

TRITURATION OF
MUSTARGEN®
(MECHLORETHAMINE HCl
for INJECTION)

WARNINGS

MUSTARGEN* (Mechlorethamine HCl) should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

This drug is **HIGHLY TOXIC** and both powder and solution must be handled and administered with care. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Avoid exposure during pregnancy. Due to the toxic properties of mechlorethamine (e.g., corrosivity, carcinogenicity, mutagenicity, teratogenicity), special handling procedures should be reviewed prior to handling and followed diligently.

Extravasation of the drug into subcutaneous tissues results in a painful inflammation. The area usually becomes indurated and sloughing may occur. If leakage of drug is obvious, prompt infiltration of the area with sterile isotonic sodium thiosulfate (1/6 molar) and application of an ice compress for 6 to 12 hours may minimize the local reaction. For a 1/6 molar solution of sodium thiosulfate, use 4.14 g of sodium thiosulfate per 100 mL of Sterile Water for Injection or 2.64 g of anhydrous sodium thiosulfate per 100 mL or dilute 4 mL of Sodium Thiosulfate Injection (10%) with 6 mL of Sterile Water for Injection.

DESCRIPTION

MUSTARGEN, an antineoplastic nitrogen mustard also known as HN2 hydrochloride, is a nitrogen analog of sulfur mustard. It is a light yellow brown, crystalline, hygroscopic powder that is very soluble in water and also soluble in alcohol.

Mechlorethamine hydrochloride is designated chemically as 2-chloro-*N*-(2-chloroethyl)-*N*-methylethanamine hydrochloride. The molecular weight is 192.52 and the melting point is 108-111°C. The empirical formula is C₅H₁₁Cl₂N•HCl, and the structural formula is: CH₃N(CH₂CH₂Cl)₂•HCl.

Trituration of MUSTARGEN is a sterile, light yellow brown crystalline powder for injection by the intravenous or intracavitary routes after dissolution. Each vial of MUSTARGEN contains 10 mg of mechlorethamine hydrochloride triturated with sodium chloride q.s. 100 mg. When dissolved with 10 mL Sterile Water for Injection or 0.9% Sodium Chloride Injection, the resulting solution has a pH of 3-5 at a concentration of 1 mg mechlorethamine HCl per mL.

CLINICAL PHARMACOLOGY

Mechlorethamine, a biologic alkylating agent, has a cytotoxic action which inhibits rapidly proliferating cells.

Pharmacokinetics and Metabolism

In water or body fluids, mechlorethamine undergoes rapid chemical transformation and combines with water or reactive compounds of cells, so that the drug is no longer present in active form a few minutes after administration.¹

INDICATIONS AND USAGE

Before using MUSTARGEN see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, and HOW SUPPLIED, Special Handling.

MUSTARGEN, administered intravenously, is indicated for the palliative treatment of Hodgkin's disease (Stages III and IV), lymphosarcoma, chronic myelocytic or chronic lymphocytic leukemia, polycythemia vera, mycosis fungoides, and bronchogenic carcinoma.

MUSTARGEN, administered intrapleurally, intraperitoneally, or intrapericardially, is indicated for the palliative treatment of metastatic carcinoma resulting in effusion.

* Registered trademark of MERCK & CO., Inc.
COPYRIGHT © MERCK & CO., Inc., 1985, 1999
All rights reserved

CONTRAINDICATIONS

The use of MUSTARGEN is contraindicated in the presence of known infectious diseases and in patients who have had previous anaphylactic reactions to MUSTARGEN.

WARNINGS

Before using MUSTARGEN, an accurate histologic diagnosis of the disease, a knowledge of its natural course, and an adequate clinical history are important. The hematologic status of the patient must first be determined. It is essential to understand the hazards and therapeutic effects to be expected. Careful clinical judgment must be exercised in selecting patients. If the indication for its use is not clear, the drug should not be used.

As nitrogen mustard therapy may contribute to extensive and rapid development of amyloidosis, it should be used only if foci of acute and chronic suppurative inflammation are absent.

