Bristol-Myers Squibb Company
Pharmaceutical Group
Material Safety Data Sheet

Code : CAS : Not Available **Rev. date :** 03-Feb-99
Status : 3 **Group :**Bulk
Manufacturer : Bristol-Myers Squibb Company
Trade Name : BMS 247550
Synonyms :
Chemical Name : Trade secret

OSHA Hazards : HTOX, NET, PCAR, PFET, PMUT, PREP, PTER, PTOR, R2, R3, R4, TO4

Exposure Control Class / Exposure Guideline : Control Class D

CERCLA/SARA : Not Applicable
Physical State : Solid
Vapor Pressure : Not Available
DOT : Toxic Solid Organic, N.O.S. (Epothilone Analog); 6.1; UN 2811, **PG III EPA HW :**

MSDS Image :
1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

BRISTOL-MYERS SQUIBB
WORLDWIDE MEDICINES GROUP
P.O. BOX 191
NEW BRUNSWICK, NJ 08903
(732) 519-3843

Product Identification

Chemical Name: Trade secret
Synonym: BMS 247550
How Supplied: Bulk substance, used within Bristol-Myers Squibb
Product Use: Drug candidate for use in treatment of malignant tumors
Chemical Family: Epothilone analog
Molecular Formula: C27H42N2O5S CAS # Not available

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EMERGENCY CONTACTS

Health: 732-519-3843 (Monday through Friday, daytime) at other times contact Chemtrec or the local poison control center

Transportation: CHEMTREC 800-424-9300. For international emergencies call CHEMTREC at 703-527-3887, collect calls accepted.

EMERGENCY OVERVIEW: This colorless crystalline powder is a research compound which has not been fully characterized. It has demonstrated potent cytotoxic activity and may be highly toxic after acute injection. The substance is a potential carcinogen and reproductive toxin. This material is assigned to BMS Exposure Control Class D. See appropriate sections for handling and

other precautions. May burn during a fire and release toxic combustion products.
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2. COMPOSITION/ INFORMATION ON INGREDIENTS

COMPONENTS	HAZARDOUS	CONCENTRATION	CAS #	EXPOSURE (Y/N)	GUIDELINE
BMS 247550	Y	100%	not available	None*	

* Material is assigned to Exposure Control Class D (range < 0.001 mg/m3). A specific exposure guideline has not yet been established.

3. HEALTH HAZARDS IDENTIFICATION

EFFECTS OF OVEREXPOSURE

Routes of Entry:

1. Inhalation: If material becomes airborne, there is potential for inhalation. The extent of systemic absorption of the material after inhalation is not known. Material that is inhaled but not absorbed may be cleared from the respiratory tract and swallowed, leading to exposure by ingestion.

2. Skin contact: Exposure may occur via skin contact if gloves and protective clothing are not worn. The extent of systemic absorption of the material after skin contact is not known.

3. Ingestion: Ingestion of large quantities of this material in an occupational setting would not be expected to occur. Ingestion of trace amounts of the material might occur if material contacts the hands and hands are not washed prior to eating, drinking, or smoking, or through clearance of inhaled material. The extent of systemic absorption of the material after ingestion is not known. However, in preliminary animal studies, significant oral bioavailability of the material was demonstrated in certain mixtures.

Acute

Ingestion: There is no information concerning the potential for this material to produce symptoms after ingestion. However, significant activity was demonstrated in animal studies after acute, oral administration.

