Bristol-Myers Squibb Company

# Material Safety Data Sheet

| 1. PRODUCT AND COMPANY IDENTIFICATION | |
|---|---|
| *Product Information* | |
| Product name | Hydroxyurea Capsules, For Oral Use |
| Version | 1.1, 05/11/2016 |
| Jurisdiction | This Safety Data Sheet was prepared for the Globally Harmonized System (GHS). |
| Active substance | Hydroxyurea |
| Synonyms | DROXIA® (hydroxyurea) Capsules, 200, 300, and 400 mg; HYDREA® (hydroxyurea) Capsules, 500 mg; SQ 1089; Hydroxyurea |
| 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. |
| *Company/Undertaking Identification* | |
| Address | **Bristol-Myers Squibb Australia Pty Ltd**<br>4 Nexus Court, Mulgrave,<br>Victoria 3170, Australia |
| Emergency Phone Number | CHEMTREC Australia (Sydney): +(61)-290372994 |

| 2. HAZARDS IDENTIFICATION | |
|---|---|
| **UN Globally Harmonized System (GHS)** | |
| Classification | Serious Eye Damage/Eye Irritation - Category 2A<br>Germ Cell Mutagenicity - Category 2<br>Toxic To Reproduction - Male Reproductive Toxicity - Category 1B<br>Toxic To Reproduction - Developmental Toxicity - Category 1B<br>Effects On Or Via Lactation<br>Specific Target Organ Systemic Toxicity (Repeated Exposure) - Category 1 |
| Symbol |  |
| Signal Word | Danger |
| Hazard Statements | Causes serious eye irritation.<br>Suspected of causing genetic defects.<br>May damage fertility (male reproductive toxicity) .<br>May damage the unborn child (developmental toxicity) .<br>May cause harm to breast-fed children.<br>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. |

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## 2. HAZARDS IDENTIFICATION

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|---|---|
| Precautionary Statements | Do not breathe dust.<br>Obtain special instructions before use.<br>Do not handle until all safety precautions have been read and understood.<br>Avoid contact during pregnancy/while nursing.<br>Wash thoroughly after handling.<br>Do not eat, drink or smoke when using this product.<br>Wear protective gloves/clothing and eye/face protection.<br>Use personal protective equipment as required. |

## 3. COMPOSITION/INFORMATION ON INGREDIENTS

| Components | Concentration | CAS-No. |
|---|---|---|
| *Hazardous components* | | |
| Hydroxyurea | 83.33 % | 127-07-1 |
| Citric Acid Anhydrous | <5 % | 77-92-9 |
| Magnesium Stearate | <5 % | 557-04-0 |
| *Other ingredients* | | |
| Non-Hazardous Ingredients | <10 % | Not available |

## 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. Discard contaminated clothing or wash before re-use. If exposed or concerned: Get medical attention/advice. |
| 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 | The need for a pre-placement physical examination and history for employees with potential exposure to this compound is to be evaluated by a physician that is thoroughly knowledgeable about both the toxicity of this compound and the extent of work place exposure. 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.<br><br>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. |

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| *5. FIRE-FIGHTING MEASURES* | |
|---|---|
| Flammable Properties | Not available |
| Extinguishing Media | Suitable extinguishing media: Dry chemical, Water spray, Foam<br><br>Unsuitable extinguishing media: Do NOT use water jet. |
| Protection of Firefighters | Specific hazards: Not available<br>Protective equipment: Use personal protective equipment. In the event of fire, wear self-contained breathing apparatus.<br>Hazardous Combustion Products: carbon oxides (COx), nitrogen oxides (NOx) |
| Other information: | Decontaminate protective clothing and equipment before reuse. |

| *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. |
| Environmental precautions | Prevent release to drains and waterways. Prevent release to the environment. |
| Containment Methods | Wet down any dust to prevent generation of aerosols, if appropriate. Cover with suitable material. |
| 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. |

| *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. |
| Storage Conditions | Store at room temperature. Protect against light. Keep away from heat, sparks and flames. Store locked up. |
| Container Requirements | Store in sturdy containers appropriate to maintain the integrity of this material for its intended use. Keep tightly closed. |

*8. EXPOSURE CONTROLS / PERSONAL PROTECTION*

| Exposure limit(s) | Company Guideline | ACGIH | OSHA | NIOSH |
|---|---|---|---|---|
| Hydroxyurea | 100 µg/m3 TWA | -- | -- | -- |
| Citric Acid Anhydrous | -- | -- | -- | -- |
| Magnesium Stearate | -- | 10 mg/m3 8 hour-TWA | -- | -- |