Usage in Pregnancy

Mechlorethamine hydrochloride can cause fetal harm when administered to a pregnant woman. MUSTARGEN has been shown to produce fetal malformations in the rat and ferret when given as single subcutaneous injections of 1 mg/kg (2-3 times the maximum recommended human dose). There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General

This drug is **HIGHLY TOXIC** and both powder and solution must be handled and administered with care. (See boxed warning and DOSAGE AND ADMINISTRATION, *Special Handling*.) Since MUSTARGEN is a powerful vesicant, it is intended primarily for intravenous use, and in most cases is given by this route. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Appropriate protective equipment should be worn when handling MUSTARGEN. Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part must be irrigated immediately with copious amounts of water, for at least 15 minutes while removing contaminated clothing and shoes, followed by 2% sodium thiosulfate solution. Medical attention should be sought immediately. Contaminated clothing should be destroyed. (See DOSAGE AND ADMINISTRATION, *Special Handling*.)

Because of the toxicity of MUSTARGEN, and the unpleasant side effects following its use, the potential risk and discomfort from the use of this drug in patients with inoperable neoplasms or in the terminal stage of the disease must be balanced against the limited gain obtainable. These gains will vary with the nature and the status of the disease under treatment. The routine use of MUSTARGEN in all cases of widely disseminated neoplasms is to be discouraged.

The use of MUSTARGEN in patients with leukopenia, thrombocytopenia, and anemia, due to invasion of the bone marrow by tumor carries a greater risk. In such patients a good response to treatment with disappearance of the tumor from the bone marrow may be associated with improvement of bone marrow function. However, in the absence of a good response or in patients who have been previously treated with chemotherapeutic agents, hematopoiesis may be further compromised, and leukopenia, thrombocytopenia and anemia may become more severe and lead to the demise of the patient.

Tumors of bone and nervous tissue have responded poorly to therapy. Results are unpredictable in disseminated and malignant tumors of different types.

Precautions must be observed with the use of MUSTARGEN and x-ray therapy or other chemotherapy in alternating courses. Hematopoietic function is characteristically depressed by either form of therapy, and neither MUSTARGEN following x-ray therapy nor x-ray therapy subsequent to the drug should be given until bone marrow function has recovered. In particular, irradiation of such areas as sternum, ribs, and vertebrae shortly after a course of nitrogen mustard may lead to hematologic complications.

MUSTARGEN has been reported to have immunosuppressive activity. Therefore, it should be borne in mind that use of the drug may predispose the patient to bacterial, viral or fungal infection.

Hyperuricemia may develop during therapy with MUSTARGEN. The problem of urate precipitation should be anticipated, particularly in the treatment of the lymphomas, and adequate methods for control of hyperuricemia should be instituted and careful attention directed toward adequate fluid intake before treatment.

Since drug toxicity, especially sensitivity to bone marrow failure, seems to be more common in chronic lymphatic leukemia than in other conditions, the drug should be given in this condition with great caution, if at all.

Extreme caution must be used in exceeding the average recommended dose. (See OVERDOSAGE.)

Laboratory Tests

Many abnormalities of renal, hepatic, and bone marrow function have been reported in patients with neoplastic disease and receiving mechlorethamine. It is advisable to check renal, hepatic, and bone marrow functions frequently.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Therapy with alkylating agents such as MUSTARGEN may be associated with an increased incidence of a second malignant tumor, especially when such therapy is combined with other antineoplastic agents or radiation therapy.

The International Agency for Research on Cancer has judged that mechlorethamine is a probable carcinogen in humans. This is supported by limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals. Young-adult female RF mice were injected intravenously with four doses of 2.4 mg/kg of mechlorethamine (0.1% solution) at 2-week intervals with observations for up to 2 years. An increased incidence of thymic lymphomas and pulmonary adenomas was observed. Painting mechlorethamine on the skin of mice for periods up to 33 weeks resulted in squamous cell tumors in 9 of 33 mice.

Mechlorethamine induced mutations in the Ames test, in *E. coli*, and *Neurospora crassa*. Mechlorethamine caused chromosome aberrations in a variety of plant and mammalian cells. Dominant lethal mutations were produced in ICR/Ha Swiss mice.

Mechlorethamine impaired fertility in the rat at a daily dose of 500 mg/kg intravenously for two weeks.

Pregnancy

Pregnancy Category D. See WARNINGS.

Nursing Mothers

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 MUSTARGEN, 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.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established by well-controlled studies. Use of MUSTARGEN in pediatric patients has been quite limited. MUSTARGEN has been used in Hodgkin's disease, stages III and IV, in combination with other oncolytic agents (MOPP schedule). The MOPP chemotherapy combination includes mechlorethamine, vincristine, procarbazine, and prednisone.^{2,3}

ADVERSE REACTIONS

Clinical use of MUSTARGEN usually is accompanied by toxic manifestations.

