

Off Patent Oncology Drugs

Generic Drug Name altretamine

Commercial Drug Name HEXALEN

Indications and Usage

HEXALEN (altretamine) is indicated for use as a single agent in the palliative treatment of patients with persistent or recurrent ovarian cancer following first-line therapy with a cisplatin and/or alkylating agent-based combination.

Dosage and Administration

HEXALEN is administered orally. Doses are calculated on the basis of body surface area.

HEXALEN may be administered either for 14 or 21 consecutive days in a 28 day cycle at a dose of 260 mg/m²/day. The total daily dose should be given as 4 divided oral doses after meals and at bedtime. There is no pharmacokinetic information supporting this dosing regimen and the effect of food on HEXALEN bioavailability or pharmacokinetics has not been evaluated.

HEXALEN should be temporarily discontinued (for 14 days or longer) and subsequently restarted at 200 mg/m²/day for any of the following situations:

Gastrointestinal intolerance unresponsive to symptomatic measures;

White blood count <2000/mm³ or granulocyte count <1000/mm³;

Platelet count <75,000/mm³;

Progressive neurotoxicity.

If neurologic symptoms fail to stabilize on the reduced dose schedule, HEXALEN should be discontinued indefinitely.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published (2-8). There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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Generic Drug Name busulfan oral

Commercial Drug Name MYLERAN

Indications and Usage

MYLERAN (busulfan) is indicated for the palliative treatment of chronic myelogenous (myeloid, myelocytic, granulocytic) leukemia.

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Dosage and Administration

Busulfan is administered orally. The usual adult dose range for remission induction is 4 to 8 mg, total dose, daily. Dosing on a weight basis is the same for both pediatric patients and adults, approximately 60 mcg/kg of body weight or 1.8 mg/m² of body surface, daily. Since the rate of fall of the leukocyte count is dose related, daily doses exceeding 4 mg per day should be reserved for patients with the most compelling symptoms; the greater the total daily dose, the greater is the possibility of inducing bone marrow aplasia.

A decrease in the leukocyte count is not usually seen during the first 10 to 15 days of treatment; the leukocyte count may actually increase during this period and it should not be interpreted as resistance to the drug, nor should the dose be increased. Since the leukocyte count may continue to fall for more than 1 month after discontinuing the drug, it is important that busulfan be discontinued prior to the total leukocyte count falling into the normal range. When the total leukocyte count has declined to approximately 15,000/mcL, the drug should be withheld.

With a constant dose of busulfan, the total leukocyte count declines exponentially; a weekly plot of the leukocyte count on semi-logarithmic graph paper aids in predicting the time when therapy should be discontinued. With the recommended dose of busulfan, a normal leukocyte count is usually achieved in 12 to 20 weeks.

During remission, the patient is examined at monthly intervals and treatment resumed with the induction dosage when the total leukocyte count reaches approximately 50,000/mcL. When remission is shorter than 3 months, maintenance therapy of 1 to 3 mg daily may be advisable in order to keep the hematological status under control and prevent rapid relapse.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. 1-8

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate

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Generic Drug Name carmustine

Commercial Drug Name BICNU

Indications and Usage

BiCNU is indicated as palliative therapy as a single agent or in established combination therapy with other approved chemotherapeutic agents in the following:

1. Brain tumors— glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma, and metastatic brain tumors.
2. Multiple myeloma— in combination with prednisone.
3. Hodgkin's Disease— as secondary therapy in combination with other approved drugs in patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.
4. Non-Hodgkin's lymphomas— as secondary therapy in combination with other approved drugs for patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.

Dosage and Administration

The recommended dose of BiCNU as a single agent in previously untreated patients is 150 to 200 mg/m² intravenously every 6 weeks. This may be given as a single dose or divided into daily injections such as 75 to 100 mg/m² on 2 successive days. When BiCNU is used in combination with other myelosuppressive drugs or in patients in whom bone marrow reserve is depleted, the doses should be adjusted accordingly.

Doses subsequent to the initial dose should be adjusted according to the hematologic response of the patient to the preceding dose. The following schedule is suggested as a guide to dosage adjustment:
(See Table)

A repeat course of BiCNU should not be given until circulating blood elements have returned to acceptable levels (Platelets above 100,000/mm³, leukocytes above 4,000/mm³), and this is usually in 6 weeks. Adequate number of neutrophils should be present on a peripheral blood smear. Blood counts should be monitored weekly and repeat courses should not be given before 6 weeks because the hematologic toxicity is delayed and cumulative.

Administration Precautions: As with other potentially toxic compounds, caution should be exercised in handling BiCNU and preparing the solution of BiCNU. Accidental contact of reconstituted BiCNU with the skin has caused transient hyperpigmentation of the affected areas. The use of gloves is recommended. If BiCNU lyophilized material or solution contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

The reconstituted solution should be used intravenously only and should be administered by IV drip. Injection of BiCNU over shorter periods of time than 1 to 2 hours may produce intense pain and burning at the site of injection.

Preparation of Intravenous Solutions: First, dissolve BiCNU with 3 mL of the supplied sterile diluent (Dehydrated Alcohol Injection, USP), Second, aseptically add 27 mL Sterile Water for Injection, USP. Each mL of resulting solution contains 3.3 mg of BiCNU in 10% ethanol. Such solutions should be protected from light.

Reconstitution as recommended results in a clear, colorless to yellowish solution which may be further diluted with 5% Dextrose Injection, USP. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Important Note: The lyophilized dosage formulation contains no preservatives and is not intended for use as a multiple dose vial.

Stability: Unopened vials of the dry drug must be stored in a refrigerator (2° C to 8° C 36° F to 46° F). The recommended storage of unopened vials provides a stable product for 2 years. After reconstitution as recommended, BiCNU is stable for 8 hours at room temperature (25° C, 77° F), protected from light.

Vials reconstituted as directed and further diluted to a concentration of 0.2 mg/mL in 5% Dextrose Injection, USP should be stored at room temperature, protected from light and utilized within 8 hours.

Glass containers were used for the stability data provided in this section. Only use glass containers for BiCNU administration.

Important Note: BiCNU has a low melting point (30.5° to 32. 0° C or 86. 9° to 89.6° F). Exposure of the drug to this temperature or above will cause the drug to liquefy and appear as an oil film on the vials. This is a sign of decomposition and vials should be discarded. If there is a question of adequate refrigeration upon receipt of this product, immediately inspect the larger vial in each individual carton. Hold the vial to a bright light for inspection. The BiCNU will appear as a very small amount

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of dry flakes or dry congealed mass. If this is evident, the BICNU is suitable for use and should be refrigerated immediately.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.¹⁻⁷ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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Generic Drug Name carmustine

Commercial Drug Name GLIADEL

Indications and Usage

GLIADEL is indicated for use as an adjunct to surgery to prolong survival in patients with recurrent glioblastoma multiforme for whom surgical resection is indicated.

Dosage and Administration

Each GLIADEL wafer contains 7.7 mg of carmustine, resulting in a dose of 61.6 mg when eight wafers are implanted. It is recommended that eight wafers be placed in the resection cavity if the size and shape of it allows. Should the size and shape not accommodate eight wafers, the maximum number of wafers as allowed should be placed. Since there is no clinical experience, no more than eight wafers should be used per surgical procedure.

Handling and Disposal 1-7 : Wafers should only be handled by personnel wearing surgical gloves because exposure to carmustine can cause severe burning and hyperpigmentation of the skin. Use of double gloves is recommended and the outer gloves should be discarded into a biohazard waste container after use. A surgical instrument dedicated to the handling of the wafers should be used for wafer implantation. If repeat neurosurgical intervention is indicated, any wafer or wafer remnant should be handled as a potentially cytotoxic agent.

GLIADEL wafers should be handled with care. The aluminum foil laminate pouches containing GLIADEL should be delivered to the operating room and remain unopened until ready to implant the wafers. The outside surface of the outer foil pouch is not sterile.

Instructions for Opening Pouch Containing GLIADEL

Figure 1: To remove the sterile inner pouch from the outer pouch, locate the folded corner and slowly pull in an outward motion.

Figure 2: Do NOT pull in a downward motion rolling knuckles over the pouch. This may exert pressure on the wafer and cause it to break.

Figure 3: Remove the inner pouch by grabbing hold of the crimped edge and pulling upward.

Figure 4: To open the inner pouch, gently hold the crimped edge and cut in an arc-like fashion around the wafer.

Figure 5: To remove the GLIADEL wafer, gently grasp the wafer with the aid of forceps and place it onto a designated sterile field.

Once the tumor is resected, tumor pathology is confirmed, and hemostasis is obtained, up to eight GLIADEL Wafers (polifeprosan 20 with carmustine implant) may be placed to cover as much of the resection cavity as possible. Slight overlapping of the wafers is acceptable. Wafers broken in half may be used, but wafers broken in more than two pieces should be discarded in a biohazard container. Oxidized regenerated cellulose (Surgicel) may be placed over the wafers to secure them against the cavity surface. After placement of the wafers, the resection cavity should be irrigated and the dura closed in a water tight fashion.

Unopened foil pouches may be kept at ambient room temperature for a maximum of six hours at a time.

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Generic Drug Name chlorambucil

Commercial Drug Name LEUKERAN

Indications and Usage

LEUKERAN (chlorambucil) is indicated in the treatment of chronic lymphatic (lymphocytic) leukemia, malignant lymphomas including lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease. It is not curative in any of these disorders but may produce clinically useful palliation.

Dosage and Administration

The usual oral dosage is 0.1 to 0.2 mg/kg body weight daily for 3 to 6 weeks as required. This usually amounts to 4 to 10 mg per day for the average patient. The entire daily dose may be given at one time. These dosages are for initiation of therapy or for short courses of treatment. The dosage must be carefully adjusted according to the response of the patient and must be reduced as soon as there is an abrupt fall in the white blood cell count. Patients with Hodgkin's disease usually require 0.2 mg/kg daily, whereas patients with other lymphomas or chronic lymphocytic leukemia usually require only 0.1 mg/kg daily. When lymphocytic infiltration of the bone marrow is present, or when the bone marrow is hypoplastic, the daily dose should not exceed 0.1 mg/kg (about 6 mg for the average patient).

Alternate schedules for the treatment of chronic lymphocytic leukemia employing intermittent, biweekly, or once-monthly pulse doses of chlorambucil have been reported. Intermittent schedules of chlorambucil begin with an initial single dose of 0.4 mg/kg. Doses are generally increased by 0.1 mg/kg until control of lymphocytosis or toxicity is observed. Subsequent doses are modified to produce mild hematologic toxicity. It is felt that the response rate of chronic lymphocytic leukemia to the biweekly or once-monthly schedule of chlorambucil administration is similar or better to that previously reported with daily administration and that hematologic toxicity was less than or equal to that encountered in studies using daily chlorambucil.

Radiation and cytotoxic drugs render the bone marrow more vulnerable to damage, and chlorambucil should be used with particular caution within 4 weeks of a full course of radiation therapy or chemotherapy. However, small doses of palliative radiation over isolated foci remote from the bone marrow will not usually depress the neutrophil and platelet count. In these cases chlorambucil may be given in the customary dosage.

It is presently felt that short courses of treatment are safer than continuous maintenance therapy. Although both methods have been effective. It must be recognized that continuous therapy may give the appearance of "maintenance" in patients who are actually in remission and have no immediate need for further drug. If maintenance dosage is used, it should not exceed 0.1 mg/kg daily and may well be as low as 0.03 mg/kg daily. A typical maintenance dose is 2 mg to 4 mg daily, or less, depending on the status of the blood counts. It may, therefore, be desirable to withdraw the drug after maximal control has been achieved since intermittent therapy reinstated at time of relapse may be as effective as continuous treatment.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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Generic Drug Name cisplatin

Commercial Drug Name PLATINOL

Indications and Usage

PLATINOL-AQ (cisplatin injection) is indicated as therapy to be employed as follows:

Metastatic Testicular Tumors: In established combination therapy with other approved chemotherapeutic agents in patients with metastatic testicular tumors who have already received appropriate surgical and/or radiotherapeutic procedures.

