	Occupational Exposure Limits have been established by: - Belgium - Spain - Ireland - Portugal - Sweden			
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Exposure Control Band	<u>Hydroxyurea</u> 2 -- The established company exposure guideline falls within Exposure Control Band 2 (range 100-1000 µg/m <sup>3</sup> ).			
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Bristol-Myers Squibb Exposure Guidelines Summary	<u>Hydroxyurea</u> Materials require particular care and handling. Adherence to this guideline should protect employees from experiencing the therapeutic and/or adverse effects of this drug.			
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Recommended Industrial Hygiene Monitoring Methods	Contact the Bristol-Myers Squibb AIHA accredited Industrial Hygiene Laboratory at 732-227-6338.			
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**EXPOSURE CONTROLS / PERSONAL PROTECTION FOR MATERIAL AS SUPPLIED**

*This mixture contains material(s) with the exposure limit(s) noted above. The mixture as supplied should be controlled during handling to limit total airborne exposure to the limit noted below or less.*

Exposure Control Band - For Operations Using Material as Supplied	<u>Hydrea Capsules, 500 mg.</u> 2 -- Material is assigned to Exposure Control Band 2 (range 100 - 1000 µg/m <sup>3</sup> ).			
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Engineering Controls and Ventilation	If significant dust is generated, use process enclosures, containment technology, or other engineering controls to keep airborne levels below recommended exposure limit. When handling small quantities in a clinical setting, good room ventilation is desirable. Specific engineering controls should not be needed. When handling broken or crushed tablets or capsules, ensure worker exposure is below the recommended exposure limit.			
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Respiratory protection	Use and selection of respiratory protection is based upon engineering controls in use and potential for aerosol generation. When engineering controls are not sufficient control exposure, wear an approved respirator with NIOSH Class 100 or high efficiency particulate (HEPA) filters or cartridges (EN 140/EN 136) when exposures are up to 10 times the exposure control guideline. Wear a loose-fitting (Tyvek or helmet type) HEPA powered-air purifying respirator (PAPR) (EN 12941) when exposures are 10-25 times the exposure control guideline. Wear a full facepiece negative pressure respirator with Class 100 or HEPA filters (EN 136) when exposures are 25-50 times the exposure control guideline. Wear a tight-fitting, full facepiece HEPA PAPR (EN 12942) when exposures are 50-100 times the exposure control guideline. Wear a hood-shroud HEPA PAPR (EN 12941) or full facepiece supplied air respirator (EN 139) operated in a pressure demand or other positive pressure mode when exposures are 100-1000 times the exposure control guideline.			
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Eye protection	Safety glasses with side-shields are recommended (EN 166). Face shields or chemical safety goggles (EN 166) may be required if splash potential exists or if corrosive materials are present. Note: Choice of eye protection may be influenced by the type of respirator which is selected.			
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Hand protection	Impervious nitrile, rubber and latex gloves are recommended (EN 420, EN 374). If material is handled in solution, the solvent should also be considered when selecting protective clothing material. Please note that employees who are allergic to natural rubber latex should use nitrile gloves.			
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Skin and body protection	Wear a laboratory coat (EN 340) when handling quantities up to 1 kilograms. For quantities over 1 kilogram, wear laboratory coat (EN 340) or coverall of low permeability (EN 1149-1). For manufacturing operations, wear coverall of low permeability (EN 1149-1).			
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**8. EXPOSURE CONTROLS / PERSONAL PROTECTION**

Hygiene	Wash hands and face before breaks and immediately after handling the product.
Environmental exposure controls	Prevent release to drains and waterways.

**9. PHYSICAL AND CHEMICAL PROPERTIES***General Information**Appearance*

Physical State	solid
Color	opaque green
Form	capsule

*Odour*

Odour	Not available
Odor Threshold	Not available

pH	Not available
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*Other information*

Bulk density	Not available
Evaporation rate	Not available
Molecular formula	Not applicable
Hydrolysis/Photolysis	Not available
Hygroscopicity	Not available
Molecular Weight	Not applicable
Log Octanol/Water Partition Coeff [log Kow]	Not available
Surface Tension	Not available
pKa	Not available
Particle Size	Not available
Solubility, Water	soluble
Specific Gravity/ Relative density	Not available
Viscosity, dynamic	Not available
Viscosity, kinematic	Not available
% Volatile	Not available

*Thermal/Stability properties*

Autoignition temperature	Not available
Boiling Point	Not available
Thermal decomposition	Not available
Explosive Limits, LEL	Not available
Explosive limits, UEL	Not available
Explosiveness	Non-explosive based on chemical structure.
Flammability	Not available
Flash point	Not available
Melting Point	145 - 146 °C
Oxidizing Potential	Non-oxidizer based on chemical structure.

