MATERIAL SAFETY DATA SHEET

SECTION 1: CHEMICAL SUBSTANCE

PRODUCT NAME: Purinethol® Tablets
COMMON NAME: mercaptopurine
CHEMICAL NAME: 1,7-Dihydro-6H-purine-6-thione monohydrate
SYNONYMS: Purinethol® (mercaptopurine) Tablets; Purinethol Tablets; Purinethol®; 6-mercaptopurine
SUBSTANCE CLASS: Purine base analogue; antimetabolite used in cancer chemotherapy

SECTION 2: HAZARDOUS INGREDIENTS

<table>
<thead>
<tr>
<th>NAME</th>
<th>CAS/EINECS/ELINCS #</th>
<th>% w/v or w/w</th>
<th>GW LIMITS (mcg/m³)</th>
<th>OTHER LIMITS (mcg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mercaptopurine</td>
<td>6112-76-1</td>
<td></td>
<td>10 mcg/m³ (8 hr TWA)</td>
<td>Not established</td>
</tr>
</tbody>
</table>

SECTION 3: HAZARDS IDENTIFICATION

The risk of health hazards may be reduced when Purinethol® Tablets are handled in unit dosage form.

Mercaptopurine is a powerful cytotoxic agent.
May be harmful if swallowed.
May be harmful if inhaled.
This substance, when used medically, has been associated with adverse effects including: bone marrow suppression leading to anemia, thrombocytopenia, leukopenia or any combination of these, liver toxicity (with jaundice and elevation of serum enzymes indicative of liver damage), skin rash and other evidence of hypersensitivity, gastrointestinal ulceration and other adverse GI effects (such as diarrhea).
May cause sensitization by skin contact.
Adverse effects observed after overdose include anorexia, nausea, vomiting and diarrhea, myelosuppression, liver dysfunction, and gastroenteritis.
Possible risk of harm to the unborn child.
Mutagen and probable human carcinogen.
Possible reproductive hazard.

See also Section 11, “Toxicological Information”.

TO THE BEST OF OUR KNOWLEDGE THE INFORMATION CONTAINED HEREIN IS ACCURATE AS OF THE DATE HEREOF. ANY DETERMINATION AS TO THE SUITABILITY OF THE PRODUCT FOR ANY PARTICULAR PURPOSE, ITS SAFE USE OR DISPOSAL SHALL BE THE RESPONSIBILITY OF THE USER. THE INFORMATION CONTAINED HEREIN IS IN NO WAY INTENDED TO SUPPLEMENT, MODIFY OR SUPERSEDE THE INFORMATION PROVIDED IN THE PRODUCT PACKAGE INSERT WITH RESPECT TO THE USE OF THE PRODUCT FOR MEDICAL PURPOSES. PLEASE REFER TO THE PRODUCT PACKAGE INSERT FOR INFORMATION REGARDING THE USE OF THE PRODUCT FOR MEDICAL PURPOSES.
SECTION 4: FIRST AID MEASURES

If in Eyes: Flush immediately with large quantities of water for 15 minutes. Obtain medical attention.

If on Skin: Remove contaminated clothing. Flush exposed skin with water and wash thoroughly with soap and water. Obtain medical attention.

If Inhaled: If not breathing, give artificial respiration or CPR. If breathing is difficult, give oxygen. Remove person to fresh air. Obtain medical attention.

If Ingested: If conscious, rinse mouth with water. Never give anything by mouth if unconscious. Obtain medical attention.

SECTION 5: FIRE / EXPLOSION HAZARDS & FIRE-FIGHTING MEASURES

FLASHPOINT/TEST METHOD: Not Determined.

LEL / UEL: Not Determined.

SPECIAL PROPERTIES RELATED TO FIRE HAZARD: As formulated, Purinethol Tablets should be dust-free. However, breakage of tablets, especially in bulk operations, could contribute to dust formation. As with any organic dust, there is potential for explosion when high concentrations are suspended in air.

STORAGE OR HANDLING CONDITIONS TO BE AVOIDED: Not Determined.

EXTINGUISHING MEDIA: Water Spray, Multipurpose Dry Chemical.

FIRE-FIGHTING PROCEDURES: Wear full protective clothing and use self-contained breathing apparatus (SCBA).