Metastatic Ovarian Tumors: In established combination therapy with other approved chemotherapeutic agents in patients with metastatic ovarian tumors who have already received appropriate surgical and/or radiotherapeutic procedures. An established combination consists of PLATINOL-AQ and CYTOXAN (cyclophosphamide). PLATINOL-AQ, as a single agent, is indicated as secondary therapy in patients with metastatic ovarian tumors refractory to standard chemotherapy who have not previously received PLATINOL-AQ therapy.

Advanced Bladder Cancer: PLATINOL-AQ is indicated as a single agent for patients with transitional cell bladder cancer which is no longer amenable to local treatments such as surgery and/or radiotherapy.

Dosage and Administration

Note: Needles or intravenous sets containing aluminum parts that may come in contact with PLATINOL-AQ should not be used for preparation or administration. Aluminum reacts with PLATINOL-AQ, causing precipitate formation and a loss of potency.

Metastatic Testicular Tumors: The usual PLATINOL-AQ dose for the treatment of testicular cancer in combination with other approved chemotherapeutic agents is 20 mg/m² I.V. daily for 5 days per cycle.

Metastatic Ovarian Tumors: The usual PLATINOL-AQ dose for the treatment of metastatic ovarian tumors in combination with CYTOXAN (cyclophosphamide) is 75-100 mg/m² I.V. per cycle once every 4 weeks, (Day 1).

The dose of CYTOXAN when used in combination with PLATINOL-AQ is 600 mg/m² I.V. once every 4 weeks, (Day 1).

For directions for the administration of CYTOXAN, refer to the CYTOXAN package insert.

In combination therapy, PLATINOL-AQ and CYTOXAN are administered sequentially.

As a single agent, PLATINOL-AQ should be administered at a dose of 100 mg/m² I.V. per cycle once every 4 weeks.

Advanced Bladder Cancer: PLATINOL-AQ (cisplatin injection) should be administered as a single agent at a dose of 50-70 mg/m² I.V. per cycle once every 3 to 4 weeks depending on the extent of prior exposure to radiation therapy and/or prior chemotherapy. For heavily pretreated patients an initial dose of 50 mg/m² per cycle repeated every four weeks is recommended.

Pretreatment hydration with 1 to 2 liters of fluid infused for 8 to 12 hours prior to a PLATINOL-AQ dose is recommended. The drug is then diluted in 2 liters of 5% Dextrose in 1/2 or 1/3 normal saline containing 37.5 g of mannitol, and infused over a 6- to 8-hour period. If diluted solution is not to be used within 6 hours, protect solution from light. Do not dilute PLATINOL-AQ in just 5% Dextrose Injection. Adequate hydration and urinary output must be maintained during the following 24 hours.

A repeat course of PLATINOL-AQ should not be given until the serum creatinine is below 1.5 mg/100 mL, and/or the BUN is below 25 mg/100 mL. A repeat course should not be given until circulating blood elements are at an acceptable level (platelets =?100,000/mm³, WBC =?4,000/mm³). Subsequent doses of PLATINOL-AQ should not be given until an audiometric analysis indicates that auditory acuity is within normal limits.

As with other potentially toxic compounds, caution should be exercised in handling the aqueous solution. Skin reactions associated with accidental exposure to cisplatin may occur. The use of gloves is recommended. If PLATINOL-AQ contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

The aqueous solution should be used intravenously only and should be administered by I.V. infusion over a 6- to 8-hour period.

NOTE TO PHARMACIST: Exercise caution to prevent inadvertent PLATINOL-AQ overdosage. Please call prescriber if dose greater than 100 mg/m² per cycle. Aluminum and flip-off seal of vial have been imprinted with the following statement: CALL DR. IF DOSE>100 MG/M²/CYCLE.

STABILITY

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PLATINOL-AQ is a sterile, multidose vial without preservatives.

Store at 15°C-25°C. Do not refrigerate. Protect unopened container from light.

The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.¹⁻⁷ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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Generic Drug Name cladribine

Commercial Drug Name LEUSTATIN

Indications and Usage

LEUSTATIN Injection is indicated for the treatment of active Hairy Cell Leukemia as defined by clinically significant anemia, neutropenia, thrombocytopenia or disease-related symptoms.

Dosage and Administration

Usual Dose

The recommended dose and schedule of LEUSTATIN Injection for active Hairy Cell Leukemia is as a single course given by continuous infusion for 7 consecutive days at a dose of 0.09 mg/kg/day. Deviations from this dosage regimen are not advised. If the patient does not respond to the initial course of LEUSTATIN Injection for Hairy Cell Leukemia, it is unlikely that they will benefit from additional courses. Physicians should consider delaying or discontinuing the drug if neurotoxicity or renal toxicity occurs (see WARNINGS).

Specific risk factors predisposing to increased toxicity from LEUSTATIN (cladribine) Injection have not been defined. In view of the known toxicities of agents of this class, it would be prudent to proceed carefully in patients with known or suspected renal insufficiency or severe bone marrow impairment of any etiology. Patients should be monitored closely for hematologic and non-hematologic toxicity (see WARNINGS and PRECAUTIONS).

Preparation and Administration of Intravenous Solutions

LEUSTATIN Injection must be diluted with the designated diluent prior to administration. Since the drug product does not contain any anti-microbial preservative or bacteriostatic agent, aseptic technique and proper environmental precautions must be observed in preparation of LEUSTATIN Injection solutions.

To prepare a single daily dose: Add the calculated dose (0.09 mg/kg or 0.09 mL/kg) of LEUSTATIN Injection to an infusion bag containing 500 mL of 0.9% Sodium Chloride Injection, USP. Infuse continuously over 24 hours. Repeat daily for a total of 7 consecutive days. The use of 5% dextrose as a diluent is not recommended because of increased degradation of cladribine. Admixtures of LEUSTATIN Injection are chemically and physically stable for at least 24 hours at room temperature under normal room fluorescent light in Baxter Viaflex† PVC infusion containers. Since limited compatibility data are available, adherence to the recommended diluents and infusion systems is advised.

(See Tables)

To prepare a 7-day infusion: The 7-day infusion solution should only be prepared with Bacteriostatic 0.9% Sodium Chloride Injection, USP (0.9% benzyl alcohol preserved). In order to minimize the risk of microbial contamination, both LEUSTATIN Injection and the diluent should be passed through a sterile 0.22 µ disposable hydrophilic syringe filter as each solution is being introduced into the infusion reservoir. First add the calculated dose of LEUSTATIN Injection (7 days x 0.09 mg/kg or mL/kg) to the infusion reservoir through the sterile filter. Then add a calculated amount of Bacteriostatic 0.9% Sodium Chloride Injection, USP (0.9% benzyl alcohol preserved) also through the filter to bring the total volume of the solution to 100 mL. After completing solution preparation, clamp off the line, disconnect and discard the filter. Aseptically aspirate air bubbles from the reservoir as necessary using the syringe and a dry second sterile filter or a sterile vent filter assembly. Reclamp the line and discard the syringe and filter assembly. Infuse continuously over 7 days. Solutions prepared with Bacteriostatic Sodium Chloride Injection for individuals weighing more than 85 kg may have reduced preservative effectiveness due to greater dilution of the benzyl alcohol preservative. Admixtures for the 7-day infusion have demonstrated acceptable chemical and physical stability for at least 7 days in the SIMS Deltac MEDICATION CASSETTE-Reservoir ‡.

(See Tables)

Since limited compatibility data are available, adherence to the recommended diluents and infusion systems is advised. Solutions containing LEUSTATIN Injection should not be mixed with other intravenous drugs or additives or infused simultaneously via a common intravenous line, since compatibility testing has not been performed. Preparations containing benzyl alcohol should not be used in neonates. (see WARNINGS)

Care must be taken to assure the sterility of prepared solutions. Once diluted, solutions of LEUSTATIN Injection should be administered promptly or stored in the refrigerator (2° to 8°C) for no more than 8 hours prior to start of administration. Vials of LEUSTATIN Injection are for single-use only. Any unused portion should be discarded in an appropriate manner (see Handling and Disposal below).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. A precipitate may occur during the exposure of LEUSTATIN (cladribine) Injection to low

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temperatures; it may be resolubilized by allowing the solution to warm naturally to room temperature and by shaking vigorously. **DO NOT HEAT OR MICROWAVE.**

Chemical Stability of Vials

When stored in refrigerated conditions between 2° to 8°C (36° to 46°F) protected from light, unopened vials of LEUSTATIN Injection are stable until the expiration date indicated on the package. Freezing does not adversely affect the solution. If freezing occurs, thaw naturally to room temperature. **DO NOT** heat or microwave. Once thawed, the vial of LEUSTATIN Injection is stable until expiry if refrigerated. **DO NOT** refreeze. Once diluted, solutions containing LEUSTATIN Injection should be administered promptly or stored in the refrigerator (2° to 8°C) for no more than 8 hours prior to administration.

Handling and Disposal

The potential hazards associated with cytotoxic agents are well established and proper precautions should be taken when handling, preparing, and administering LEUSTATIN Injection. The use of disposable gloves and protective garments is recommended. If LEUSTATIN Injection contacts the skin or mucous membranes, wash the involved surface immediately with copious amounts of water. Several guidelines on this subject have been published. (2-8) There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate. Refer to your Institution's guidelines and all applicable state/local regulations for disposal of cytotoxic waste.

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Generic Drug Name cyclophosphamide

Commercial Drug Name CYTOXAN

Indications and Usage

Malignant Diseases

CYTOXAN, although effective alone in susceptible malignancies, is more frequently used concurrently or sequentially with other antineoplastic drugs. The following malignancies are often susceptible to CYTOXAN treatment:

1. Malignant lymphomas (Stages III and IV of the Ann Arbor staging system), Hodgkin's disease, lymphocytic lymphoma (nodular or diffuse), mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma.
2. Multiple myeloma.
3. Leukemias: Chronic lymphocytic leukemia, chronic granulocytic leukemia (it is usually ineffective in acute blastic crisis), acute myelogenous and monocytic leukemia, acute lymphoblastic (stem cell) leukemia in children (CYTOXAN given during remission is effective in prolonging its duration).
4. Mycosis fungoides (advanced disease).
5. Neuroblastoma (disseminated disease).
6. Adenocarcinoma of the ovary.
7. Retinoblastoma.
8. Carcinoma of the breast.

Nonmalignant Disease

Biopsy Proven "MinimalChange" Nephrotic Syndrome in Children

CYTOXAN is useful in carefully selected cases of biopsy proven "minimal change" nephrotic syndrome in children but should not be used as primary therapy. In children whose disease fails to respond adequately to appropriate adrenocorticosteroid therapy or in whom the adrenocorticosteroid therapy produces or threatens to produce intolerable side effects, CYTOXAN may induce a remission. CYTOXAN is not indicated for the nephrotic syndrome in adults or for any other renal disease.

Dosage and Administration

Treatment of Malignant Diseases

Adults and Children

When used as the only oncolytic drug therapy, the initial course of CYTOXAN for patients with no hematologic deficiency usually consists of 40 to 50 mg/kg given intravenously in divided doses over a period of 2 to 5 days. Other intravenous regimens include 10 to 15 mg/kg given every 7 to 10 days or 3 to 5 mg/kg twice weekly.