Local Toxicity

Thrombosis and thrombophlebitis may result from direct contact of the drug with the intima of the injected vein. Avoid high concentration and prolonged contact with the drug, especially in cases of elevated pressure in the antebrachial vein (e.g., in mediastinal tumor compression from severe vena cava syndrome).

Systemic Toxicity

General: Hypersensitivity reactions, including anaphylaxis, have been reported. Nausea, vomiting and depression of formed elements in the circulating blood are dose-limiting side effects and usually occur with the use of full doses of MUSTARGEN. Jaundice, alopecia, vertigo, tinnitus and diminished hearing may occur infrequently. Rarely, hemolytic anemia associated with such diseases as the lymphomas and chronic lymphocytic leukemia may be precipitated by treatment with alkylating agents including MUSTARGEN. Also, various chromosomal abnormalities have been reported in association with nitrogen mustard therapy.

MUSTARGEN is given preferably at night in case sedation for side effects is required. Nausea and vomiting usually occur 1 to 3 hours after use of the drug. Emesis may disappear in the first 8 hours, but nausea may persist for 24 hours. Nausea and vomiting may be so severe as to precipitate vascular accidents in patients with a hemorrhagic tendency. Premedication with antiemetics, in addition to sedatives, may help control severe nausea and vomiting. Anorexia, weakness and diarrhea may also occur.

Hematologic: The usual course of MUSTARGEN (total dose of 0.4 mg/kg either given as a single intravenous dose or divided into two or four daily doses of 0.2 or 0.1 mg/kg, respectively) generally produces a lymphocytopenia within 24 hours after the first injection; significant granulocytopenia occurs within 6 to 8 days and lasts for 10 days to 3 weeks. Agranulocytosis appears to be relatively infrequent and recovery from leukopenia in most cases is complete within two weeks of the maximum reduction. Thrombocytopenia is variable but the time course of the appearance and recovery from reduced platelet counts generally parallels the sequence of granulocyte levels. In some cases severe thrombocytopenia may lead to bleeding from the gums and gastrointestinal tract, petechiae, and small subcutaneous hemorrhages; these symptoms appear to be transient and in most cases disappear with return to a normal platelet count. However, a severe and even uncontrollable depression of the hematopoietic system occasionally may follow the usual dose of MUSTARGEN, particularly in patients with widespread disease and debility and in patients previously treated with other antineoplastic agents or x-ray. Persistent pancytopenia has been reported. In rare instances, hemorrhagic complications may be due to hyperheparinemia. Erythrocyte and hemoglobin levels may decline during the first 2 weeks after therapy but rarely significantly. Depression of the hematopoietic system may be found up to 50 days or more after starting therapy.

Integumentary: Occasionally, a maculopapular skin eruption occurs, but this may be idiosyncratic and does not necessarily recur with subsequent courses of the drug. Erythema multiforme has been observed. Herpes zoster, a common complicating infection in patients with lymphomas, may first appear after therapy is instituted and on occasion may be precipitated by treatment. Further treatment should be discontinued during the acute phase of this illness to avoid progression to generalized herpes zoster.

Reproductive: Since the gonads are susceptible to MUSTARGEN, treatment may be followed by delayed catamenia, oligomenorrhea, or temporary or permanent amenorrhea. Impaired spermatogenesis, azoospermia, and total germinal aplasia have been reported in male patients treated with alkylating agents, especially in combination with other drugs. In some instances spermatogenesis may return in patients in remission, but this may occur only several years after intensive chemotherapy has been discontinued. Patients should be warned of the potential risk to their reproductive capacity.

OVERDOSAGE

With total doses exceeding 0.4 mg/kg of body weight for a single course, severe leukopenia, anemia, thrombocytopenia and a hemorrhagic diathesis with subsequent delayed bleeding may develop. Death may follow. The only treatment in instances of excessive dosage appears to be repeated blood product transfusions, antibiotic treatment of complicating infections and general supportive measures.

The intravenous LD₅₀ of MUSTARGEN is 2 mg/kg and 1.6 mg/kg in the mouse and rat, respectively. The oral LD₅₀ for mechlorethamine hydrochloride is 20 mg/kg and 10 mg/kg in the mouse and rat, respectively.