Inhalation: There is no information concerning the potential for this material to produce symptoms after inhalation. Most dusts may cause mechanical irritation (resulting in coughing, sneezing, tearing of the eyes) after high exposure. Note: This material may be dissolved in a solution of Cremophor® EL (polyoxyethylated castor oil) and/or ethanol and further diluted with solutions for intravenous administration. Inhalation exposure could occur as a result of spills of these solutions. In some instances of inhalation exposure to another cytotoxic drug (with similar mechanism of action), dissolved in such a solution, health care workers reported a wide variety of symptoms and signs, including: dizziness, headache, nausea, swelling of the lip, tongue, and throat, burning sensations in the eyes, wheezing, upper respiratory tract irritation, dry cough, shortness of breath, exacerbation of pre-existing asthma, rash, periorbital numbness, photosensitivity, flushing, palpitations, and chest tightness or pain. It is not known whether these symptoms were due to exposure to the cytotoxic drug, Cremophor® EL, ethanol, or to some other cause.

Skin Contact
a. Toxic: There is no information concerning the potential of this material to produce systemic symptoms after skin contact.
b. Irritation: There is no information concerning the potential of this solid material to produce local skin irritation. Note: This material may be dissolved in a solution of Cremophor® EL and/or ethanol and further diluted with solutions for intravenous administration. Skin exposure could occur as a result of spills of these solutions. In some instances of skin exposure to another cytotoxic drug (with similar mechanism of action), dissolved in such a solution, health care workers reported symptoms and signs that included: tingling and/or burning sensations of the skin, skin redness or blotches, contact dermatitis, pruritis (itching), cellulitis, substernal chest pain, and shortness of breath. It is not known whether these symptoms were due to exposure to the cytotoxic drug, Cremophor® EL, ethanol, or to some other cause.
c. Sensitization: There is no information concerning the potential of this material to produce skin sensitization.

Eye Contact: There is no information concerning the potential of this material to produce ocular irritation or lesions. In the absence of this information, the material should be handled as a potential eye irritant.

Chronic: There is no specific data in humans or animals concerning the chronic toxicity of this material. However, BMS 247550 has demonstrated potent cytotoxic activity in vitro and in acute and subacute animal studies, where intravenous administration resulted in bone marrow depression as well as gastrointestinal, testicular, and peripheral nerve toxicity. While data are not yet available for this compound, other cytotoxic drugs with similar mechanisms of action have proven to be carcinogenic, mutagenic, teratogenic, embryotoxic, and fetotoxic.

Exposure Guideline Summary: BMS 247550 is a research compound being evaluated as a potential therapeutic agent for the treatment of malignant solid tumors, including those of the colon and ovary. By analogy to other cytotoxic drugs with similar mechanisms of action, it is expected to be toxic to particular organ systems in humans when administered systemically and has the potential to cause chromosomal damage, fetal damage, and cancer. In contrast to other drugs with similar mechanisms of action, BMS 247550 has the potential for significant activity when ingested. An exposure guideline has not been established for this material. However, it is recommended that it be handled as an Exposure Control Class D substance. Exposures to this substance should be maintained as low as reasonably possible. Precautions are detailed in the relevant sections of this MSDS.

Carcinogen Lists IARC: No NTP: No OSHA: No

Target Organs: Preliminary animal studies suggest that the hematopoietic, gastrointestinal, peripheral nervous, and reproductive systems are the major target organs for toxicity of this compound. Other organ systems which undergo rapid cellular division may also be targets after systemic exposure. Potential exists for systemic hypersensitivity reactions to this compound or to other components of solutions in which it is dissolved prior to use, such as Cremophore® EL.

Medical Conditions Aggravated by Exposure: While there are no specific data available, therapeutic doses of this material might aggravate anemia or other manifestations of bone marrow suppression.

Medical Surveillance Recommendation: A pre-placement physical examination and history for employees with potential exposure to BMS 247550 is recommended, with laboratory assessment including complete blood count with differential, liver function tests, blood urea nitrogen and creatinine, and a urine dipstick. Periodic follow-up examinations and laboratory testing should be provided in accordance with institutional policy, overseen by a physician thoroughly knowledgeable about the toxicity of the substance, the extent of workplace exposure, and the use of personal protective equipment. A permanent registry of all staff who routinely prepare or administer this drug should be considered. Personnel who are pregnant, breast-feeding, or concerned with other reproductive issues should be encouraged to consult with the occupational health physician monitoring workers health. If respiratory protection is required (see Section 8), further periodic medical evaluation and pulmonary function testing is indicated.