Oral CYTOXAN dosing is usually in the range of 1 to 5 mg/kg/day for both initial and maintenance dosing.

Many other regimens of intravenous and oral CYTOXAN have been reported. Dosages must be adjusted in accord with evidence of anti-tumor activity and/or leukopenia. The total leukocyte count is a good, objective guide for regulating dosage. Transient decreases in the total white blood cell count to 2000 cells/mm³ (following short courses) or more persistent reduction to 3000 cells/mm³ (with continuing therapy) are tolerated without serious risk of infection if there is no marked granulocytopenia.

When CYTOXAN is included in combined cytotoxic regimens, it may be necessary to reduce the dose of CYTOXAN as well as that of the other drugs.

CYTOXAN and its metabolites are dialyzable although there are probably quantitative differences depending upon the dialysis system being used. Patients with compromised renal function may show some measurable changes in pharmacokinetic parameters of CYTOXAN metabolism, but there is no consistent evidence indicating a need for CYTOXAN dosage modification in patients with renal function impairment.

Treatment of Nonmalignant Diseases

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Biopsy Proven "Minimal Change" Nephrotic Syndrome in Children

An oral dose of 2.5 to 3 mg/kg daily for a period of 60 to 90 days is recommended. In males, the incidence of oligospermia and azoospermia increases if the duration of CYTOXAN treatment exceeds 60 days. Treatment beyond 90 days increases the probability of sterility. Adrenocorticosteroid therapy may be tapered and discontinued during the course of CYTOXAN therapy. See PRECAUTIONS section concerning hematologic monitoring.

Preparation and Handling of Solutions

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

Lyophilized CYTOXAN should be prepared for parenteral use by adding Sterile Water for Injection, USP, to the vial and shaking to dissolve. Use the quantity of diluent shown below to reconstitute the product.

Lyophilized CYTOXAN

Dosage Strength Quantity of Diluent

100 mg 5 mL

200 mg 10 mL

500 mg 20—25 mL

1g 50 mL

2g 80—100 mL

Solutions of Lyophilized CYTOXAN may be injected intravenously, intramuscularly, intraperitoneally, or intrapleurally or they may be infused intravenously in the following:

Dextrose Injection, USP (5% dextrose)

Dextrose and Sodium Chloride Injection, USP (5% dextrose and 0.9% sodium chloride)

5% Dextrose and Ringer's Injection

Lactated Ringer's Injection, USP

Sodium Chloride Injection, USP (0.45% sodium chloride)

Sodium Lactate Injection, USP (1/6 molar sodium lactate)

Reconstituted Lyophilized CYTOXAN are chemically and physically stable for 24 hours at room temperature or for six days in the refrigerator; it does not contain any antimicrobial preservative and thus care must be taken to assure the sterility of prepared solutions.

The osmolarities of solutions of Lyophilized CYTOXAN and normal saline are found in the following table:

Lyophilized CYTOXAN mOsm/L

4 mL diluent per 100 mg cyclophosphamide 219

5 mL diluent per 100 mg cyclophosphamide 172

Lyophilized CYTOXAN is slightly hypotonic.

Extemporaneous liquid preparations of CYTOXAN for oral administration may be prepared by dissolving Lyophilized CYTOXAN in Aromatic Elixir, N.F. Such preparations should be stored under refrigeration in glass containers and used within 14 days.

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Generic Drug Name cytarabine

Commercial Drug Name CYTOSAR-U

Indications and Usage

Cytarabine in combination with other approved anticancer drugs is indicated for remission induction in acute non-lymphocytic leukemia of adults and children. It has also been found useful in the treatment of acute lymphocytic leukemia and the blast phase of chronic myelocytic leukemia. Intrathecal administration of cytarabine is indicated in the prophylaxis and treatment of meningeal leukemia.

Dosage and Administration

Cytarabine is not active orally. The schedule and method of administration varies with the program of therapy to be used. Cytarabine may be given by intravenous infusion or injection, subcutaneously, or intrathecally. Thrombophlebitis has occurred at the site of drug injection or infusion in some patients, and rarely patients have noted pain and inflammation at subcutaneous injection sites. In most instances, however, the drug has been well-tolerated.

Patients can tolerate higher total doses when they receive the drug by rapid intravenous injection as compared with infusion. This phenomenon is related to the drug's rapid inactivation and brief exposure of susceptible normal and neoplastic cells to significant levels after rapid injection. Normal and neoplastic cells seem to respond in somewhat parallel fashion to these different modes of administration and no clear-cut clinical advantage has been demonstrated for either.

In the induction therapy of acute non-lymphocytic leukemia, the usual cytarabine dose in combination with other anticancer drugs is 100 mg/m²/day by continuous IV infusion (days 1 to 7) or 100 mg/m² IV every 12 hours (days 1 to 7).

The literature should be consulted for the current recommendations for use in acute lymphocytic leukemia.

Intrathecal Use In Meningeal Leukemia

Cytarabine has been used intrathecally in acute leukemia in doses ranging from 5 to 75 mg/m² of body surface area. The frequency of administration varied from once a day for 4 days to once every 4 days. The most frequently used dose was 30 mg/m² every 4 days until cerebrospinal fluid findings were normal, followed by one additional treatment.²⁴⁻²⁸ The dosage schedule is usually governed by the type and severity of central nervous system manifestations and the response to previous therapy.

If used intrathecally, do not use a diluent containing benzyl alcohol. Many clinicians reconstitute with autologous spinal fluid or preservative-free 0.9% Sodium Chloride Injection USP and use immediately.

Cytarabine given intrathecally may cause systemic toxicity and careful monitoring of the hemopoietic system is indicated. Modification of other anti leukemia therapy may be necessary. Major toxicity is rare. The most frequently reported reactions after intrathecal administration were nausea, vomiting, and fever; these reactions are mild and self-limiting. Paraplegia has been reported.²⁹ Necrotizing leukoencephalopathy occurred in five children; these patients had also been treated with intrathecal methotrexate and hydrocortisone, as well as by central nervous system radiation.³⁰ Isolated neurotoxicity has been reported.³¹ Blindness occurred in two patients in remission whose treatment had consisted of combination systemic chemotherapy, prophylactic central nervous system radiation and intrathecal cytarabine.³²

When cytarabine is administered both intrathecally and intravenously within a few days, there is an increased risk of spinal cord toxicity. However, in serious life-threatening disease, concurrent use of intravenous and intrathecal cytarabine is left to the discretion of the treating physician.⁴⁹

Focal leukemic involvement of the central nervous system may not respond to intrathecal cytarabine and may better be treated with radiotherapy.

The 100 mg vial may be reconstituted for intravenous and subcutaneous use with 5 mL Bacteriostatic Water for Injection USP with benzyl alcohol. The resulting solution contains 20 mg of cytarabine per mL. (Do not use Bacteriostatic Water for Injection USP with benzyl alcohol as a diluent for intrathecal use. See WARNINGS section.)

The 500 mg vial may be reconstituted for intravenous and subcutaneous use with 10 mL Bacteriostatic Water for Injection USP with benzyl alcohol. The resulting solution contains 50 mg of cytarabine per mL. (Do not use Bacteriostatic Water for Injection USP with benzyl alcohol as a diluent for intrathecal use. See WARNINGS section.)

The 1 g vial may be reconstituted for intravenous and subcutaneous use with 10 mL Bacteriostatic Water for Injection USP with benzyl alcohol. The resulting solution contains 100 mg of cytarabine per mL. (Do not use Bacteriostatic Water for Injection USP with benzyl alcohol as a diluent for intrathecal use. See WARNINGS section.)

The 2 g vial may be reconstituted for intravenous and subcutaneous use with 20 mL Bacteriostatic Water for Injection USP

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with benzyl alcohol. The resulting solution contains 100 mg of cytarabine per mL. (Do not use Bacteriostatic Water for Injection USP with benzyl alcohol as a diluent for intrathecal use. See WARNINGS section.)

If used intrathecally many clinicians reconstitute with preservative-free 0.9% Sodium Chloride Injection USP and use immediately.

The pH of the reconstituted solutions is about 5. Solutions reconstituted with Bacteriostatic Water for Injection USP with benzyl alcohol may be stored at controlled room temperature, 15° to 30°C (59° to 86°F), for 48 hours. Discard any solutions in which a slight haze develops.

Solutions reconstituted without a preservative should be used immediately.

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

Chemical Stability in Infusion Solutions

Chemical stability studies were performed by HPLC on cytarabine infusion solutions. These studies showed that when the reconstituted cytarabine was added to Water for Injection USP, 5% Dextrose Injection USP or 0.9% Sodium Chloride Injection USP, 93 to 99 percent of the cytarabine was present after 192 hours storage at room temperature. This chemical stability information in no way indicates that it would be acceptable practice to infuse a cytarabine admixture well after the preparation time. Good professional practice suggests that administration of compounded admixtures should be as soon after preparation as feasible.

Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.³³⁻³⁹ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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Generic Drug Name dacarbazine

Commercial Drug Name DTIC-DOME

Indications and Usage

DTIC-Dome is indicated in the treatment of metastatic malignant melanoma. In addition, DTIC-Dome is also indicated for Hodgkin's disease as a secondary-line therapy when used in combination with other effective agents.

Dosage and Administration

Malignant Melanoma: The recommended dosage is 2 to 4.5mg/kg/day for 10 days. Treatment may be repeated at 4 week intervals. 2

An alternate recommended dosage is 250mg/square meter body surface/day I.V. for 5 days. Treatment may be repeated every 3 weeks. 3,4

Hodgkin's Disease: The recommended dosage of DTIC-Dome in the treatment of Hodgkin's disease is 150mg/ square meter body surface/day for 5 days, in combination with other effective drugs. Treatment may be repeated every 4 weeks. 5 An alternative recommended dosage is 375mg/ square meter body surface on day 1, in combination with other effective drugs, to be repeated every 15 days. 6

DTIC-Dome (dacarbazine) 100mg/vial and 200mg/vial are reconstituted with 9.9 mL and 19.7 mL, respectively, of Sterile Water for Injection, U.S.P. The resulting solution contains 10mg/mL of dacarbazine having a pH of 3.0 to 4.0. The calculated dose of the resulting solution is drawn into a syringe and administered only intravenously.

The reconstituted solution may be further diluted with 5% dextrose injection, U.S.P. or sodium chloride injection, U.S.P. and administered as an intravenous infusion.

After reconstitution and prior to use, the solution in the vial may be stored at 4°C for up to 72 hours or at normal room conditions (temperature and light) for up to 8 hours. If the reconstituted solution is further diluted in 5% dextrose, injection, U.S.P. or sodium chloride injection, U.S.P., the resulting solution may be stored at 4°C for up to 24 hours or at normal room conditions for up to 8 hours.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. 7 - 12 There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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Generic Drug Name dactinomycin

Commercial Drug Name COSMEGEN

Indications and Usage

COSMEGEN, as part of a combination chemotherapy and/or multi-modality treatment regimen, is indicated for the treatment of Wilms' tumor, childhood rhabdomyosarcoma, Ewing's sarcoma and metastatic, nonseminomatous testicular cancer.

COSMEGEN is indicated as a single agent, or as part of a combination chemotherapy regimen, for the treatment of gestational trophoblastic neoplasia.

COSMEGEN, as a component of regional perfusion, is indicated for the palliative and/or adjunctive treatment of locally recurrent or locoregional solid malignancies

Dosage and Administration

Toxic reactions due to COSMEGEN are frequent and may be severe (see ADVERSE REACTIONS), thus limiting in many instances the amount that may be administered. However, the severity of toxicity varies markedly and is only partly dependent on the dose employed.

