MATERIAL SAFETY DATA SHEET (MSDS)

NEUŁEXIN® (TRIMETREXATE GLUCURONATE) FOR INJECTION

Prepared: February 2001
Supersedes: November 1997 (Original)

SECTION 1 - COMPANY IDENTIFICATION

MedImmune Oncology, Inc.                  FOR EMERGENCY SOURCE INFORMATION
(formerly U.S. Bioscience, Inc.)          CONTACT:
35 West Watkins Mill Rd.                 Telephone: (800) 949-3789 (USA)
Gaithersburg, Maryland 20878 USA       FAX: (800) 959-4033 (USA)

SECTION 2 - PRODUCT IDENTIFICATION & COMPOSITION

TRADE NAME: NeuTrexin®                     SYNONYMS:
SYNONYMS: Trimetrexate Glucuronate For
Intravenous Infusion
Trimetrexate Glucuronate For Injection

DRUG CLASSIFICATION: Non-classical folate antagonist

ACTIVE COMPONENT: Common Name: Trimetrexate Glucuronate
Chemical Name: (1) 2,4-Quinazolinediamine, 5-methyl-6-[[3,4,5-
trimethoxyphenyl]amino]methyl]
(2) 2,4-Diamino-5-methyl-6-[[3,4,5-
trimethoxyanilino)methyl][quinazoline]

CAS Number: 82952645
% By Weight: 62 %

OTHER COMPONENT: Common Name: D-Glucuronic Acid
Chemical Name: D-Glucuronic Acid
CAS Number: 6556-12-3
% By Weight: 38 %

SECTION 3 - POTENTIAL HEALTH HAZARDS

In the occupational setting, under normal conditions for the proper handling and use of NeuTrexin, no
potential health hazards are anticipated. However, should NeuTrexin (powder or reconstituted solution)
come into contact with the skin, eyes, or be inhaled, ingested or injected, the following may occur:

**SKIN CONTACT:** Irritation, and/or rash.

**EYE CONTACT:** Irritation and tearing.

**INHALATION:** Inhalation may result in the absorption of NeuTrexin through the lungs. Depending on the quantity of NeuTrexin inhaled, potential side effects may include coughing and irritation of the lungs, nausea, vomiting, rash and/or fever. Hematologic, hepatic, renal and GI toxicities have been associated with NeuTrexin use and may be experienced if NeuTrexin is inhaled.

**INGESTION:** Immediate side effects may include nausea, vomiting, rash and/or fever. Depending on the quantity of NeuTrexin ingested other potential side effects may include abdominal cramps, diarrhea and/or hematologic, hepatic, renal and GI toxicities.

**INJECTION:** Side effects may include nausea, vomiting, rash, fever and/or hematologic, renal, GI and hepatic toxicities.

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**SECTION 4 - FIRST AID MEASURES**

**SKIN CONTACT:** Remove contaminated clothing. Wash affected area with soap or mild detergent and water for 15 minutes. Observe for signs of irritation. If irritation is present, seek medical attention.

**EYE CONTACT:** Wash eyes with large amounts of water for 15 minutes. Seek medical attention.

**INHALATION:** Remove to fresh air. Seek medical attention.

**INGESTION:** Seek medical attention. Do not induce vomiting.

**INJECTION:** Seek medical attention.

**NOTE TO PHYSICIAN:** NeuTrexin is a folate antagonist. Under approved indication usage of this product, concurrent leucovorin (leucovorin protection) must be administered to avoid potentially serious or life-threatening toxicities. Consult the NeuTrexin Package Insert for additional information and recommended product handling procedures.

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**SECTION 5 - FIRE FIGHTING MEASURES**

**EXTINGUISHING MEDIA:** CO₂, dry chemicals, foam, water.

**SPECIAL HAZARDS:** NeuTrexin may emit toxic fumes or vapors under fire conditions.

**SPECIAL FIRE FIGHTING PROCEDURES:** Self-contained breathing apparatus, protective clothing.
**SECTION 6 - ACCIDENTAL RELEASE MEASURES**

**SPILL:** Wear appropriate protective clothing, suitable eye protection, and chemically compatible gloves (latex). For spill of reconstituted solution: Isolate spill area and use paper or cloth towels to clean up solution. For spill of powder: Isolate spill area and clean up powder with wetted paper or cloth towels. Avoid generating powder/dust. Place spillage in appropriate container labeled for hazardous (cytotoxic) waste disposal. Wash all contaminated surfaces with a 5% solution of Sodium Hypochlorite. Following decontamination, wash the spill site with water. Wash any contaminated clothing before reuse.

**OCCUPATIONAL EXPOSURE LIMIT (OEL):** Not established.

**SECTION 7 - HANDLING & STORAGE**

Observe all federal, state, and local regulations. Store per label and other instructions to ensure product integrity. Protect against physical damage.

**SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION**

**EYE:** Good safety practices should provide for the use of appropriate eye protection when preparing and administering cytotoxic drug products.