SECTION 6: SPILL AND LEAK PROCEDURES

SPILL RESPONSE PROCEDURES (Liquid, Solid, Gas/Vapor):

Protective equipment may be necessary for spills. (See Section 8, “Exposure Controls / Personal Protection” for guidance).

For small quantities associated with normal therapeutic use, collect spillage, minimizing dust generation, and transfer to a closed waste container for disposal. For large or bulk quantities, collect spillage by carefully wet wiping or HEPA vacuuming and place in a labeled, sealed container for disposal. Wash spill area (floor or other contact surfaces) with a suitable cleaning solvent, like dilute alkaline permanganate solution then wash with water. Clean area with soap and water.

SECTION 7: HANDLING AND STORAGE

HANDLING: Avoid exposure by any route. Use only in well-ventilated area with limited access. Properly identify (signage and labeling) potential hazards in designated work areas.

No open handling of powders or uncoated tablets unless precautions have been taken to prevent exposure. Handling of solids and solutions should be conducted in designated areas to minimize surface contamination. Aerosol-generating procedures should be conducted in a laboratory fume hood or with other suitable local exhaust ventilation. Decontaminate equipment and surfaces that
SECTION 7: HANDLING AND STORAGE (cont'd)

HANDLING (cont’d): may have come in contact with the compound. Wash hands and other exposed skin thoroughly before leaving the work area.

STORAGE: Store at 15° to 25° C (59° to 77° F) in a dry place. Keep in original container tightly closed. Protect from light.

SECTION 8: EXPOSURE CONTROLS / PERSONAL PROTECTION

ENGINEERING CONTROLS: No special ventilation requirements for normal therapeutic dosage and administration. For dusty processes, use process containment, local exhaust ventilation or other engineering controls to keep airborne concentrations below the occupational exposure limit (OEL).

PERSONAL PROTECTION:

Respiratory: Not required under normal conditions of therapeutic use and storage. Respiratory protective equipment may be necessary to provide additional protection for dusty processes and in the absence of sufficient engineering controls. Use NIOSH approved respiratory protection to control airborne levels below the OEL. See Section 5 - “Fire / Explosion Hazards & Fire-Fighting Measures” for respiratory protection in the event of a fire.

Eye: Workers should wear adequate eye protection to prevent eye contact.

Clothing: Adequate protective clothing should be worn to prevent occupational skin contact.

Gloves: Use impermeable (e.g., latex) gloves to prevent skin contact. Double glove as necessary and dispose of outer gloves according to federal, state, and local regulations.

WORK PRACTICES: Special care should be taken to ensure that contaminated clothing, equipment, and surfaces are properly cleaned after use. Wash hands and other areas of skin contact thoroughly after handling this material. Contaminated clothing should be disposed of or cleaned. Potentially contaminated clothing should be packaged for laundering to prevent exposure of laundry personnel.

SECTION 9: PHYSICAL / CHEMICAL PROPERTIES

APPEARANCE AND ODOR: Purinethol® Tablets are pale yellow to buff, scored tablets imprinted with “PURINETHOL” and “04A”.

PHYSICAL STATE (liquid/solid/gas): Solid.

MELTING POINT (deg. C): Not determined for Purinethol® Tablets. The melting point of mercaptopurine, the active ingredient in Purinethol® Tablets, is approximately 300° C with decomposition.

SOLUBILITY/MISCIBILITY (% w/v): Not determined for Purinethol® Tablets. The solubility of mercaptopurine, the active ingredient in Purinethol® Tablets, is 0.26 mg/mL at 37° C in water.

SECTION 10: STABILITY AND REACTIVITY

CHEMICAL STABILITY: Stable.
SECTION 10: STABILITY AND REACTIVITY (cont’d)

CONDITIONS TO AVOID: Not determined.

INCOMPATIBILITY WITH OTHER MATERIALS: Not determined for Purinethol Tablets. No known incompatibilities have been identified for mercaptopurine, the active ingredient in Purinethol Tablets.

HAZARDOUS DECOMPOSITION PRODUCTS: Hazardous decomposition products of Purinethol Tablets have not been determined. Thermal decomposition products of mercaptopurine, the active ingredient in Purinethol Tablets, include toxic and/or corrosive oxides of nitrogen and sulfur.