Intravenous Use

The dosage of COSMEGEN varies depending on the tolerance of the patient, the size and location of the neoplasm, and the use of other forms of therapy. It may be necessary to decrease the usual dosages suggested below when additional chemotherapy or radiation therapy is used concomitantly or has been used previously.

The dosage for COSMEGEN is calculated in micrograms (mcg). The dose intensity per 2-week cycle for adults or children should not exceed 15 mcg/kg/day or 400-600 mcg/m²/day intravenously for five days. Calculation of the dosage for obese or edematous patients should be performed on the basis of surface area in an effort to more closely relate dosage to lean body mass.

A wide variety of single agent and combination chemotherapy regimens with COSMEGEN may be employed. Because chemotherapeutic regimens are constantly changing, dosing and administration should be performed under the direct supervision of physicians familiar with current oncologic practices and new advances in therapy. The following suggested regimens are based upon a review of current literature concerning therapy with COSMEGEN and are on a per cycle basis.

Wilms' Tumor, Childhood Rhabdomyosarcoma and Ewing's Sarcoma

Regimens of 15 mcg/kg intravenously daily for five days administered in various combinations and schedules with other chemotherapeutic agents have been utilized in the treatment of Wilms' tumor, rhabdomyosarcoma and Ewing's sarcoma.

Metastatic Nonseminomatous Testicular Cancer

1000 mcg/m² intravenously on Day 1 as part of a combination regimen with cyclophosphamide, bleomycin, vinblastine, and cisplatin.

Gestational Trophoblastic Neoplasia

12 mcg/kg intravenously daily for five days as a single agent.

500 mcg intravenously on Days 1 and 2 as part of a combination regimen with etoposide, methotrexate, folinic acid, vincristine, cyclophosphamide and cisplatin.

Regional Perfusion in Locally Recurrent and Locoregional Solid Malignancies

The dosage schedules and the technique itself vary from one investigator to another; the published literature, therefore, should be consulted for details. In general, the following doses are suggested.

50 mcg (0.05 mg) per kilogram of body weight for lower extremity or pelvis.

35 mcg (0.035 mg) per kilogram of body weight for upper extremity.

It may be advisable to use lower doses in obese patients, or when previous chemotherapy or radiation therapy has been employed.

Preparation of Solution for Intravenous Administration

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This drug is HIGHLY TOXIC and both powder and solution must be handled and administered with care (see boxed warning and HOW SUPPLIED , Special Handling). Since COSMEGEN is extremely corrosive to soft tissues, it is intended for intravenous use. 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 COSMEGEN. 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. Medical attention should be sought immediately. Contaminated clothing should be destroyed and shoes cleaned thoroughly before reuse. (See HOW SUPPLIED , Special Handling .)

Reconstitute COSMEGEN by adding 1.1 mL of Sterile Water for Injection (without preservative) using aseptic precautions. The resulting solution of COSMEGEN will contain approximately 500 mcg (0.5 mg) per mL.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. When reconstituted, COSMEGEN is a clear, gold-colored solution.

Once reconstituted, the solution of COSMEGEN can be added to infusion solutions of Dextrose Injection 5 percent or Sodium Chloride Injection either directly or to the tubing of a running intravenous infusion.

Although reconstituted COSMEGEN is chemically stable, the product does not contain a preservative and accidental microbial contamination might result. Any unused portion should be discarded. Use of water containing preservatives (benzyl alcohol or parabens) to reconstitute COSMEGEN for Injection, results in the formation of a precipitate.

Partial removal of COSMEGEN from intravenous solutions by cellulose ester membrane filters used in some intravenous in-line filters has been reported.

Since dactinomycin is extremely corrosive to soft tissue, precautions for materials of this nature should be observed.

If the drug is given directly into the vein without the use of an infusion, the "two-needle technique" should be used. Reconstitute and withdraw the calculated dose from the vial with one sterile needle. Use another sterile needle for direct injection into the vein.

Discard any unused portion of the COSMEGEN solution.

Management of Extravasation

Care in the administration of COSMEGEN will reduce the chance of perivenous infiltration (see boxed warning and ADVERSE REACTIONS). It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of COSMEGEN, extravasation may occur with or without an accompanying burning or stinging sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If extravasation is suspected, intermittent application of ice to the site for 15 minutes q.i.d. for 3 days may be useful. The benefit of local administration of drugs has not been clearly established. Because of the progressive nature of extravasation reactions, close observation and plastic surgery consultation is recommended. Blistering, ulceration and/or persistent pain are indications for wide excision surgery, followed by split-thickness skin grafting.

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Generic Drug Name daunorubicin

Commercial Drug Name CERUBIDINE

Indications and Usage

Cerubidine in combination with other approved anticancer drugs is indicated for remission induction in acute nonlymphocytic leukemia (myelogenous, monocytic, erythroid) of adults and for remission induction in acute lymphocytic leukemia of children and adults

Dosage and Administration

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

Principles: In order to eradicate the leukemic cells and induce a complete remission, a profound suppression of the bone marrow is usually required. Evaluation of both the peripheral blood and bone marrow is mandatory in the formulation of appropriate treatment plans.

It is recommended that the dosage of Cerubidine be reduced in instances of hepatic or renal impairment. For example, using serum bilirubin and serum creatinine as indicators of liver and kidney function, the following dose modifications are recommended:

(See Table)

Representative Dose Schedules and Combination for the Approved Indication of Remission Induction in Adult Acute Nonlymphocytic Leukemia:

In Combination: For patients under age 60, Cerubidine 45 mg/m² /day IV on days 1, 2, and 3 of the first course and on days 1, 2 of subsequent courses AND cytosine arabinoside 100 mg/m² /day IV infusion daily for 7 days for the first course and for 5 days for subsequent courses.

For patients 60 years of age and above, Cerubidine 30 mg/m² /day IV on days 1, 2, and 3 of the first course and on days 1, 2 of subsequent courses AND cytosine arabinoside 100 mg/m² /day IV infusion daily for 7 days for the first course and for 5 days for subsequent courses. This Cerubidine dose-reduction is based on a single study and may not be appropriate if optimal supportive care is available.

The attainment of a normal-appearing bone marrow may require up to three courses of induction therapy. Evaluation of the bone marrow following recovery from the previous course of induction therapy determines whether a further course of induction treatment is required.

Representative Dose Schedule and Combination for the Approved Indication of Remission Induction in Pediatric Acute Lymphocytic Leukemia:

In Combination: Cerubidine 25 mg/m² IV on day 1 every week, vincristine 1.5 mg/m² IV on day 1 every week, prednisone 40 mg/m² PO daily. Generally, a complete remission will be obtained within four such courses of therapy; however, if after four courses the patient is in partial remission, an additional one or, if necessary, two courses may be given in an effort to obtain a complete remission.

In children less than 2 years of age or below 0.5 m² body surface area, it has been recommended that the Cerubidine dosage calculation should be based on weight (1 mg/kg) instead of body surface area.

Representative Dose Schedules and Combination for the Approved Indication of Remission Induction in Adult Acute Lymphocytic Leukemia:

In Combination: Cerubidine 45 mg/m² /day IV on days 1, 2, and 3 AND vincristine 2 mg IV on days 1, 8, and 15; prednisone 40 mg/m² /day PO on days 1 through 22, then tapered between days 22 to 29; L-asparaginase 500 IU/kg/day x 10 days IV on days 22 through 32.

The contents of a vial should be reconstituted with 4 mL of Sterile Water for Injection and agitated gently until the material has completely dissolved. The sterile vial contents provide 20 mg of daunorubicin, with 5 mg of daunorubicin per mL. The desired dose is withdrawn into a syringe containing 10 mL to 15 mL of 0.9% Sodium Chloride Injection, USP and then injected into the tubing or sidearm in a rapidly flowing IV infusion of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP. Cerubidine should not be administered mixed with other drugs or heparin.

Storage and Handling: Store unreconstituted powder at controlled room temperature, 15° to 30° C (59° to 86° F). The reconstituted solution is stable for 24 hours at room temperature and 48 hours under refrigeration. It should be protected from exposure to sunlight. Protect from light. Retain in carton until time of use.

If Cerubidine contacts the skin or mucosae, the area should be washed thoroughly with soap and water. Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. 1-7

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There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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Generic Drug Name doxorubicin

Commercial Drug Name ADRIAMYCIN

Indications and Usage

ADRIAMYCIN PFS and ADRIAMYCIN RDF have been used successfully to produce regression in disseminated neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumor, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, transitional cell bladder carcinoma, thyroid carcinoma, gastric carcinoma, Hodgkin's disease, malignant lymphoma and bronchogenic carcinoma in which the small cell histologic type is the most responsive compared to other cell types.

Dosage and Administration

Care in the administration of ADRIAMYCIN PFS and ADRIAMYCIN RDF will reduce the chance of perivenous infiltration (see WARNINGS). It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of doxorubicin, extravasation may occur with or without an accompanying burning or stinging sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If extravasation is suspected, intermittent application of ice to the site for 15 min. q.i.d. × 3 days may be useful. The benefit of local administration of drugs has not been clearly established. Because of the progressive nature of extravasation reactions, close observation and plastic surgery consultation is recommended. Blistering, ulceration and/or persistent pain are indications for wide excision surgery, followed by split-thickness skin grafting.

The most commonly used dose schedule when used as a single agent is 60 to 75 mg/m² as a single intravenous injection administered at 21-day intervals. The lower dosage should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration. ADRIAMYCIN PFS and ADRIAMYCIN RDF have been used concurrently with other approved chemotherapeutic agents. Evidence is available that in some types of neoplastic disease combination chemotherapy is superior to single agents. The benefits and risks of such therapy continue to be elucidated. When used in combination with other chemotherapy drugs, the most commonly used dosage of doxorubicin is 40 to 60 mg/m² given as a single intravenous injection every 21 to 28 days. Doxorubicin dosage must be reduced in case of hyperbilirubinemia as follows:

Plasma bilirubin concentration (mg/dL)	Dosage reduction (%)
1.2-3.0	50
3.1-5.0	75

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Generic Drug Name estramustine

Commercial Drug Name *EMCYT*

Indications and Usage

EMCYT Capsules are indicated in the palliative treatment of patients with metastatic and/or progressive carcinoma of the prostate.

Dosage and Administration

The recommended daily dose is 14 mg per kg of body weight (ie, one 140 mg capsule for each 10 kg or 22 lb of body weight), given in 3 or 4 divided doses. Most patients in studies in the United States have been treated at a dosage range of 10 to 16 mg per kg per day.

Patients should be instructed to take EMCYT Capsules at least 1 hour before or 2 hours after meals. EMCYT should be swallowed with water. Milk, milk products, and calcium-rich foods or drugs (such as calcium-contraining antacids) must not be taken simultaneously with EMCYT.

Patients should be treated for 30 to 90 days before the physician determines the possible benefits of continued therapy. Therapy should be continued as long as the favorable response lasts. Some patients have been maintained on therapy for more than 3 years at doses ranging from 10 to 16 mg per kg of body weight per day.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. 1-7 There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Off Patent Oncology Drugs

Generic Drug Name etoposide

Commercial Drug Name VEPESID

Indications and Usage

VePesid (etoposide) is indicated in the management of the following neoplasms:

Refractory Testicular Tumors: VePesid For Injection in combination therapy with other approved chemotherapeutic agents in patients with refractory testicular tumors who have already received appropriate surgical, chemotherapeutic, and radiotherapeutic therapy.

Adequate data on the use of VePesid Capsules in the treatment of testicular cancer are not available.