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| ***8. EXPOSURE CONTROLS / PERSONAL PROTECTION*** | |
|---|---|
| Exposure Control Band | Hydroxyurea<br>***2*** -- The established company exposure guideline falls within Exposure Control Band 2 (range 100-1000 µg/m3). |
| Bristol-Myers Squibb Exposure Guidelines Summary | Hydroxyurea<br>Materials require particular care and handling. Adherence to this guideline should protect employees from experiencing the therapeutic and/or adverse effects of this drug. |
| Recommended Industrial Hygiene Monitoring Methods | Contact the Bristol-Myers Squibb AIHA accredited Industrial Hygiene Laboratory at (USA) 732-227-6338.<br><br>General - The health hazard risk of handling this material is dependent on many factors, including physical form, % API in material being handled, duration and frequency of process task, and effectiveness of controls. If it is necessary to handle this compound outside of engineering controls, an exposure risk assessment should be conducted and procedures documented by a qualified EHS professional. |
| ***EXPOSURE CONTROLS / PERSONAL PROTECTION FOR MATERIAL AS SUPPLIED*** | |
| This formulation contains an active pharmaceutical ingredient (API) with the guideline limit noted above. To keep the API below the recommended guideline, the material as supplied should be controlled during handling to limit total airborne aerosol exposure to: 120 µg/m³. | |
| Engineering Controls and Ventilation | Use process enclosures, containment technology, or other engineering controls to keep airborne levels below recommended exposure limit. When handling quantities up to 150 milligrams, a standard laboratory with general laboratory dilution ventilation (e.g. 6-12 air changes per hour) is appropriate. When handling quantities from 150 milligrams to 1 kilogram, work in a standard laboratory using a fume hood; biological safety cabinet(Class II, all types), approved vented enclosure; specific local exhaust. Quantities exceeding 1 kilogram should be handled in a designated laboratory. A laminar flow/powder containment booth is recommended for handling >1 kilograms of active substance. For manufacturing and pilot plant operations, use semi to closed material transfer systems and containment of open operations. HEPA filtration for recirculation of exhaust is required.<br>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. |
| 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. |
| 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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| ***8. EXPOSURE CONTROLS / PERSONAL PROTECTION*** | |
|---|---|
| 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. |
| 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). |
| Hygiene | Wash hands and face before breaks and immediately after handling the product. |

| ***9. PHYSICAL AND CHEMICAL PROPERTIES*** | |
|---|---|
| *Appearance* | |
| Physical State | solid |
| Color | opaque green opaque pink opaque purple opaque blue-green |
| Form | capsule |
| *Other information* | |
| Molecular Weight | Not applicable |
| Molecular formula | Not applicable |
| Bulk density | Not available |
| Evaporation rate | Not available |
| Hydrolysis/Photolysis | Not available |
| Hygroscopicity | Not available |
| Log Octanol/Water Partition Coefficient [log Kow] | |
| Surface Tension | Not available |
| Odor | Not available |
| Odor Threshold | Not available |
| pH | Not available |
| pKa | Not available |
| Particle Size | Not available |
| Solubility, Water | soluble |
| Specific Gravity/ Relative density | Not available |
| Viscosity | 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 | |
| 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 |

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| | |
|---|---|
| Saturated Vapor Concentration | Not available |

| **10. STABILITY AND REACTIVITY** | |
|---|---|
| *Stability* | |
| Chemical Stability | Stable under normal conditions. |
| Conditions to avoid | Not available |
| Incompatible products | Not available |
| Hazardous decomposition products | Hazardous decomposition products formed under fire conditions.: carbon oxides (COx), nitrogen oxides (NOx) |
| Hazardous reactions | None known. |
| *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.). |

| **11. TOXICOLOGICAL INFORMATION** | |
|---|---|
| Routes of Entry | Ingestion, inhalation, Eye contact, Skin contact |
| Eye Irritation | Hydroxyurea<br>Mildly irritating to eyes.<br>Citric Acid Anhydrous<br>Irritating to eyes.<br>Magnesium Stearate<br>May cause mechanical irritation. |
| Skin Irritation | Hydroxyurea<br>Mildly irritating to skin<br>Citric Acid Anhydrous<br>Mildly and/or transiently irritating to skin. |
| Respiratory Irritation | Citric Acid Anhydrous<br>Irritating to respiratory tract. |
| Sensitization | Hydroxyurea<br>Not a dermal sensitizer |

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## *11. TOXICOLOGICAL INFORMATION*