*Vapor Properties*

Vapor Density	Not available
Vapor Pressure	Not available
Saturated Vapor Concentration	Not available

**10. STABILITY AND REACTIVITY***Stability*

Chemical Stability	Stable under normal conditions.
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Conditions to avoid	Not available
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Materials to avoid	Not available
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Hazardous decomposition products	Hazardous decomposition products formed under fire conditions.: carbon oxides (COx), nitrogen oxides (NOx)
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Hazardous reactions	None known.
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*Sensitivity to static discharge/Dust exp.*

Summary Statements	Although material has not been specifically tested, fine dust suspended in air in sufficient concentration and in the presence of an ignition source may pose a potential explosion hazard. Provide appropriate bonding and grounding protection to control static charge. Powder handling equipment such as dust collectors, dryers, and mills may require additional protective measures (e.g. explosion venting, inerting, etc.).
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**11. TOXICOLOGICAL INFORMATION**

Routes of Entry	Ingestion, Inhalation, Eye contact, Skin contact
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Eye Irritation	<u>Hydroxyurea</u> Mildly irritating to eyes.
	<u>Citric Acid Anhydrous</u> Severely irritating to eyes.
	<u>Magnesium Stearate</u> May cause mechanical irritation.

Skin Irritation	<u>Hydroxyurea</u> Mildly irritating to skin
	<u>Citric Acid Anhydrous</u> Mildly and/or transiently irritating to skin.
	<u>Magnesium Stearate</u> May cause mechanical irritation.

Respiratory Irritation	<u>Citric Acid Anhydrous</u> Dust may cause irritation.
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**11. TOXICOLOGICAL INFORMATION**

Sensitization	<u>Hydroxyurea</u> Not a dermal sensitizer
Acute Toxicity Study	<b>Acute Oral</b> <u>Hydroxyurea</u> LD50 (Rat): 5,760 mg/kg LD50 (Mouse): 7,330 mg/kg  <u>Citric Acid Anhydrous</u> LD50 (Rat): 3,000 mg/kg LD50 (Mouse): 5,040 mg/kg LDlo (rabbit): 7,000 mg/kg
Repeated Dose Toxicity	<u>Hydroxyurea</u> 1 - 12 Weeks Oral (1/week - daily) Rat, dog, monkey Study : LOAEL = 50 mg/kg (males and females). High dose effects include: decreased weight gain, anorexia, depression, hypoactivity, vomiting, decreased white blood cell count, decreased red blood cell count, increase in heart rate, mortality. High dose microscopic effects include: lungs, bone marrow, spleen, liver, testes, kidney, bladder, gallbladder, intestine.  <u>Magnesium Stearate</u> 3 months Dietary Rat Study : NOAEL = 2,500 mg/kg Low dose effects include: decreased weight gain, liver effects, kidney stones.
Genetic Toxicity	<u>Hydroxyurea</u> <b>in vitro</b> Ames reverse-mutation assay -- positive Chromosome aberrations assay -- positive DNA repair assay -- positive Yeast reverse-mutation assay -- positive mouse lymphoma cells -- positive <b>in vivo</b> micronucleus assay (Mouse) -- positive Mammalian sister chromatid exchange assay (Rodents) -- positive <b>Mutagenicity Assessment</b> Several studies were conducted. This material was positive in a battery of in vivo and in vitro genotoxicity assays.  <u>Citric Acid Anhydrous</u> <b>in vitro</b> Ames reverse-mutation assay -- negative Yeast reverse-mutation assay -- negative <b>in vivo</b> 5 D dominant lethal assay (Rat) -- negative <b>Mutagenicity Assessment</b> This material was negative in a battery of in vivo and in vitro genotoxicity assays.

**11. TOXICOLOGICAL INFORMATION****Carcinogenicity**Hydroxyurea**Carcinogenicity Assessment**

There is inadequate evidence for carcinogenicity in animals. Some secondary cancers developed in persons with other cancers who were treated with this drug, either alone or in combination with other anticancer drugs. It is not known whether these were a result of the treatment with this drug, with one of the other drugs, or a result of progression of the underlying disease. Not classifiable as to its carcinogenicity to humans.

Citric Acid Anhydrous

2 Years Dietary (daily) Rat Study : No treatment-related tumors were observed.

Magnesium Stearate**Carcinogenicity Assessment**

Not classifiable as to its carcinogenicity to humans.