Small Cell Lung Cancer: VePesid For Injection and/or Capsules in combination with other approved chemotherapeutic agents as first line treatment in patients with small cell lung cancer.

Dosage and Administration

Note: Plastic devices made of acrylic or ABS (a polymer composed of acrylonitrile, butadiene, and styrene) have been reported to crack and leak when used with undiluted VePesid For Injection.

VePesid For Injection: The usual dose of VePesid For Injection in testicular cancer in combination with other approved chemotherapeutic agents ranges from 50 to 100 mg/m²/day on days 1 through 5 to 100 mg/m²/day on days 1, 3, and 5.

In small cell lung cancer, the VePesid For Injection dose in combination with other approved chemotherapeutic drugs ranges from 35 mg/m²/day for 4 days to 50 mg/m²/day for 5 days.

For recommended dosing adjustments in patients with renal impairment, see PRECAUTIONS section.

Chemotherapy courses are repeated at 3- to 4-week intervals after adequate recovery from any toxicity.

VePesid (etoposide) Capsules: In small cell lung cancer, the recommended dose of VePesid Capsules is two times the I.V. dose rounded to the nearest 50 mg. The dosage, by either route, should be modified to take into account the myelosuppressive effects of other drugs in the combination or the effects of prior x-ray therapy or chemotherapy which may have compromised bone marrow reserve.

Administration Precautions: As with other potentially toxic compounds, caution should be exercised in handling and preparing the solution of VePesid. Skin reactions associated with accidental exposure to VePesid may occur. The use of gloves is recommended. If VePesid solution contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

Preparation for Intravenous Administration: VePesid For Injection must be diluted prior to use with either 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP, to give a final concentration of 0.2 to 0.4 mg/mL. If solutions are prepared at concentrations above 0.4 mg/mL, precipitation may occur. Hypotension following rapid intravenous administration has been reported, hence, it is recommended that the VePesid solution be administered over a 30- to 60-minute period. A longer duration of administration may be used if the volume of fluid to be infused is a concern. VePesid should not be given by rapid intravenous injection.

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

Stability: Unopened vials of VePesid For Injection are stable for 24 months at room temperature (25°C). Vials diluted as recommended to a concentration of 0.2 or 0.4 mg/mL are stable for 96 and 24 hours, respectively, at room temperature (25°C) under normal room fluorescent light in both glass and plastic containers.

VePesid Capsules must be stored under refrigeration 2°-8°C (36°- 46°F). The capsules are stable for 24 months under such refrigeration conditions.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.4-10 There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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Generic Drug Name floxuridine

Commercial Drug Name FUDR

Indications and Usage

FUDR is effective in the palliative management of gastrointestinal adenocarcinoma metastatic to the liver, when given by continuous regional intra-arterial infusion in carefully selected patients who are considered incurable by surgery or other means. Patients with known disease extending beyond an area capable of infusion via a single artery should, except in unusual circumstances, be considered for systemic therapy with other chemotherapeutic agents.

Dosage and Administration

Each vial must be reconstituted with 5 mL of sterile water for injection to yield a solution containing approximately 100 mg of floxuridine/mL. The calculated daily dose(s) of the drug is then diluted with 5% dextrose or 0.9% sodium chloride injection to a volume appropriate for the infusion apparatus to be used. The administration of FUDR is best achieved with the use of an appropriate pump to overcome pressure in large arteries and to ensure a uniform rate of infusion.

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

The recommended therapeutic dosage schedule of FUDR by continuous arterial infusion is 0.1 to 0.6 mg/kg/day. The higher dosage ranges (0.4 mg to 0.6 mg) are usually employed for hepatic artery infusion because the liver metabolizes the drug, thus reducing the potential for systemic toxicity. Therapy can be given until adverse reactions appear. (See PRECAUTIONS section.) When these side effects have subsided, therapy may be resumed. The patient should be maintained on therapy as long as response to FUDR continues.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. 1 - 6 There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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Generic Drug Name fluorouracil

Commercial Drug Name ADRUCIL

Indications and Usage

ADRUCIL Injection is effective in the palliative management of carcinoma of the colon, rectum, breast, stomach and pancreas.

Dosage and Administration

General Instructions

ADRUCIL Injection should be administered only intravenously, using care to avoid extravasation. No dilution is required.

All dosages are based on the patient's actual weight. However, the estimated lean body mass (dry weight) is used if the patient is obese or if there has been a spurious weight gain due to edema, ascites or other forms of abnormal fluid retention.

It is recommended that prior to treatment each patient be carefully evaluated in order to estimate as accurately as possible the optimum initial dosage of ADRUCIL.

Dosage

Twelve mg/kg are given intravenously once daily for four successive days. The daily dose should not exceed 800 mg. If no toxicity is observed, 6 mg/kg are given on the 6th, 8th, 10th and 12th days unless toxicity occurs. No therapy is given on the 5th, 7th, 9th or 11th days. Therapy is to be discontinued at the end of the 12th day, even if no toxicity has become apparent. (See WARNINGS and PRECAUTIONS sections.) Poor risk patients or those who are not in an adequate nutritional state (see CONTRA

INDICATIONS

and WARNINGS sections) should receive 6 mg/kg/day for three days. If no toxicity is observed, 3 mg/kg may be given on the 5th, 7th and 9th days unless toxicity occurs. No therapy is given on the 4th, 6th or 8th days. The daily dose should not exceed 400 mg.

A sequence of injections on either schedule constitutes a "course of therapy".

Maintenance Therapy

In instances where toxicity has not been a problem, it is recommended that therapy be continued using either of the following schedules:

1. Repeat dosage of first course every 30 days after the last day of the previous course of treatment.
2. When toxic signs resulting from the initial course of therapy have subsided, administer a maintenance dosage of 10 to 15 mg/kg/week as a single dose. Do not exceed 1 g per week.

The patient's reaction to the previous course of therapy should be taken into account in determining the amount of the drug to be used, and the dosage should be adjusted accordingly. Some patients have received from 9 to 45 courses of treatment during periods which ranged from 12 to 60 months.

Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If a precipitate occurs due to exposure to low temperatures, resolubilize by heating to 140°F and shaking vigorously; allow to cool to body temperature before using.

Off Patent Oncology Drugs

Generic Drug Name idarubicin

Commercial Drug Name IDAMYCIN PFS

Indications and Usage

IDAMYCIN PFS Injection in combination with other approved antileukemic drugs is indicated for the treatment of acute myeloid leukemia (AML) in adults. This includes French-American-British (FAB) classifications M1 through M7.

Dosage and Administration

For induction therapy in adult patients with AML the following dose schedule is recommended:

IDAMYCIN PFS Injection 12 mg/m² daily for 3 days by slow (10 to 15 min) intravenous injection in combination with cytarabine. The cytarabine may be given as 100 mg/m² daily by continuous infusion for 7 days or as cytarabine 25 mg/m² intravenous bolus followed by cytarabine 200 mg/m² daily for 5 days continuous infusion. In patients with unequivocal evidence of leukemia after the first induction course, a second course may be administered. Administration of the second course should be delayed in patients who experience severe mucositis, until recovery from this toxicity has occurred, and a dose reduction of 25% is recommended. In patients with hepatic and/or renal impairment, a dose reduction of IDAMYCIN PFS should be considered. IDAMYCIN PFS should not be administered if the bilirubin level exceeds 5 mg%. (See WARNINGS.)

The benefit of consolidation in prolonging the duration of remissions and survival is not proven. There is no consensus regarding optional regimens to be used for consolidation. (See CLINICAL STUDIES for doses used in U.S. Clinical studies.)

Preparation and Administration Precautions

Caution in handling the solution must be exercised as skin reactions associated with IDAMYCIN PFS may occur. Skin accidentally exposed to IDAMYCIN PFS should be washed thoroughly with soap and water and if the eyes are involved, standard irrigation techniques should be used immediately. The use of goggles, gloves, and protective gowns is recommended during preparation and administration of the drug.

Care in the administration of IDAMYCIN PFS will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions such as urticaria and erythematous streaking. During intravenous administration of IDAMYCIN PFS extravasation may occur with or without an accompanying stinging or burning sensation even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If it is known or suspected that subcutaneous extravasation has occurred, it is recommended that intermittent ice packs (1/2 hour immediately, then 1/2 hour 4 times per day for 3 days) be placed over the area of extravasation and that the affected extremity be elevated. Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and plastic surgery consultation obtained early if there is any sign of a local reaction such as pain, erythema, edema or vesication. If ulceration begins or there is severe persistent pain at the site of extravasation, early wide excision of the involved area should be considered. 1

IDAMYCIN PFS should be administered slowly (over 10 to 15 minutes) into the tubing of a freely running intravenous infusion of Sodium Chloride Injection, USP (0.9%) or 5% Dextrose Injection, USP. The tubing should be attached to a Butterfly needle or other suitable device and inserted preferably into a large vein.

Incompatibility

Unless specific compatibility data are available, IDAMYCIN PFS should not be mixed with other drugs. Precipitation occurs with heparin. Prolonged contact with any solution of an alkaline pH will result in degradation of the drug.

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

Handling and Disposal Procedures for handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. 2-8 There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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Generic Drug Name lomustine

Commercial Drug Name CEEENU

Indications and Usage

CeeNU has been shown to be useful as a single agent in addition to other treatment modalities, or in established combination therapy with other approved chemotherapeutic agents in the following:

Brain tumors: both primary and metastatic, in patients who have already received appropriate surgical and/or radiotherapeutic procedures.

Hodgkin's Disease: secondary therapy in combination with other approved drugs in patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.

Dosage and Administration

The recommended dose of CeeNU in adult and pediatric patients as a single agent in previously untreated patients is 130 mg/m² as a single oral dose every 6 weeks. In individuals with compromised bone marrow function, the dose should be reduced to 100 mg/m² every 6 weeks. When CeeNU is used in combination with other myelosuppressive drugs, the doses should be adjusted accordingly.

Doses subsequent to the initial dose should be adjusted according to the hematologic response of the patient to the preceding dose. The following schedule is suggested as a guide to dosage adjustment:
(See Table)

A repeat course of CeeNU should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/mm³; leukocytes above 4000/mm³) and this is usually in 6 weeks. Adequate number of neutrophils should be present on a peripheral blood smear. Blood counts should be monitored weekly and repeat courses should not be given before 6 weeks because the hematologic toxicity is delayed and cumulative.

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Generic Drug Name mechloroethamine

Commercial Drug Name MUSTARGEN

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.

Dosage and 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.

Off Patent Oncology Drugs

Generic Drug Name melphalan

Commercial Drug Name ALKERAN

Indications and Usage

ALKERAN Tablets are indicated for the palliative treatment of multiple myeloma and for the palliation of non-resectable epithelial carcinoma of the ovary.

Dosage and Administration

Multiple Myeloma

The usual oral dose is 6 mg (3 tablets) daily. The entire daily dose may be given at one time. The dose is adjusted, as required, on the basis of blood counts done at approximately weekly intervals. After 2 to 3 weeks of treatment, the drug should be discontinued for up to 4 weeks during which time the blood count should be followed carefully. When the white blood cell and platelet counts are rising, a maintenance dose of 2 mg daily may be instituted. Because of the patient-to-patient variation in melphalan plasma levels following oral administration of the drug, several investigators have recommended that the dosage of ALKERAN be cautiously escalated until some myelosuppression is observed in order to assure that potentially therapeutic levels of the drug have been reached.