DOSAGE AND ADMINISTRATION

Not for oral administration

Intravenous Administration

The dosage of MUSTARGEN varies with the clinical situation, the therapeutic response and the magnitude of hematologic depression. A total dose of 0.4 mg/kg of body weight for each course usually is given either as a single dose or in divided doses of 0.1 to 0.2 mg/kg per day. Dosage should be based on ideal dry body weight. The presence of edema or ascites must be considered so that dosage will be based on actual weight unaugmented by these conditions.

The margin of safety in therapy with MUSTARGEN is narrow and considerable care must be exercised in the matter of dosage. Repeated examinations of blood are mandatory as a guide to subsequent therapy. (See OVERDOSAGE.)

Within a few minutes after intravenous injection, MUSTARGEN undergoes chemical transformation, combines with reactive compounds, and is no longer present in its active form in the blood stream. Subsequent courses should not be given until the patient has recovered hematologically from the previous course; this is best determined by repeated studies of the peripheral blood elements awaiting their return to normal levels. It is often possible to give repeated courses of MUSTARGEN as early as three weeks after treatment.

Preparation of Solution for Intravenous Administration

This drug is **HIGHLY TOXIC** and both powder and solution must be handled and administered with care. (See boxed warning and DOSAGE AND ADMINISTRATION, *Special Handling*.) Since MUSTARGEN is a powerful vesicant, it is intended primarily for intravenous use, and in most cases is

given by this route. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Appropriate protective equipment should be worn when handling MUSTARGEN. Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part must be irrigated immediately with copious amounts of water, for at least 15 minutes while removing contaminated clothing and shoes, followed by 2% sodium thiosulfate solution. Medical attention should be sought immediately. Contaminated clothing should be destroyed. (See DOSAGE AND ADMINISTRATION, *Special Handling*.)

Each vial of MUSTARGEN contains 10 mg of mechlorethamine hydrochloride triturated with sodium chloride q.s. 100 mg. In neutral or alkaline aqueous solution it undergoes rapid chemical transformation and is highly unstable. Although solutions prepared according to instructions are acidic and do not decompose as rapidly, they should be prepared immediately before each injection since they will decompose on standing. When reconstituted, MUSTARGEN is a clear colorless solution. *Do not use if the solution is discolored or if droplets of water are visible within the vial prior to reconstitution.*

Using a sterile 10 mL syringe, inject 10 mL of Sterile Water for Injection or 10 mL Sodium Chloride Injection into a vial of MUSTARGEN. With the needle (syringe attached) still in the rubber stopper, shake the vial several times to dissolve the drug completely. The resultant solution contains 1 mg of mechlorethamine hydrochloride per mL.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Special Handling

Animal studies have shown mechlorethamine to be corrosive to skin and eyes, a powerful vesicant, irritating to the mucous membranes of the respiratory tract and highly toxic by the oral route. It has also been shown to be carcinogenic, mutagenic and teratogenic. Due to the drug's toxic properties, appropriate precautions including the use of appropriate safety equipment are recommended for the preparation of MUSTARGEN for parenteral administration. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Avoid exposure during pregnancy. The National Institutes of Health presently recommends that the preparation of injectable antineoplastic drugs should be performed in a Class II laminar flow biological safety cabinet.¹⁷ Personnel preparing drugs of this class should wear chemical resistant, impervious gloves, safety goggles, outer garments and shoe covers. Additional body garments should be used based upon the task being performed (e.g., sleevelets, apron, gauntlets, disposable suits) to avoid exposed skin surfaces and inhalation of vapors and dust. Appropriate techniques should be used to remove potentially contaminated clothing.

Several other guidelines for proper handling and disposal of antineoplastic drugs have been published and should be considered.¹⁸⁻²³

Accidental Contact Measures

Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part must be irrigated immediately with copious amounts of water, for at least 15 minutes while removing contaminated clothing and shoes, followed by 2% sodium thiosulfate solution. Medical attention should be sought immediately. Contaminated clothing should be destroyed. (See PRECAUTIONS, *General* and DOSAGE AND ADMINISTRATION, *Preparation of Solution for Intravenous Administration*.)

Technique for Intravenous Administration

Withdraw into the syringe the calculated volume of solution required for a single injection. *Dispose of any remaining solution after neutralization* (see below). Although the drug may be injected directly into any suitable vein, it is injected preferably into the rubber or plastic tubing of a flowing intravenous infusion set. This reduces the possibility of severe local reactions due to extravasation or high concentration of the drug. Injecting the drug into the tubing rather than adding it to the entire volume of the infusion fluid minimizes a chemical reaction between the drug and the solution. The rate of injection apparently is not critical provided it is completed within a few minutes.