| | |
|---|---|
| Acute Toxicity Study | **Acute Oral**<br>Hydroxyurea<br>LD50 (rat): 5,760 mg/kg<br>LD50 (mouse): 7,330 mg/kg<br><br>Citric Acid Anhydrous<br>LD50 (rat): 3,000 mg/kg<br>LD50 (mouse): 5,040 mg/kg<br>LDlo (rabbit): 7,000 mg/kg<br><br>**Acute Dermal**<br>Citric Acid Anhydrous<br>LD50 (rat): > 2,000 mg/kg |
| Repeated Dose Toxicity | Hydroxyurea<br>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.<br><br>Magnesium Stearate<br>3 months dietary rat study : NOAEL = 2,500 mg/kg Low dose effects include (< = 100 mg/kg): decreased weight gain, liver effects, kidney stones. |
| Genetic Toxicity | Hydroxyurea<br>**In vitro**<br>Ames reverse-mutation assay -- positive<br>Chromosome aberrations assay -- positive<br>DNA repair assay -- positive<br>Yeast reverse-mutation assay -- positive<br>mouse lymphoma cells -- positive<br>**in vivo**<br>micronucleus assay (mouse) -- positive<br>Mammalian sister chromatid exchange assay (Rodents) -- positive<br>**Mutagenicity Assessment**<br>Several studies were conducted. This material was positive in a battery of in vivo and in vitro genotoxicity assays.<br><br>Citric Acid Anhydrous<br>**In vitro**<br>Ames reverse-mutation assay -- negative<br>Yeast reverse-mutation assay -- negative<br>**in vivo**<br>5 D dominant lethal assay (rat) -- negative<br>**Mutagenicity Assessment**<br>This material was negative in a battery of in vivo and in vitro genotoxicity assays. |

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## *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 rat study : No treatment-related tumors were observed.

Magnesium Stearate

**Carcinogenicity Assessment**

Not classifiable as to its carcinogenicity to humans.

| **Carcinogenicity** | **ACGIH** | **OSHA** | **NTP** | **IARC** |
|---|---|---|---|---|
| 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.

Human experience

**Experiences with Human Exposure**

Hydroxyurea

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 -

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## *11. TOXICOLOGICAL INFORMATION*

| | |
|---|---|
| | delayed effect include: bone marrow suppression, pancreas effects, pulmonary fibrosis, autoimmune symptoms, second cancers, peripheral nervous system toxicity, impaired spermatogenesis. |
| Target Organs | Hydroxyurea<br>bone marrow, male reproductive organs, gastrointestinal tract, liver, skin, pancreas, kidney, lungs, peripheral nervous system |
| Symptoms | Hydroxyurea<br>See "Human Experience".<br><br>Citric Acid Anhydrous<br>redness and swelling of eyes<br><br>Magnesium Stearate<br>redness and swelling of eyes, skin flushing, nausea, vomiting, diarrhoea, dehydration, lowered blood pressure, cardiac irregularities, CNS depression, respiratory disorder, paralysis |
| Pharmacokinetics/ Toxicokinetics | Hydroxyurea<br>Absorption: Not available<br>Distribution: Not available<br>Metabolism: Not available<br>Elimination: Half-life = 3 - 4 Hour(s) (Human). |
| Other Toxicity Information | Not available |

## *12. ECOLOGICAL INFORMATION*

**Ecotoxicological Information (Aquatic)**

**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) : > 100 mg/l.

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

Citric Acid Anhydrous

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

**Ecotoxicological Information (Terrestrial)** Not available

**Chemical fate information**

**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

Continued

## *12. ECOLOGICAL INFORMATION*

**Summary Statements**

**Aquatic toxicity**

Hydroxyurea Capsules, For Oral Use

Experimental data indicate low potential for acute harm to aquatic invertebrates

## *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 in all modes.

## *15. OTHER REGULATORY INFORMATION*

**United States of America**

| | |
|---|---|
| OSHA Hazard Classification | |
| 313 Toxic Release Inventory | No components listed on the SARA 313 inventory. |
| TSCA Inventory | Not listed. Food, drug and cosmetic products are exempt from TSCA. |

**International**

**Europe**

| | |
|---|---|
| EINECS/ELINCS Number | Hydroxyurea: 204-821-7<br>Citric Acid Anhydrous: 201-069-1<br>Sodium Phosphate Dibasic, Anhydrous: 231-448-7<br>Magnesium Stearate: 209-150-3 |

DRUG PRODUCT

| | |
|---|---|
| Classification | Medicinal products are exempt from classification and labeling requirements under EU Regulation (EC) No 1272/2008. |

## *16. OTHER INFORMATION*

*SDS preparation information*

| | |
|---|---|
| Prepared by | Research and Development Environment, Health and Safety 1-732-227-7380 |
| Prepared on | 04/10/2015 |
| | This Safety Data Sheet was reformatted in accordance with the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) for the United States of America (USA) (CFR 1910.1200), European Union (EU) (EC 1272/2008) and United Nations (UN). |

*Other information*

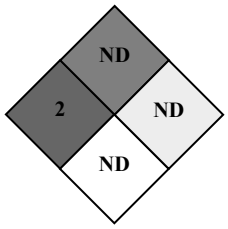
Continued

HMIS

| | |
|---|---|
| Health | 2* |
| Flammability | Not Determined (ND) |
| Reactivity | Not Determined (ND) |
| Personal protective equipment | See Section 8. |

NFPA

| | |
|---|---|
| Health | 2 |
| Fire | ND |
| Reactivity | ND |
| Special | ND |




The information contained in this SDS 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.

End of Safety Data Sheet