SEE ALSO SECTION 11: TOXICOLOGICAL INFORMATION

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4. FIRST AID MEASURES

Ingestion: Seek medical attention immediately. Induction of vomiting should be considered for significant ingestions if the person is conscious and not experiencing convulsions. Never give anything by mouth to an unconscious person.

Inhalation: Remove exposed person to fresh air. If person is not breathing, give artificial respiration. If breathing is difficult, administer oxygen. Get medical attention immediately.

Skin Contact: Remove contaminated clothing. Wash thoroughly with soap and water for 15 minutes. If hives, facial edema, difficulty in breathing, wheezing, or lightheadedness develops, get medical attention immediately. If local irritation, rash, or swelling develops around the site of contamination, seek medical attention.

Eye Contact: Hold eyelids apart and flush with plenty of water for at least 15 minutes. Get medical attention.

In a medical emergency, contact the Bristol-Myers Squibb Medical Department, (908) 519-2861, in New Brunswick, NJ, or a

physician or poison control center. Any case of illness (including allergic reactions) or injury resulting from, or associated with, exposure to this compound should be reported to the Bristol-Myers Squibb Medical Department and the appropriate Bristol-Myers Squibb Safety Department as soon as possible.

Note to physicians: This compound is a research compound being evaluated for use in the treatment of solid tumors and has not yet been fully characterized. It is likely to be administered intravenously in a mixture with a surfactant such as Cremophore® EL (polyoxyethylated castor oil), although oral formulations may be developed. This compound may be carcinogenic, mutagenic, teratogenic, embryotoxic and fetotoxic. Toxicity to the hematopoietic, gastrointestinal, peripheral nervous, and reproductive systems is likely at therapeutic doses. Hypersensitivity reactions to the drug substance or other components of admixtures are possible and may require treatment with epinephrine, diphenhydramine, and corticosteroids.

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5. FIRE FIGHTING MEASURES

Flash point: Not determined
Autoignition Temperature: Not determined
Flammability limits
LEL: Not determined
UEL: Not determined

Combustibility of Dusts: Fine powders are considered to be potentially combustible and represent an explosion hazard. Provide appropriate bonding and grounding protection to control static charges. Powder handling systems such as dust collectors, dryers, and mills may require additional protective measures (such as explosion venting).

Extinguishing Media: In case of fire, use water, carbon dioxide, foam, or dry chemical.

Firefighting Instructions: Firefighters should wear self-contained breathing apparatus (SCBA), flame and chemical resistant clothing, boots and gloves. Evacuate personnel to upwind direction, and remove unneeded material. Cool container(s) with water from maximum distance. Fight fire from a maximum distance or use an unmanned monitor. Divert fire run-off to a safe area. Keep unnecessary people away; isolate hazard area and deny entry. Move container from the fire area if you can do it without risk. Apply cooling water to sides of containers that are exposed to flames until well after fire is out. Stay away from ends of tanks.

Hazardous Combustion Products: May include oxides of carbon, nitrogen, and sulfur and possibly compounds with carcinogenic potential.

Unusual Hazards: This material is a potent, cytotoxic, anti-cancer drug. As with similar drugs, it may itself be carcinogenic, mutagenic, teratogenic, embryotoxic and fetotoxic. Avoid all skin contact, inhalation, and ingestion. Avoid sparks, heat, and open flame. If material contacts protective clothing or equipment, decontaminate prior to reuse.