**ORAL:** Do not permit eating, drinking and/or smoking when working with this product.

**RESPIRATORY:** Respiratory protection is generally not required under normal handling of this product.

**SKIN:** Good safety practices should be applied when handling cytotoxic drugs. Chemically compatible gloves (latex) should be used when handling this product.

**SECTION 9 - PHYSICAL & CHEMICAL PROPERTIES**

**APPEARANCE, COLOR & ODOR:** Pale greenish-yellow powder or cake. NeuTrexin forms a pale greenish-yellow solution when reconstituted with 5% Dextrose Injection, USP or Sterile Water for Injection, USP.

**Molecular Wt.** (1): 369.42

**Melting Range** (1): 212° to 228°C

**Flash Point** (1): Not applicable

**Ignition Temperature** (1): Not applicable

**Vapor Pressure** (1): Not applicable

**Density** (1): Not applicable

**Solubility** (1)(2):

- Water mg/mL < 0.1 mg/mL
- pH 7.4 Buffer < 0.1 mg/mL
- pH 4.0 Buffer 0.4 mg/mL
- 0.1 N HCl 1.1 mg/mL
- Methyl Alcohol 0.6 mg/mL
Secti 10 - Toxicology Information

Trimetrexate has been shown to be fetotoxic and teratogenic in rats and rabbits. Rats administered 1.5 and 2.5mg/kg/day intravenously on gestational days 6-15 showed substantial postimplantation loss and severe inhibition of material weight gain. Trimetrexate administered intravenously to rats at 0.5 and 1.0 mg/kg/day on gestational days 6-15 retarded normal fetal development and was teratogenic. Rats administered trimetrexate intravenously at daily doses of 2.5 and 5.0 mg/kg/day on gestational days 5-18 resulted in significant maternal and fetal toxicity. In rabbits, trimetrexate at 0.1 mg/kg/day was teratogenic in the absence of significant maternal toxicity. These effects were observed using doses 1/20 to 1/2 the equivalent human therapeutic dose based on a mg/m² basis. Teratogenic effects included skeletal, visceral, ocular, and cardiovascular abnormalities. Carcinogenesis: Long term studies in animals to evaluate the carcinogenic potential of trimetrexate have not been performed.

Mutagenesis: Trimetrexate was not mutagenic when tested using the standard Ames Salmonella mutagenicity assay with and without metabolic activation. Trimetrexate did not induce mutations in Chinese hamster lung cells or sister-chromatid exchange in Chinese hamster ovary cells. Trimetrexate did not induce an increase in the chromosomal aberration frequency of cultured Chinese hamster lung cells; trimetrexate showed no clastogenic activity in mouse micronucleus assay.

Impairment of Fertility: No studies have been conducted to evaluate the potential of trimetrexate to impair fertility. However, during standard toxicity studies conducted in mice and rats, degeneration of the testes and spermatocytes including the arrest of spermatogenesis was observed.

Secti 11 - Ecological & Disposal Information

Degradability: Trimetrexate is not degraded by water. Trimetrexate is known to degrade in the dry and liquid state via oxidation. The oxidation of trimetrexate by both enzymatic and non-enzymatic catalysis will be the process responsible for its ultimate destruction.

Disposal: NeuTrexin is not a RCRA listed or a toxicity characteristic waste regulated under the Federal hazardous waste regulations. State toxicity characteristic classifications may be the same, or more stringent than the Federal standards. Therefore, waste materials must be disposed of in accordance with all federal, state, and local regulations. All waste should be incinerated through a permitted Treatment, Storage, and Disposal Facility (TSDF).

Secti 12 - Transportation Information

Ship as non-regulated material. The toxicity does not warrant shipment as a hazardous material (DOT) or
as a dangerous good (IATA). Transport at conditions consistent with label and other instructions to ensure product integrity. Package to prevent container breakage, protect against physical damage.

**SECTION 13 - REGULATORY INFORMATION**

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<th>REGULATORY INFORMATION</th>
<th>Status</th>
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<td>TSCA STATUS:</td>
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<td>CERCLA SECTION 103 (40 CFR 302.4):</td>
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<td>SARA SECTION 302 (40 CFR 355.30):</td>
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<td>SARA SECTION 304 (40 CFR 355.40):</td>
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<td>SARA SECTION 313 (40 CFR 372.65):</td>
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<td>CALIFORNIA PROPOSITION 65:</td>
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<td>SARA ACUTE HAZARD (40 CFR 370.21):</td>
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**SECTION 14 - OTHER**

All information presented above is believed to be correct, but does not purport to be all inclusive and should be used only as a guide. MedImmune Oncology, Inc. shall not be held liable for any damage resulting from the inappropriate handling of and exposure to this product.

**LITERATURE CITED:** (reprints enclosed as marked below with an * - no reprints attached for FAX or e-m)

*NeuTrexin® (trimetrexate glucuronate) package insert, MedImmune Oncology, Inc. Product information as of November, 2000.