Other dosage regimens have been used by various investigators. Osserman and Takatsuki have used an initial course of 10 mg/day for 7 to 10 days.^{2,3} They report that maximal suppression of the leukocyte and platelet counts occurs within 3 to 5 weeks and recovery within 4 to 8 weeks. Continuous maintenance therapy with 2 mg/day is instituted when the white blood cell count is greater than 4,000 cells/mcL and the platelet count is greater than 100,000 cells mcL. Dosage is adjusted to between 1 and 3 mg/day depending upon the hematological response. It is desirable to try to maintain a significant degree of bone marrow depression so as to keep the leukocyte count in the range of 3,000 to 3,500 cells/mcL.

Hoogstraten et al have started treatment with 0.15 mg/kg per day for 7 days⁴. This is followed by a rest period of at least 14 days, but it may be as long as 5 to 6 weeks. Maintenance therapy is started when the white blood cell and platelet counts are rising. The maintenance dose is 0.05 mg/kg per day or less and is adjusted according to the blood count.

Available evidence suggests that about one third to one half of the patients with multiple myeloma show a favorable response to oral administration of the drug.

One study by Alexanian et al has shown that the use of ALKERAN in combination with prednisone significantly improves the percentage of patients with multiple myeloma who achieve palliation.⁵ One regimen has been to administer courses of ALKERAN at 0.25 mg/kg per day for 4 consecutive days or 0.20 mg/kg per day for 5 consecutive days for a total dose of 1 mg/kg per course. These 4- to 5-day courses are then repeated every 4 to 6 weeks if the granulocyte count and the platelet count have returned to normal levels.

It is to be emphasized that response may be very gradual over many months; it is important that repeated courses or continuous therapy be given since improvement may continue slowly over many months, and the maximum benefit may be missed if treatment is abandoned too soon.

In patients with moderate to severe renal impairment, currently available pharmacokinetic data do not justify an absolute recommendation on dosage reduction to those patients but it may be prudent to use a reduced dose initially.

Epithelial Ovarian Cancer

One commonly employed regimen for the treatment of ovarian carcinoma has been to administer ALKERAN at a dose of 0.2 mg/kg daily for 5 days as a single course. Courses are repeated every 4 to 5 weeks depending upon hematologic tolerance.^{6,7}

Administration Precautions

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.⁸⁻¹⁴

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Off Patent Oncology Drugs

Generic Drug Name mercaptopurine

Commercial Drug Name PURINETHOL

Indications and Usage

PURINETHOL (mercaptopurine) is indicated for remission induction and maintenance therapy of acute lymphatic leukemia. The response to this agent depends upon the particular subclassification of acute lymphatic leukemia and the age of the patient (pediatric patient or adult).

Acute Lymphatic (Lymphocytic, Lymphoblastic) Leukemia: Given as a single agent for remission induction, PURINETHOL induces complete remission in approximately 25% of pediatric patients and 10% of adults. However, reliance upon PURINETHOL alone is not justified for initial remission induction of acute lymphatic leukemia since combination chemotherapy with vincristine, prednisone, and L-asparaginase results in more frequent complete remission induction than with PURINETHOL alone or in combination. The duration of complete remission induced in acute lymphatic leukemia is so brief without the use of maintenance therapy that some form of drug therapy is considered essential. PURINETHOL, as a single agent, is capable of significantly prolonging complete remission duration; however, combination therapy has produced remission duration longer than that achieved with PURINETHOL alone.

Acute Myelogenous (and Acute Myelomonocytic) Leukemia: As a single agent, PURINETHOL will induce complete remission in approximately 10% of pediatric patients and adults with acute myelogenous leukemia or its subclassifications. These results are inferior to those achieved with combination chemotherapy employing optimum treatment schedules.

Central Nervous System Leukemia: PURINETHOL is not effective for prophylaxis or treatment of central nervous system leukemia.

Other Neoplasms: PURINETHOL is not effective in chronic lymphatic leukemia, the lymphomas (including Hodgkin's Disease), or solid tumors.

Dosage and Administration

Induction Therapy: PURINETHOL is administered orally. The dosage which will be tolerated and be effective varies from patient to patient, and therefore careful titration is necessary to obtain the optimum therapeutic effect without incurring excessive, unintended toxicity. The usual initial dosage for pediatric patients and adults is 2.5 mg/kg of body weight per day (100 to 200 mg in the average adult and 50 mg in an average 5-year-old child). Pediatric patients with acute leukemia have tolerated this dose without difficulty in most cases; it may be continued daily for several weeks or more in some patients. If, after 4 weeks at this dosage, there is no clinical improvement and no definite evidence of leukocyte or platelet depression, the dosage may be increased up to 5 mg/kg daily. A dosage of 2.5 mg/kg per day may result in a rapid fall in leukocyte count within 1 to 2 weeks in some adults with acute lymphatic leukemia and high total leukocyte counts.

The total daily dosage may be given at one time. It is calculated to the nearest multiple of 25 mg. The dosage of PURINETHOL should be reduced to one third to one quarter of the usual dose if allopurinol is given concurrently. Because the drug may have a delayed action, it should be discontinued at the first sign of an abnormally large or rapid fall in the leukocyte or platelet count. If subsequently the leukocyte count or platelet count remains constant for 2 or 3 days, or rises, treatment may be resumed.

Maintenance Therapy: Once a complete hematologic remission is obtained, maintenance therapy is considered essential. Maintenance doses will vary from patient to patient. A usual daily maintenance dose of PURINETHOL is 1.5 to 2.5 mg/kg per day as a single dose. It is to be emphasized that in pediatric patients with acute lymphatic leukemia in remission, superior results have been obtained when PURINETHOL has been combined with other agents (most frequently with methotrexate) for remission maintenance. PURINETHOL should rarely be relied upon as a single agent for the maintenance of remissions induced in acute leukemia.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. 26 - 32

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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Generic Drug Name methotrexate

Commercial Drug Name METHOTREX

Indications and Usage

Neoplastic Diseases

Methotrexate is indicated in the treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole.

In acute lymphocytic leukemia, methotrexate is indicated in the prophylaxis of meningeal leukemia and is used in maintenance therapy in combination with other chemotherapeutic agents. Methotrexate is also indicated in the treatment of meningeal leukemia.

Methotrexate is used alone or in combination with other anticancer agents in the treatment of breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungoides, and lung cancer, particularly squamous cell and small cell types. Methotrexate is also used in combination with other chemotherapeutic agents in the treatment of advanced stage non-Hodgkin's lymphomas.

Methotrexate in high doses followed by leucovorin rescue in combination with other chemotherapeutic agents is effective in prolonging relapse-free survival in patients with non-metastatic osteosarcoma who have undergone surgical resection or amputation for the primary tumor.

Psoriasis

Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation. It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune responses.

Rheumatoid Arthritis

Methotrexate is indicated in the management of selected adults with severe, active, classical or definite rheumatoid arthritis (ARA criteria) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose NSAIDs and usually a trial of at least one or more disease-modifying antirheumatic drugs.

Aspirin, nonsteroidal anti-inflammatory agents, and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. (See PRECAUTIONS, Drug Interactions.) Steroids may be reduced gradually in patients who respond to methotrexate. Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, or cytotoxic agents, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

Dosage and Administration

Neoplastic Diseases

Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained. Methotrexate sodium injection and for injection may be given by the intramuscular, intravenous, intra-arterial or intrathecal route. However, the preserved formulation contains Benzyl Alcohol and must not be used for intrathecal or high dose therapy. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Choriocarcinoma and similar trophoblastic diseases: Methotrexate is administered orally or intramuscularly in doses of 15 to 30 mg daily for a five-day course. Such courses are usually repeated for 3 to 5 times as required, with rest periods of one or more weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24 hour quantitative analysis of urinary chorionic gonadotropin (hCG), which should return to normal or less than 50 IU/24 hr usually after the third or fourth course and usually be followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of methotrexate after normalization of hCG is usually recommended. Before each course of the drug careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumor drugs has been reported as being useful.

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended.

Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these disease states in doses similar to those recommended for choriocarcinoma.

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Leukemia: Acute lymphoblastic leukemia in children and young adolescents is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common.

Methotrexate alone or in combination with steroids was used initially for induction of remission in acute lymphoblastic leukemias. More recently corticosteroid therapy, in combination with other antileukemic drugs or in cyclic combinations with methotrexate included, has appeared to produce rapid and effective remissions. When used for induction, methotrexate in doses of 3.3 mg/m² in combination with 60 mg/m² of prednisone, given daily, produced remissions in 50% of patients treated, usually within a period of 4 to 6 weeks. Methotrexate in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m². It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

A variety of combination chemotherapy regimens have been used for both induction and maintenance therapy in acute lymphoblastic leukemia. The physician should be familiar with the new advances in antileukemic therapy.

Meningeal Leukemia: In the treatment or prophylaxis of meningeal leukemia, methotrexate must be administered intrathecally. Preservative free methotrexate is diluted to a concentration of 1 mg/mL in an appropriate sterile, preservative free medium such as 0.9% Sodium Chloride Injection, USP.

The cerebrospinal fluid volume is dependent on age and not on body surface area. The CSF is at 40% of the adult volume at birth and reaches the adult volume in several years.

Intrathecal methotrexate administration at a dose of 12 mg/m² (maximum 15 mg) has been reported to result in low CSF methotrexate concentrations and reduced efficacy in children and high concentrations and neurotoxicity in adults. The following dosage regimen is based on age instead of body surface area:

(See table)

In one study in patients under the age of 40, this dosage regimen appeared to result in more consistent CSF methotrexate concentrations and less neurotoxicity. Another study in children with acute lymphocytic leukemia compared this regimen to a dose of 12 mg/m² (maximum 15 mg), a significant reduction in the rate of CNS relapse was observed in the group whose dose was based on age.

Because the CSF volume and turnover may decrease with age, a dose reduction may be indicated in elderly patients.

For the treatment of meningeal leukemia, intrathecal methotrexate may be given at intervals of 2 to 5 days. However, administration at intervals of less than 1 week may result in increased subacute toxicity. Methotrexate is administered until the cell count of the cerebrospinal fluid returns to normal. At this point one additional dose is advisable. For prophylaxis against meningeal leukemia, the dosage is the same as for treatment except for the intervals of administration. On this subject, it is advisable for the physician to consult the medical literature.

Untoward side effects may occur with any given intrathecal injection and are commonly neurological in character. Large doses may cause convulsions. Methotrexate given by the intrathecal route appears significantly in the systemic circulation and may cause systemic methotrexate toxicity. Therefore, systemic antileukemic therapy with the drug should be appropriately adjusted, reduced, or discontinued. Focal leukemic involvement of the central nervous system may not respond to intrathecal chemotherapy and is best treated with radiotherapy.

Lymphomas: In Burkitt's tumor, Stages I-II, methotrexate has produced prolonged remissions in some cases. Recommended dosage is 10 to 25 mg/day orally for 4 to 8 days. In Stage III, methotrexate is commonly given concomitantly with other antitumor agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 to 2.5 mg/kg daily.

Mycosis Fungoides: Therapy with methotrexate appears to produce clinical remissions in one half of the cases treated. Dosage is usually 2.5 to 10 mg daily by mouth for weeks or months. Dose levels of drug and adjustment of dose regimen by reduction or cessation of drug are guided by patient response and hematologic monitoring. Methotrexate has also been given intramuscularly in doses of 50 mg once weekly or 25 mg 2 times weekly.

Osteosarcoma: An effective adjuvant chemotherapy regimen requires the administration of several cytotoxic chemotherapeutic agents. In addition to high-dose methotrexate with leucovorin rescue, these agents may include doxorubicin, cisplatin, and the combination of bleomycin, cyclophosphamide and dactinomycin (BCD) in the doses and schedule shown in the table below.