Intracavitary Administration

Nitrogen mustard has been used by intracavitary administration with varying success in certain malignant conditions for the control of pleural,⁴⁻¹³ peritoneal,^{5,6,9,11-16} and pericardial,^{5,11-13} effusions caused by malignant cells.

The technique and the dose used by any of these routes varies. Therefore, if MUSTARGEN is given by the intracavitary route, the published articles concerning such use should be consulted. *Because of the inherent risks involved, the physician should be experienced in the appropriate injection techniques, and be thoroughly aware of the indications, dosages, hazards, and precautions as set forth in the published*

literature. When using MUSTARGEN by the intracavitary route, the general precautions concerning this agent should be borne in mind.

As a general guide, reference is made especially to the techniques of Weisberger et al.^{5,11-13} Intracavitary use is indicated in the presence of pleural, peritoneal, or pericardial effusion due to metastatic tumors. Local therapy with nitrogen mustard is used only when malignant cells are demonstrated in the effusion. Intracavitary injection is not recommended when the accumulated fluid is chylous in nature, since results are likely to be poor.

Paracentesis is first performed with most of the fluid being removed from the pleural or peritoneal cavity. The intracavitary use of MUSTARGEN may exert at least some of its effect through production of a chemical poudrage. Therefore, the removal of excess fluid allows the drug to more easily contact the peritoneal and pleural linings. For intrapleural or intrapericardial injection nitrogen mustard is introduced directly through the thoracentesis needle. For intraperitoneal injection it is given through a rubber catheter inserted into the trocar used for paracentesis or through a No. 18 gauge needle inserted at another site. This drug should be injected slowly, with frequent aspiration to ensure that a free flow of fluid is present. If fluid cannot be aspirated, pain and necrosis due to injection of solution outside the cavity may occur.^{5,11-13} Free flow of fluid also is necessary to prevent injection into a loculated pocket and to ensure adequate dissemination of nitrogen mustard.

The usual dose of nitrogen mustard for intracavitary injection is 0.4 mg/kg of body weight, though 0.2 mg/kg (or 10 to 20 mg) has been used by the intrapericardial route.^{5,11-13} The solution is prepared, as previously described for intravenous injection, by adding 10 mL of Sterile Water for Injection or 10 mL of Sodium Chloride Injection to the vial containing 10 mg of mechlorethamine hydrochloride. (Amounts of diluent of 50 to 100 mL of normal saline have also been used.^{4,5}) The position of the patient should be changed every 5 to 10 minutes for an hour after injection to obtain more uniform distribution of the drug throughout the serous cavity. The remaining fluid may be removed from the pleural or peritoneal cavity by paracentesis 24 to 36 hours later. The patient should be followed carefully by clinical and x-ray examination to detect reaccumulation of fluid.

Pain occurs rarely with intrapleural use; it is common with intraperitoneal injection and is often associated with nausea, vomiting, and diarrhea of 2 to 3 days duration. Transient cardiac irregularities may occur with intrapericardial injection. Death, possibly accelerated by nitrogen mustard, has been reported following the use of this agent by the intracavitary route.⁹ Although absorption of MUSTARGEN when given by the intracavitary route is probably not complete because of its rapid deactivation by body fluids, the systemic effect is unpredictable. The acute side effects such as nausea and vomiting are usually mild. Bone marrow depression is generally milder than when the drug is given intravenously. Care should be taken to avoid use by the intracavitary route when other agents which may suppress bone marrow function are being used systemically.

Neutralization of Equipment and Unused Solution

To clean rubber gloves, tubing, glassware, etc., after giving MUSTARGEN, soak them in an aqueous solution containing equal volumes of sodium thiosulfate (5%) and sodium bicarbonate (5%) for 45 minutes. Excess reagents and reaction products are washed away easily with water. Any unused injection solution should be neutralized by mixing with an equal volume of sodium thiosulfate/sodium bicarbonate solution. Allow the mixture to stand for 45 minutes. Vials that have contained MUSTARGEN should be treated in the same way with thiosulfate/bicarbonate solution before disposal.

HOW SUPPLIED

No. 7753 — Trituration of MUSTARGEN is a light yellow brown crystalline powder, each vial containing 10 mg of mechlorethamine hydrochloride with sodium chloride q.s. 100 mg, and is supplied as follows:

NDC 0006-7753-31 in treatment sets of 4 vials.