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6. ACCIDENTAL RELEASE MEASURES

Spill/Clean-up: Particular care is necessary when cleaning up a spill. Wear appropriate protective equipment/clothing to clean spills. Moisten material to minimize dust generation during pick-up and/or use a HEPA vacuum. Clean spill area with a deactivating solution, if appropriate, followed by detergent and water after spill pick-up, and ventilate spill area after material has been picked up. Use of a substance, such as bleach, to chemically inactivate a compound should be considered for these materials, particularly for oncology drugs. Handle waste materials, e.g., gloves spill papers, as appropriate for chemically and pharmacologically similar materials. For these potent materials, classification as a release restricted material and disposal by incineration is advisable. If the material is present together with other hazardous materials, e.g. flammable solvents, additional handling/disposal requirements may be necessary. Consult with site environmental/safety manager for specific questions. A disposable laboratory coat or gown, impermeable double gloves (latex or nitrile), a respirator with HEPA cartridges and safety goggles should be worn as a minimum precaution. Additional protective clothing/equipment may be needed depending on the quantity spilled and the extent of the spill.

SEE ALSO SECTION 8 FOR APPROPRIATE PROTECTIVE CLOTHING/EQUIPMENT WHICH SHOULD BE WORN

DURING SPILL CLEAN-UP.

7. HANDLING AND STORAGE

Handling Precautions: Avoid ingestion, inhalation, skin, or eye contact with this material. Avoid generating dusts. If material is handled in solution, use particular care to avoid generating mists or aerosols. Handle as a cytotoxic, anti-cancer agent.

Container Requirements: Store in sturdy containers and use unbreakable outer container. Avoid use of breakable containers, such as glass, when possible.

Storage Conditions: Store at room temperature. Also, see Section 10.

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8. EXPOSURE CONTROLS AND PERSONAL PROTECTION

Ventilation Requirements: Control airborne concentration to as low as reasonably achievable by enclosure of processes or local ventilation as required. In general, work in a hood, biological safety cabinet, glove box vented to the outside, or with specific local exhaust vented to the outside is recommended. HEPA filtered exhaust is preferred and should be utilized for new installations.

Respiratory Protection: It is advisable to consult an industrial hygienist when selecting a respirator, especially when larger quantities are to be handled or if material is to be handled together with solvents or other compounds. Respirators should be selected depending on the quantity handled and potential for dust or aerosol generation. For powder handling, when engineering controls are not sufficient to control exposure, wear an approved respirator(1) with HEPA filters appropriate for exposure potential or a supplied air respirator. Self-contained breathing apparatus should be available for emergency use.

(1) NIOSH approves respiratory protection in the United States.

Eye Protection: Wear safety goggles (ANSI Z87.1). Choice of eye protection may be influenced by the type of respirator which is selected.

Protective Gloves: Wear chemically impervious gloves appropriate for highly toxic material whenever the potential exists for skin contact. If material is handled in solution, the solvent should also be considered when selecting glove material. Gloves should be changed regularly and removed immediately after overt contamination. Double gloving is recommended when potential for skin contact exists.

Special Clothing: Wear chemically impervious, disposable, coveralls with closed front, long sleeves, elastic cuffs, and boots if the potential exists for significant dermal contact. Remove disposable clothing prior to leaving the work area. When material is handled in solution, the solvent should also be considered when selecting material for protective clothing.
Hygiene: Wash hands, forearms, and face thoroughly after handling compound and before eating, smoking, using lavatory, and at end of day.

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9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance/Physical State/Color: Crystalline colorless powder; may form long, needle shaped crystals
Boiling point: Not applicable
Evaporation rate: Not applicable
Flash point: Not applicable
Freezing point: Not determined
Melting point (degrees C): approximately 192 C
Octanol/water partition coefficient: Not determined
Odor (threshold): Not determined
pH: Not determined
Solubility in water: < 200 µg/mL at room temperature. Increased to 1-1.5 mg/mL in aqueous vehicles containing 10% EtOH/10% surfactant (Tween 80 or Cremophore® EL).