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The starting dose for high dose methotrexate treatment is 12 grams/m². If this dose is not sufficient to produce a peak serum methotrexate concentration of 1,000 micromolar (10⁻³ mol/L) at the end of the methotrexate infusion, the dose may be escalated to 15 grams/m² in subsequent treatments. If the patient is vomiting or is unable to tolerate oral medication, leucovorin is given IV or IM at the same dose and schedule.

(See table)

*Link MP, Goorin AM, Miser AW, et al: The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N Engl J of Med 1986; 314(No.25):1600-1606.

?See each respective package insert for full prescribing information. Dosage modifications may be necessary because of drug-induced toxicity.

When these higher doses of methotrexate are to be administered, the following safety guidelines should be closely observed.

GUIDELINES FOR METHOTREXATE THERAPY WITH LEUCOVORIN RESCUE

Administration of methotrexate should be delayed until recovery if:

- the WBC count is less than 1500/microliter

- the neutrophil count is less than 200/microliter

- the platelet count is less than 75,000/microliter

- the serum bilirubin level is greater than 1.2 mg/dL

- the SGPT level is greater than 450 U

- mucositis is present, until there is evidence of healing

- persistent pleural effusion is present; this should be drained dry prior to infusion.

Adequate renal function must be documented.

Serum creatinine must be normal, and creatinine clearance must be greater than 60 mL/min, before initiation of therapy.

Serum creatinine must be measured prior to each subsequent course of therapy. If serum creatinine has increased by 50% or more compared to a prior value, the creatinine clearance must be measured and documented to be greater than 60 mL/min (even if the serum creatinine is still within the normal range).

Patients must be well hydrated, and must be treated with sodium bicarbonate for urinary alkalinization.

Administer 1,000 mL/m² of intravenous fluid over 6 hours prior to initiation of the methotrexate infusion. Continue hydration at 125 mL/m²/hr (3 liters/m²/day) during the methotrexate infusion, and for 2 days after the infusion has been completed. Alkalinize urine to maintain pH above 7.0 during methotrexate infusion and leucovorin calcium therapy. This can be accomplished by the administration of sodium bicarbonate orally or by incorporation into a separate intravenous solution. Repeat serum creatinine and serum methotrexate 24 hours after starting methotrexate and at least once daily until the methotrexate level is below 5x10⁻⁸ mol/L (0.05 micromolar).

The table below provides guidelines for leucovorin calcium dosage based upon serum methotrexate levels. (See table below.)

Patients who experience delayed early methotrexate elimination are likely to develop nonreversible oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved.

Some patients will have abnormalities in methotrexate elimination, or abnormalities in renal function following methotrexate administration, which are significant but less severe than the abnormalities described in the table below. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (eg. medications which may interfere with

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methotrexate binding to serum albumin, or elimination) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

CAUTION: DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY.

Psoriasis and Rheumatoid Arthritis

The patient should be fully informed of the risks involved and should be under constant supervision of the physician. (See Information for Patients Under PRECAUTIONS.) Assessment of hematologic, hepatic, renal, and pulmonary function should be made by history, physical examination, and laboratory tests before beginning, periodically during, and before reinstating methotrexate therapy. (See PRECAUTIONS.) Appropriate steps should be taken to avoid conception during methotrexate therapy. (See PRECAUTIONS AND CONTRAINDICATIONS.)

Weekly therapy may be instituted with the RHEUMATREX Methotrexate Sodium 2.5 mg Tablet Dose Packs which are designed to provide doses over a range of 5 mg to 15 mg administered as a single weekly dose. The dose packs are not recommended for administration of methotrexate in weekly doses greater than 15 mg. All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects. (See ADVERSE REACTIONS.) Maximal myelosuppression usually occurs in seven to ten days.

Psoriasis: Recommended Starting Dose Schedules

1. Weekly single oral, IM or IV dose schedule: 10 to 25 mg per week until adequate response is achieved.
2. Divided oral dose schedule: 2.5 mg at 12-hour intervals for three doses.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded.

Once optimal clinical response has been achieved, each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

Rheumatoid Arthritis: Recommended Starting Dosage Schedules

1. Single oral doses of 7.5 mg once weekly.
2. Divided oral dosages of 2.5 mg at 12 hour intervals for 3 doses given as a course once weekly.

Dosages in each schedule may be adjusted gradually to achieve an optimal response, but not ordinarily to exceed a total weekly dose of 20 mg. Limited experience shows a significant increase in the incidence and severity of serious toxic reactions, especially bone marrow suppression, at doses greater than 20 mg/wk.

Once response has been achieved, each schedule should be reduced, if possible, to the lowest possible effective dose.

Therapeutic response usually begins within 3 to 6 weeks and the patient may continue to improve for another 12 weeks or more.

The optimal duration of therapy is unknown. Limited data available from long-term studies indicate that the initial clinical improvement is maintained for at least two years with continued therapy. When methotrexate is discontinued, the arthritis usually worsens within 3 to 6 weeks.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.³⁻⁸ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

RECONSTITUTION OF LYOPHILIZED POWDERS

Reconstitute immediately prior to use.

Methotrexate Sodium for Injection should be reconstituted with an appropriate sterile, preservative free medium such as 5% Dextrose Solution, USP, or Sodium Chloride Injection, USP. Reconstitute the 20 mg vial to a concentration no greater than 25 mg/mL. The 1 gram vial should be reconstituted with 19.4 mL to a concentration of 50 mg/mL. When high doses of methotrexate are administered by IV infusion, the total dose is diluted in 5% Dextrose Solution.

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For intrathecal injection, reconstitute to a concentration of 1 mg/mL with an appropriate sterile, preservative free medium such as Sodium Chloride Injection, USP.

DILUTION INSTRUCTIONS FOR LIQUID

METHOTREXATE SODIUM INJECTION PRODUCTS

Methotrexate Sodium Injection, Contains Preservative

If desired, the solution may be further diluted with a compatible medium such as Sodium Chloride Injection, USP. Storage for 24 hours at a temperature of 21 to 25°C results in a product which is within 90% of label potency.

Methotrexate LPFSodium (methotrexate sodium injection), Isotonic, Preservative Free, for Single Use Only

If desired, the solution may be further diluted immediately prior to use with an appropriate sterile, preservative free medium such as 5% Dextrose Solution, USP or Sodium Chloride Injection, USP.

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Generic Drug Name mitomycin C

Commerical Drug Name MUTAMYCIN

Indications and Usage

Mitozytrex is not recommended as single-agent, primary therapy. Mitomycin has been shown to be useful in the therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed. Mitozytrex is not recommended to replace appropriate surgery and/or radiotherapy.

Dosage and Administration

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Generic Drug Name mitotane

Commercial Drug Name LYSODREN

Indications and Usage

LYSODREN is indicated in the treatment of inoperable adrenal cortical carcinoma of both functional and nonfunctional types.

Dosage and Administration

The recommended treatment schedule is to start the patient at 2 to 6 g of LYSODREN per day in divided doses, either three or four times a day. Doses are usually increased incrementally to 9 to 10 g per day. If severe side effects appear, the dose should be reduced until the maximum tolerated dose is achieved. If the patient can tolerate higher doses and improved clinical response appears possible, the dose should be increased until adverse reactions interfere. Experience has shown that the maximum tolerated dose (MTD) will vary from 2 to 16 g per day, but has usually been 9 to 10 g per day. The highest doses used in the studies to date were 18 to 19 g per day.

Treatment should be instituted in the hospital until a stable dosage regimen is achieved.

Treatment should be continued as long as clinical benefits are observed. Maintenance of clinical status or slowing of growth of metastatic lesions can be considered clinical benefits if they can clearly be shown to have occurred.

If no clinical benefits are observed after 3 months at the maximum tolerated dose, the case would generally be considered a clinical failure. However, 10% of the patients who showed a measurable response required more than 3 months at the MTD. Early diagnosis and prompt institution of treatment improve the probability of a positive clinical response. Clinical effectiveness can be shown by reduction in tumor mass; reduction in pain, weakness or anorexia; and reduction of symptoms and signs due to excessive steroid production.

A number of patients have been treated intermittently with treatment being restarted when severe symptoms have reappeared. Patients often do not respond after the third or fourth such course. Experience accumulated to date suggests that continuous treatment with the maximum possible dosage of LYSODREN is the best approach.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. 1-7 There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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Generic Drug Name pegademase

Commercial Drug Name ADAGEN

Indications and Usage

ADAGEN (pegademase bovine) Injection is indicated for enzyme replacement therapy for adenosine deaminase (ADA) deficiency in patients with severe combined immunodeficiency disease (SCID) who are not suitable candidates for or who have failed bone marrow transplantation. ADAGEN (pegademase bovine) Injection is recommended for use in infants from birth or in children of any age at the time of diagnosis. ADAGEN (pegademase bovine) Injection is not intended as a replacement for HLA identical bone marrow transplant therapy. ADAGEN (pegademase bovine) Injection is also not intended to replace continued close medical supervision and the initiation of appropriate diagnostic tests and therapy (e.g., antibiotics, nutrition, oxygen, gammaglobulin) as indicated for intercurrent illnesses.

Dosage and Administration

Before prescribing ADAGEN (pegademase bovine) Injection the physician should be thoroughly familiar with the details of this prescribing information. For further information concerning the essential monitoring of ADAGEN (pegademase bovine) Injection therapy, the prescribing physician should contact ENZON, Inc., 20 Kingsbridge Road, Piscataway, NJ 08854. Telephone 732 980-4560. Fax 732 980-4566.

ADAGEN (pegademase bovine) Injection is recommended for use in infants from birth or in children of any age at the time of diagnosis.

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

ADAGEN (pegademase bovine) Injection should not be diluted nor mixed with any other drug prior to administration.

ADAGEN (pegademase bovine) Injection should be administered every 7 days as an intramuscular injection. The dosage of ADAGEN (pegademase bovine) Injection should be individualized. The recommended dosing schedule is 10 U/kg for the first dose, 15 U/kg for the second dose, and 20 U/kg for the third dose. The usual maintenance dose is 20 U/kg per week. Further increases of 5 U/kg/week may be necessary, but a maximum single dose of 30 U/kg should not be exceeded. Plasma levels of ADA more than twice the upper limit of 35 $\mu\text{mol/hr/mL}$ have occurred on occasion in several patients, and have been maintained for several weeks in one patient who received twice weekly injections (20 U/kg per dose) of ADAGEN (pegademase bovine) Injection. No adverse effects have been observed at these higher levels; there is no evidence that maintaining pre-injection plasma ADA above 35 $\mu\text{mol/hr/mL}$ produces any additional clinical benefits.

Dose proportionality has not been established and patients should be closely monitored when the dosage is increased. ADAGEN (pegademase bovine) Injection is not recommended for intravenous administration. The optimal dosage and schedule of administration should be established for each patient based on monitoring of plasma ADA activity levels (trough levels before maintenance injection) and biochemical markers of ADA deficiency (primarily red cell dATP content). Since improvement in immune function follows correction of metabolic abnormalities, maintenance dosage in individual patients should be aimed at achieving the following biochemical goals: 1) maintain plasma ADA activity (trough levels before maintenance injection) in the range of 15-35 $\mu\text{mol/hr/mL}$ (assayed at 37°C); and 2) decline in erythrocyte dATP to =0.005-0.015 $\mu\text{mol/mL}$ packed erythrocytes, or =1% of the total erythrocyte adenine nucleotide (ATP + dATP) content, with a normal ATP level, as measured in a pre-injection sample. In addition, continued monitoring of immune function and clinical status is essential in any patient with a primary immunodeficiency disease and should be continued in patients undergoing treatment with ADAGEN (pegademase bovine) Injection.