HAZARDOUS POLYMERIZATION: Not Determined.

SECTION 11: TOXICOLOGICAL INFORMATION

THE RISK OF HEALTH HAZARDS MAY BE REDUCED WHEN PURINETHOL TABLETS ARE HANDLED IN UNIT DOSAGE FORM.

PHARMACOLOGICAL ACTIVITY: Purinethol Tablets (mercaptopurine) is a potent cytotoxic agent and is indicated for remission induction and maintenance therapy of acute lymphatic leukemia.

OCCUPATIONAL EXPOSURE LIMITS: For mercaptopurine, the active ingredient in Purinethol Tablets, the Glaxo Wellcome estimated safe working level is an eight hour time-weighted average (TWA) of 10 mcg/m³.

ACUTE TOXICITY: The approximate lethal dose of mercaptopurine following single oral administration was:

\[ \text{LD50 (mouse)} = 1250 \text{ mg/kg} \]

There is limited experience with Purinethol in the occupational setting. However, with sufficient exposure, this substance may result in adverse effects such as those observed in investigative and medicinal use (also see “Repeat Dose Toxicity” and “Clinical Safety”, below). The most consistent, dose-related toxicity defined in medicinal use is suppression of bone marrow function. This may be manifest by anemia (decreased numbers of red blood cells), thrombocytopenia (decreased platelet count), leukopenia (decreased white cell number) or any combination of these. Mercaptopurine is also hepatotoxic (toxic to the liver) in animals and man; symptoms include jaundice and hyperbilirubinemia and elevation of serum enzymes indicative of liver damage (alkaline phosphatase, serum transaminases).

REPEAT DOSE TOXICITY: In the occupational setting, repeated overexposure to mercaptopurine may result in the same adverse effects which have been observed when this substance is used medicinally. The major toxicities of mercaptopurine are related to myelosuppression, hepatotoxicity, and gastrointestinal toxicity (see “Clinical Safety”, below). Adverse changes in immune system function may also accompany exposure to this substance.

IRRITATION: There are no data on the potential of this substance to irritate the eyes. There are no data on the skin irritation potential of this substance.

SENSITIZATION: In medicinal use, hypersensitivity reactions to mercaptopurine have been reported. Hypersensitivity reactions have also been reported following skin contact.
SECTION 11: TOXICOLOGICAL INFORMATION (cont’d)

REPRODUCTIVE EFFECTS: There is evidence of mercaptopurine-induced embryotoxicity and teratogenicity in rats, mice, and rabbits during standard tests.

The effect of mercaptopurine on human fertility is unknown for either males or females. For recommended dosage and administration, mercaptopurine is classified as "Pregnancy Category D"; mercaptopurine can cause fetal harm when administered to a pregnant woman. Women receiving mercaptopurine in the first trimester of pregnancy have an increased incidence of abortion; the risk of malformation in offspring surviving first trimester exposure is not accurately known. In a series of twenty-eight women receiving mercaptopurine after the first trimester of pregnancy, three mothers died undelivered, one delivered a stillborn child, and one aborted; there were no cases of macroscopically abnormal fetuses. There are no adequate and well controlled studies of mercaptopurine in pregnant women. Since such experiences cannot exclude the possibility of fetal damage, mercaptopurine should be used during pregnancy only if the benefit clearly justifies the possible risk to the fetus, and particular caution should be given to the use of mercaptopurine in the first trimester of pregnancy. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Purinethol Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Medical evaluation of exposure and attention to compliance with standard operating procedures and/or other workplace health and safety directives is advised.

GENOTOXICITY: Mercaptopurine has been shown to be mutagenic in the Ames assay and mouse lymphoma cells. Mercaptopurine causes chromosomal damage in mammalian cell cultures and in the rat micronucleus test. Mercaptopurine causes chromosomal aberrations in animals and man and induces dominant-lethal mutations in male mice.

CARCINOGENICITY: Mercaptopurine is a probable human carcinogen, but the extent of the risk is unknown.