Specific gravity: 1.19 g/cm3
Vapor density: Not determined
Vapor Pressure: Not determined
Viscosity: Not determined

10. STABILITY AND REACTIVITY

Stability: Solid drug substance exhibited 3% degradation after two weeks storage at 50 C. The product exhibited some susceptibility to photocatalyzed degradation. Stability in aqueous solutions was poor: at 25 C, in 50 mM phosphate buffer at pH 7 (pH of maximum stability), 5% degradation occurred in 2 hours.

Incompatibilities: Strong oxidizers, acids, and bases.

Conditions of Reactivity: Not determined.

Hazardous Decomposition Products: Oxides of carbon, nitrogen, sulfur, and possibly other compounds with carcinogenic potential.

Hazardous Polymerization: Not observed during degradation study.

Explosion data relative to mechanical impact: No specific data is available. Handle to prevent damage to the container during shipping.
Explosion data relative to static discharge: No specific data. Provide suitable bonding and grounding for containers and process equipment to control static charges. Powder handling equipment such as dust collectors, dryers, and mills may require additional protective measures.

11. TOXICOLOGICAL INFORMATION

RTECS # (U.S.): None

ACUTE

LD 50: Not tested.

LC 50: Not tested.

Maximum non-lethal dose in rats was 15 mg/kg.

CHRONIC

Carcinogenicity: No specific information is available.

Mutagenicity: No specific information is available.

Teratogenicity: No specific information is available.

Reproductive Effects: No specific information is available.

Toxicological synergistic products: No specific information is available.

OTHER

A preliminary, acute toxicology study in rats used intravenous bolus doses of 15, 30, and 60 mg/kg. All doses were associated with bone marrow, gastrointestinal, testicular, and peripheral nervous system toxicity. The higher two doses were also associated with lethality. In general, females were noted to be more susceptible then males. The single dose which was severely toxic to 10% of rats (STD10) was estimated to be 26 mg/kg.

In a 5-day study in mice, with daily intravenous dosing of 4.8 or 48 mg/kg, rear limb paresis was observed in both groups; histopathologic examination revealed axonal degeneration of peripheral nerves.

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12. ECOLOGICAL INFORMATION

Ecotoxicological Information: No information is available.

Chemical Fate Information: No information is available.

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13. DISPOSAL CONSIDERATIONS

Disposal: Treat waste product and contaminated materials as hazardous material. Incineration at an approved facility is recommended. Dispose of in accordance with all local, state and federal regulations or with the regulations of the country in which the material is used.

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14. TRANSPORT INFORMATION

DOMESTIC
Proper shipping name: Toxic solid organic, n.o.s. (Epothilone analog)
Hazard Class, UN Number, Packing Group: 6.1, UN 2811, III
Label requirements: Toxic
Placard requirements: Toxic

INTERNATIONAL
Proper shipping name: Toxic solid organic, n.o.s. (Epothilone analog)
Hazard Class, UN Number, Packing Group: 6.1, UN 2811, III
Label requirements: Toxic
Placard requirements: Toxic

Refer to Federal and international regulations for additional information.

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15. REGULATORY/STATUTORY INFORMATION -- not meant to be all inclusive

U.S. Federal: Recommended OSHA Hazard Communication Standard 1910.1200 labeling requirements: May cause cancer based on analogy to similar drugs with animal test data. May cause birth defects based on analogy to similar drugs with animal test data.

International: Toxic

EC Labeling: Toxic

In addition, since there is only limited information concerning potential health effects, the following statement is recommended:

CAUTION - SUBSTANCE NOT FULLY TESTED.

16. OTHER INFORMATION

February 1, 1999 This is the first MSDS to be issued for BMS 247550

This material is a research compound which has not been completely characterized. Treat as an unknown, potentially hazardous, carcinogenic material. Personnel who handle this material should avoid ingestion, inhalation, eye, and skin contact. Standard good laboratory safety procedures and good manufacturing practices should be followed when handling this substance.

The information contained in this MSDS is believed to be accurate and represents the best information 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.

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