<b>Carcinogenicity</b>	<b>ACGIH</b>	<b>IARC</b>	<b>NTP</b>
Hydroxyurea	--	3	--
Citric Acid Anhydrous	--	--	--
Magnesium Stearate	A4	--	--

**Reproductive Toxicity**Hydroxyurea**Assessment Reproductive Toxicity**

Several studies were conducted. Compound may cause injury to male reproductive organs. See also "Repeated Dose Toxicity" for information on reproductive effects. This compound and/or its metabolites may be excreted into the milk.

Citric Acid Anhydrous**Assessment Reproductive Toxicity**

Data indicate that this compound is not a reproductive hazard.

**Developmental Toxicity**Hydroxyurea**Developmental Toxicity Assessment**

Several developmental studies were conducted. Effects include: malformations fetal death developmental delay Selective developmental toxicant

Citric Acid Anhydrous**Developmental Toxicity Assessment**

Did not show teratogenic effects in animal experiments.



**11. TOXICOLOGICAL INFORMATION**

Human experience	<p><b>Experiences with Human Exposure</b></p> <p><u>Hydroxyurea</u> General effects therapeutic use low exposure - acute effects include: headache, fever, chills, dizziness, confusion, hallucinations, seizure disorders, drowsiness, nausea, vomiting, inflammation of the mouth, anorexia, constipation, diarrhoea, shortness of breath, labored respiration, lung inflammation, cough, itching, rash, alopecia, skin lesions, gangrene, nail changes, eye effects, painful urination. low exposure - delayed effect include: bone marrow suppression, pancreas effects, pulmonary fibrosis, autoimmune symptoms, second cancers, peripheral nervous system toxicity, impaired spermatogenesis.</p>
Target Organs	<p><u>Hydroxyurea</u> bone marrow, male reproductive organs, gastrointestinal tract, liver, skin, pancreas, kidney, lungs, peripheral nervous system</p> <p><u>Magnesium Stearate</u> central nervous system, cardiovascular system</p>
Symptoms	<p><u>Hydroxyurea</u> See "Human Experience".</p> <p><u>Citric Acid Anhydrous</u> labored respiration, noisy respiration, chest pain, breathing difficulties, shortness of breath, lung inflammation, redness and swelling of eyes, gastrointestinal disturbance, convulsions, tooth effects</p> <p><u>Magnesium Stearate</u> redness and swelling of eyes, skin flushing, nausea, vomiting, diarrhoea, dehydration, lowered blood pressure, cardiac irregularities, CNS depression, respiratory disorder, paralysis</p>
Pharmacokinetics/ Toxicokinetics	<p><u>Hydroxyurea</u> Absorption: Not available Distribution: Not available Metabolism: Not available Elimination: Half-life = 3 - 4 Hour(s) (Human).</p>
Other Toxicity Information	Not available

**12. ECOLOGICAL INFORMATION****Ecotoxicity effects****Acute Toxicity to Fish**Citric Acid Anhydrous

LC50 (Lepomis macrochirus, 96 H) : 1,516 mg/l.

LC50 (Leuciscus idus (Golden orfe), 96 H) : 440 mg/l.

**Acute Toxicity to Aquatic Invertebrates**Hydroxyurea

EC50 (Daphnia magna (Water flea), 48 H) : &gt; 100 mg/l.

NOEC (Daphnia magna (Water flea), 48 H) : &gt; 100 mg/l.

Citric Acid Anhydrous

EC50 (Daphnia magna (Water flea), 72 H) : 120 mg/l.

**Aquatic toxicity**

Experimental data indicate low potential for acute harm to aquatic invertebrates

**Mobility**

Not available

**Persistence and degradability****Biodegradation**Hydroxyurea

Ultimate aerobic biodegradation (28 D) : 5 % Not readily biodegradable.

Citric Acid Anhydrous

Inherent biodegradation (48 H) : 98 % ; Readily biodegradable - rapidly biodegrades in the environment

**Summary Statements****Aquatic toxicity**Hydrea Capsules, 500 mg.

Experimental data indicate low potential for acute harm to aquatic invertebrates

**PBT and vPvB Assessment:**

Not available

**13. DISPOSAL CONSIDERATIONS****Advice On Disposal And Packaging**

Disposal should be in accordance with applicable regional, national and local laws and regulations. Local regulations may be more stringent than regional or national requirements. This information presented only applies to the material as supplied.

**Other information**

Disposal by incineration is recommended.