CLINICAL SAFETY: The most frequent, serious adverse effects of Purinethol are myelosuppression resulting in leukopenia, thrombocytopenia and anemia, and hepatotoxicity. Life-threatening infections and bleeding have been observed as a consequence of mercaptopurine-induced granulocytopenia and thrombocytopenia. A small number of deaths have been reported, which may be attributed to hepatic toxicity after administration of mercaptopurine. Hepatic damage can occur with any dosage, but seems to occur with more frequency when doses of 2.5 mg/kg/day are exceeded. Hepatotoxicity has been associated, in some cases, with anorexia, diarrhea, jaundice, ascites, and hepatic encephalopathy. Symptoms of mercaptopurine-induced hepatotoxicity may include: jaundice, hepatomegaly, or anorexia with tenderness in the right hypochondrium, deterioration in liver function studies, toxic hepatitis, or biliary stasis. Monitoring of serum transaminase levels, alkaline phosphatase, and bilirubin levels may allow early detection of hepatotoxicity.

Intestinal ulceration has been reported with medicinal use of mercaptopurine. Nausea, vomiting, and anorexia are uncommon during initial administration. Mild diarrhea and sprue-like symptoms have been noted occasionally, but it is difficult at present to attribute these to the medication. Oral lesions are rarely
SECTION 11: TOXICOLOGICAL INFORMATION (cont’d)

CLINICAL SAFETY (cont’d):  seen, and when they occur they resemble thrush rather than antifolic ulcerations. An increased risk of pancreatitis may be associated with the investigational use of Purinethol® in inflammatory bowel disease.

Administration of Purinethol® has been associated with skin rashes and hyperpigmentation. Drug fever has been very rarely reported.

Signs and symptoms of overdosage may be immediate such as anorexia, nausea, vomiting and diarrhea; or delayed such as myelosuppression, liver dysfunction, and gastroenteritis. If a patient is seen immediately following an accidental overdosage of the drug, it may be useful to induce emesis.

There are rare individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effects of mercaptopurine and prone to developing rapid bone marrow suppression following the initiation of treatment.

SECTION 12: ECOLOGICAL INFORMATION

ENVIRONMENTAL FATE:  Mercaptopurine monohydrate compartmentalizes into the aquatic environment.

ENVIRONMENTAL EFFECTS:  Mercaptopurine monohydrate is unlikely to bioaccumulate and biodegrade. It shows toxicity to aquatic receptors at 72 mg/L.

ENVIRONMENTAL TEST RESULTS:

<table>
<thead>
<tr>
<th>STUDY NAME</th>
<th>RESULTS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water Solubility:</td>
<td>0.105 mg/ml (20.5°C)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.26 mg/ml (37°C)</td>
<td></td>
</tr>
<tr>
<td>Octanol/Water Partition Coefficient:</td>
<td>Log P &lt;-2.03</td>
<td></td>
</tr>
<tr>
<td>Aerobic Biodegradation (water)</td>
<td>28 days</td>
<td></td>
</tr>
<tr>
<td>Activated sludge respiration inhibition test</td>
<td>&gt;1000 mg/L</td>
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</tr>
<tr>
<td>Acute toxicity to Daphnia</td>
<td>EC50=72 mg/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NOEC=32 mg/L</td>
<td></td>
</tr>
</tbody>
</table>

SECTION 13: WASTE DISPOSAL

ROUTINE:  Unused product should be disposed of at an approved facility in accordance with federal, state and local regulations.

ACCIDENTAL RELEASE:  Clean up spills immediately, observing precautions in Section 8 - “Personal Protection”. Remove or decontaminate all residues in accordance with federal, state and local regulations.

SECTION 14: TRANSPORTATION INFORMATION

Component 1 or Formulation 1:  Purinethol® Tablets

US Department of Transportation
Proper Shipping Name:  Not regulated in transportation
SECTION 14: TRANSPORTATION INFORMATION (cont'd)

IATA/ICAO
Proper Shipping Name: Not regulated in transportation

IMDG
Proper Shipping Name: Not regulated in transportation

RQ: None
Marine Pollutant: No

SECTION 15: REGULATORY INFORMATION

EC PACKAGING AND LABELING FOR SUPPLY: Not determined.

OTHER LEGISLATION: Not determined.

SECTION 16: OTHER INFORMATION

REVISION DATE: 06/23/99
SUPERSEDES: 12/04/97