Storage

Store at controlled room temperature 15-30°C (59-86°F). Protect from light and humidity. Solutions of mechlorethamine HCl decompose on standing; therefore, solutions of the drug should be prepared immediately before use.


REFERENCES

1. Calabresi, P.; Parks, R.E., Jr.: Antiproliferative agents and drugs used for immunosuppression, in "The Pharmacological Basis of Therapeutics", L.S. Goodman; A. Gilman (eds.), Ed. 6, New York, Macmillan, 1980, p. 1263.
2. Kolygin, B.A.: Combination chemotherapy of Hodgkin's disease in children, *Cancer Philadelphia* 38: 1494-1497, Oct. 1976.
3. Young, R.C.; DeVita, V.T.; Johnson, R.E.: Hodgkin's disease in childhood, *Blood* 42: 163-174, Aug. 1973.
4. Bass, B.H.: Nitrogen mustard in the palliation of lung cancer, *Brit. Med. J.* 1: 617-620, Feb. 27, 1960.

MUSTARGEN®
(Mechlorethamine HCl)

7417933

5. Bonte, F.J.; Storaasli, J.P.; Weisberger, A.S.: Comparative evaluation of radioactive colloidal gold and nitrogen mustard in the treatment of serous effusions of neoplastic origin, *Radiol.* 67: 63-66, July 1956.
 6. Fullerton, C.W.; Reed, P.I.: Nitrogen mustard in treatment of pleural and peritoneal effusions, *Can. Med. Ass. J.* 79: 190-191, Aug. 1, 1958.
 7. Harris, M.S.: The use of chemotherapy for carcinoma of the lung, *J. Int. Coll. Surg.* 34: 666-673, Nov. 1960.
 8. Hepper, N.G.G.; Carr, D.T.: Intrapleural use of nitrogen mustard in malignant pleural effusion, *Minn. Med.* 43: 374-376, June 1960.
 9. Levison, V.B.: Nitrogen mustard in palliation of malignant effusions, *Brit. Med. J.* 1: 1143-1145, Apr. 22, 1961.
 10. Taylor, L.: A technique for intrapleural administration of nitrogen mustard compounds, *Amer. J. Med. Sci.* 233: 538-541, May 1957.
 11. Weisberger, A.S.: Direct instillation of nitrogen mustard in the management of malignant effusions, *Ann. N.Y. Acad. Sci.* 68: 1091-1096, Apr. 24, 1958.
 12. Weisberger, A.S.; Bonte, F.J.; Suhrland, L.G.: Management of malignant serous effusions, *Geriat.* 11: 23-30, Jan. 1956.
 13. Weisberger, A.S.; Levine, B.; Storaasli, J.P.: Use of nitrogen mustard in treatment of serous effusions of neoplastic origin, *J. Amer. Med. Ass.* 159: 1704-1707, Dec. 31, 1958.
 14. Brown, F.E.; Wright, H.K.: Hypovolemia following intraperitoneal nitrogen mustard therapy, *Surg. Gynecol. & Obstet.* 121: 528-530, Sept. 1965.
 15. Greenwald, E.S.: Cancer chemotherapy, *N.Y. Med. J.* 66: 2532-2548, Oct. 1, 1966.
 16. Rohn, R.J.; Bond, W.H.: Some indications for the use of chemotherapy in neoplastic disorders, *J. Ind. Med. Ass.* 50: 417-428, Apr. 1957.
 17. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.
 18. AMA Council Report: Guidelines for Handling Parenteral Antineoplastics, *JAMA* 253: 1590-1592, 1985.
 19. National Study Commission on Cytotoxic Exposure-Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc. D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
 20. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents, *Med. J. Australia* 1: 426-428, 1983.
 21. Jones, R.B., et al: Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center, Ca - *A Cancer Journal for Clinicians* Sept/Oct, 258-263, 1983.
 22. American Society of Hospital Pharmacists: Technical assistance bulletin on handling cytotoxic and hazardous drugs, *Am. J. Hosp. Pharm.* 47: 1033-1049, 1990.
 23. Controlling Occupational Exposure to Hazardous Drugs (OSHA Work-Practice Guidelines), *Am. J. Health-Syst. Pharm.* 53: 1669-1685, 1996.
-

 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

Issued December 2002
Printed in USA