**14. TRANSPORT INFORMATION**

This material is not a dangerous good for the purpose of transportation.

**15. REGULATORY INFORMATION**

EINECS/ELIN	Hydroxyurea: 204-821-7
CS/Registration	Citric Acid Anhydrous: 201-069-1
Number	Sodium Phosphate Dibasic, Anhydrous: 231-448-7
	Magnesium Stearate: 209-150-3

**EU Globally Harmonized System (GHS)**

Classification	Serious Eye Damage/Eye Irritation - Category 2
	Germ Cell Mutagenicity - Category 2
	Toxic To Reproduction - Male Reproductive Toxicity - Category 1B
	Toxic To Reproduction - Developmental Toxicity - Category 1B
	Effects on or via lactation

**15. REGULATORY INFORMATION**

Specific Target Organ Systemic Toxicity (Repeated Exposure) - Category 1

Symbol



Signal Word

Danger

Hazard  
Statements

Causes serious eye irritation.  
 Suspected of causing genetic defects.  
 May damage fertility. (male reproductive toxicity) .  
 May damage the unborn child. (developmental toxicity) .  
 May cause harm to breast-fed children.  
 Causes damage to organs (bone marrow, male reproductive organs, gastrointestinal tract, liver, skin, pancreas, kidney, lungs, peripheral nervous system, central nervous system, cardiovascular system) through prolonged or repeated exposure.

Precautionary  
Statements

Do not breathe dust/fume/gas/mist/vapours/spray.  
 Use personal protective equipment as required.  
 Wash thoroughly after handling.  
 Do not eat, drink or smoke when using this product.  
 Obtain special instructions before use.  
 Avoid contact during pregnancy/while nursing.

**EU Directive 1999/45/EC****BULK MATERIAL**

Symbol(s)

T: Toxic

R-phrases(s)

R46: May cause heritable genetic damage.  
 R48/25: Toxic: danger of serious damage to health by prolonged exposure if swallowed.  
 R60: May impair fertility.  
 R61: May cause harm to the unborn child.  
 R64: May cause harm to breastfed babies.  
 R68: Possible risks of irreversible effects.

S-phrases(s)

S22: Do not breathe dust.  
 S36/37/39: Wear suitable protective clothing, gloves and eye/face protection.  
 S38: In case of insufficient ventilation, wear suitable respiratory equipment.  
 S45: In case of accident or if you feel unwell, seek medical advice immediately (show label where possible).  
 S53: Avoid exposure - obtain special instructions before use.  
 S60: This material and its container must be disposed of as hazardous waste.

**DRUG PRODUCT**

Classification

Medicinal products are exempt from classification and labeling requirements under EU Preparations Directive 1999/45/EC.

**UN Globally Harmonized System (GHS)**

Classification

Serious Eye Damage/Eye Irritation - Category 2A  
 Germ Cell Mutagenicity - Category 2  
 Toxic To Reproduction - Male Reproductive Toxicity - Category 1B  
 Toxic To Reproduction - Developmental Toxicity - Category 1B

**15. REGULATORY INFORMATION**

Effects On Or Via Lactation  
Specific Target Organ Systemic Toxicity (Repeated Exposure) - Category 1

Symbol



Signal Word

Danger

Hazard  
Statements

Causes serious eye irritation.  
Suspected of causing genetic defects.  
May damage fertility. (male reproductive toxicity) .  
May damage the unborn child. (developmental toxicity) .  
May cause harm to breast-fed children.  
Causes damage to organs (bone marrow, male reproductive organs, gastrointestinal tract, liver, skin, pancreas, kidney, lungs, peripheral nervous system, central nervous system, cardiovascular system) through prolonged or repeated exposure.

Precautionary  
Statements

Refer to HAZARDS IDENTIFICATION section.

**16. OTHER INFORMATION***Text of R phrases mentioned in Section 3*

R48/25: Toxic: danger of serious damage to health by prolonged exposure if swallowed.  
R60: May impair fertility.  
R61: May cause harm to the unborn child.  
R64: May cause harm to breastfed babies.  
R68: Possible risks of irreversible effects.

*Recommended Restrictions for Use:*

Not available

*MSDS preparation information*

Prepared by Research and Development Environment, Health and Safety 1-732-227-7380  
Prepared on 17.05.2012

This is the first EU Safety Data Sheet issued for this material.

The information contained in this MSDS is believed to be accurate and represents the best information reasonably available at the time of preparation. However, we make no warranty, express or implied, with respect to such information. and we assume no liability from its use.