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Generic Drug Name pentostatin

Commercial Drug Name NIPENT

Indications and Usage

NIPENT is indicated as single-agent treatment for both untreated and alpha-interferon-refractory hairy cell leukemia patients with active disease as defined by clinically significant anemia, neutropenia, thrombocytopenia, or disease-related symptoms.

Dosage and Administration

It is recommended that patients receive hydration with 500 to 1,000 mL of 5% Dextrose in 0.5 Normal Saline or equivalent before NIPENT administration. An additional 500 mL of 5% Dextrose or equivalent should be administered after NIPENT is given.

The recommended dosage of NIPENT for the treatment of hairy cell leukemia is 4 mg/m² every other week. NIPENT may be administered intravenously by bolus injection or diluted in a larger volume and given over 20 to 30 minutes. (See Preparation of Intravenous Solution .)

Higher doses are not recommended.

No extravasation injuries were reported in clinical studies.

The optimal duration of treatment has not been determined. In the absence of major toxicity and with observed continuing improvement, the patient should be treated until a complete response has been achieved. Although not established as required, the administration of two additional doses has been recommended following the achievement of a complete response.

All patients receiving NIPENT at 6 months should be assessed for response to treatment. If the patient has not achieved a complete or partial response, treatment with NIPENT should be discontinued.

Off Patent Oncology Drugs

Generic Drug Name plicamycin

Commercial Drug Name MITHRACIN

Indications and Usage

Mithracin is a potent antineoplastic agent which has been shown to be useful in the treatment of carefully selected hospitalized patients with malignant tumors of the testis in whom successful treatment by surgery and/or radiation is impossible. Also, on the basis of limited clinical experience to date, it may be considered in the treatment of certain symptomatic patients with hypercalcemia and hypercalciuria associated with a variety of advanced neoplasms.

The use of Mithracin in other types of neoplastic disease is not recommended at the present time.

Dosage and Administration

The daily dose of Mithracin is based on the patient's body weight. If a patient has abnormal fluid retention such as edema, hydrothorax or ascites, the patient's ideal weight rather than actual body weight should be used to calculate the dose.

Treatment of Testicular Tumors: In the treatment of patients with testicular tumors the recommended daily dose of Mithracin (plicamycin) is 25 to 30 mcg (0.025-0.030 mg) per kilogram of body weight. Therapy should be continued for a period of 8 to 10 days unless significant side effects or toxicity occur during therapy. A course of therapy consisting of more than 10 daily doses is not recommended. Individual daily doses should not exceed 30 mcg (0.030 mg) per kilogram of body weight.

In those patients with responsive tumors, some degree of tumor regression is usually evident within 3 or 4 weeks following the initial course of therapy. If tumor masses remain unchanged following an initial course of therapy, additional courses of therapy at monthly intervals are warranted.

When a significant tumor regression is obtained, it is suggested that additional courses of therapy be given at monthly intervals until a complete regression of tumor masses is achieved or until definite tumor progression or new tumor masses occur in spite of continued courses of therapy.

Treatment of Hypercalcemia and Hypercalciuria: Reversal of hypercalcemia and hypercalciuria can usually be achieved with Mithracin at doses considerably lower than those recommended for use in the treatment of testicular tumors.

In hypercalcemia and hypercalciuria associated with advanced malignancy the recommended course of treatment with Mithracin is 25 mcg (0.025 mg) per kilogram of body weight per day for 3 or 4 days.

If the desired degree of reversal of hypercalcemia or hypercalciuria is not achieved with the initial course of therapy, additional courses of therapy may then be administered at intervals of one week or more to achieve the desired result or to maintain serum calcium and urinary calcium excretion at normal levels. It may be possible to maintain normal calcium balance with single, weekly doses or with a schedule of 2 or 3 doses per week.

NOTE : BECAUSE OF THE DRUG'S TOXICITY AND THE LIMITED CLINICAL EXPERIENCE TO DATE IN THESE INDICATIONS, THE FOLLOWING RECOMMENDATIONS SHOULD BE KEPT IN MIND BY THE PHYSICIAN.

CONSIDER CASES OF HYPERCALCEMIA AND HYPERCALCIURIA NOT RESPONSIVE TO CONVENTIONAL TREATMENT.

APPLY SAME CONTRAINDICATIONS AND PRECAUTIONARY MEASURES AS IN ANTITUMOR TREATMENT.

RENAL FUNCTION SHOULD BE CAREFULLY MONITORED BEFORE, DURING, AND AFTER TREATMENT.

BENEFITS OF USE DURING PREGNANCY OR IN WOMEN OF CHILDBEARING AGE SHOULD BE WEIGHED AGAINST POTENTIAL TOXICITY TO EMBRYO OR FETUS.

ADMINISTRATION

By IV administration only. The appropriate daily dose of Mithracin should be diluted in one liter of 5% Dextrose Injection, USP or Sodium Chloride Injection, USP and administered by slow intravenous infusion over a period of 4 to 6 hours. Rapid direct intravenous injection of Mithracin should be avoided as it may be associated with a higher incidence and greater severity of gastrointestinal side effects. Extravasation of solutions of Mithracin may cause local irritation and cellulitis at injection sites. Should thrombophlebitis or perivascular cellulitis occur, the infusion should be terminated and reinstated at another site. The application of moderate heat to the site of extravasation may help to disperse the compound and minimize discomfort and local tissue irritation. The use of antiemetic compounds prior to and during treatment with Mithracin may be helpful in relieving nausea and vomiting.

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published. 3 - 8 There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Off Patent Oncology Drugs

Generic Drug Name procarbazine

Commercial Drug Name MATULANE

Indications and Usage

Matulane is indicated for use in combination with other anticancer drugs for the treatment of Stage III and IV Hodgkin's disease. Matulane is used as part of the MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) regimen.

Dosage and Administration

The following doses are for administration of the drug as a single agent. When used in combination with other anticancer drugs, the Matulane dose should be appropriately reduced, e.g., in the MOPP regimen, the Matulane dose is 100 mg/m² daily for 14 days. All dosages are based on the patient's actual weight. However, the estimated lean body mass (dry weight) is used if the patient is obese or if there has been a spurious weight gain due to edema, ascites or other forms of abnormal fluid retention.

Adults: To minimize the nausea and vomiting experienced by a high percentage of patients beginning Matulane therapy, single or divided doses of 2 to 4 mg/kg/day for the first week are recommended. Daily dosage should then be maintained at 4 to 6 mg/kg/day until maximum response is obtained or until the white blood count falls below 4000/mm³ or the platelets fall below 100,000/mm³. When maximum response is obtained, the dose may be maintained at 1 to 2 mg/kg/day. Upon evidence of hematologic or other toxicity (see PRECAUTIONS section), the drug should be discontinued until there has been satisfactory recovery. After toxic side effects have subsided, therapy may then be resumed at the discretion of the physician, based on clinical evaluation and appropriate laboratory studies, at a dosage of 1 to 2 mg/kg/day.

Pediatric Patients: Very close clinical monitoring is mandatory. Undue toxicity, evidenced by tremors, coma and convulsions, has occurred in a few cases. Dosage, therefore, should be individualized. The following dosage schedule is provided as a guideline only.

Fifty (50) mg per square meter of body surface per day is recommended for the first week. Dosage should then be maintained at 100 mg per square meter of body surface per day until maximum response is obtained or until leukopenia or thrombocytopenia occurs. When maximum response is attained, the dose may be maintained at 50 mg per square meter of body surface per day. Upon evidence of hematologic or other toxicity (see PRECAUTIONS section), the drug should be discontinued until there has been satisfactory recovery, based on clinical evaluation and appropriate laboratory tests. After toxic side effects have subsided, therapy may then be resumed.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. 1-6 There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Off Patent Oncology Drugs

Generic Drug Name streptozocin

Commercial Drug Name ZANOSAR

Indications and Usage

ZANOSAR is indicated in the treatment of metastatic islet cell carcinoma of the pancreas. Responses have been obtained with both functional and nonfunctional carcinomas. Because of its inherent renal toxicity, therapy with this drug should be limited to patients with symptomatic or progressive metastatic disease.

Dosage and Administration

ZANOSAR should be administered intravenously by rapid injection or short/prolonged infusion. It is not active orally. Although it has been administered intraarterially, this is not recommended pending further evaluation of the possibility that adverse renal effects may be evoked more rapidly by this route of administration.

Two different dosage schedules have been employed successfully with ZANOSAR.

Daily Schedule—The recommended dose for daily intravenous administration is 500 mg/m² of body surface area for five consecutive days every six weeks until maximum benefit or until treatment-limiting toxicity is observed. Dose escalation on this schedule is not recommended.

Weekly Schedule—The recommended initial dose for weekly intravenous administration is 1000 mg/m² of body surface area at weekly intervals for the first two courses (weeks). In subsequent courses, drug doses may be escalated in patients who have not achieved a therapeutic response and who have not experienced significant toxicity with the previous course of treatment. However, A SINGLE DOSE OF 1500 mg/m² BODY SURFACE AREA SHOULD NOT BE EXCEEDED as a greater dose may cause azotemia. When administered on this schedule, the median time to onset of response is about 17 days and the median time to maximum response is about 35 days. The median total dose to onset of response is about 2000 mg/m² body surface area and the median total dose to maximum response is about 4000 mg/m² body surface area.

The ideal duration of maintenance therapy with ZANOSAR has not yet been clearly established for either of the above schedules.

For patients with functional tumors, serial monitoring of fasting insulin levels allows a determination of biochemical response to therapy. For patients with either functional or nonfunctional tumors, response to therapy can be determined by measurable reductions of tumor size (reduction of organomegaly, masses, or lymph nodes).

Reconstitute ZANOSAR with 9.5 mL of Dextrose Injection USP, or 0.9% Sodium Chloride Injection USP. The resulting pale-gold solution will contain 100 mg of streptozocin and 22 mg of citric acid per mL. Where more dilute infusion solutions are desirable, further dilution in the above vehicles is recommended. The total storage time for streptozocin after it has been placed in solution should not exceed 12 hours. This product contains no preservatives and is not intended as a multiple-dose vial.

Caution in the handling and preparation of the powder and solution should be exercised, and the use of gloves is recommended. If the sterile powder of ZANOSAR or a solution prepared from ZANOSAR contacts the skin or mucosae, immediately wash the affected area with soap and water.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.¹⁻⁷ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Off Patent Oncology Drugs

Generic Drug Name teniposide

Commercial Drug Name VUMON

Indications and Usage

VUMON, in combination with other approved anticancer agents, is indicated for induction therapy in patients with refractory childhood acute lymphoblastic leukemia.

Dosage and Administration

NOTE : Contact of undiluted VUMON with plastic equipment or devices used to prepare solutions for infusion may result in softening or cracking and possible drug product leakage. This effect has not been reported with diluted solutions of VUMON.

In order to prevent extraction of the plasticizer DEHP [di(2-ethylhexyl)phthalate], solutions of VUMON should be prepared in non-DEHP containing LVP containers such as glass or polyolefin plastic bags or containers.

VUMON solutions should be administered with non-DEHP containing I.V. administration sets.

In one study, childhood ALL patients failing induction therapy with a cytarabine-containing regimen were treated with the combination of VUMON 165 mg/m² and cytarabine 300 mg/m² intravenously, twice weekly for 8-9 doses. In another study, patients with childhood ALL refractory to vincristine/prednisone-containing regimens were treated with the combination of VUMON 250 mg/m² and vincristine 1.5 mg/m² intravenously, weekly for 4-8 weeks and prednisone 40 mg/m² orally × 28 days.

Adequate data in patients with hepatic insufficiency and/or renal insufficiency are lacking, but dose adjustments may be necessary for patients with significant renal or hepatic impairment.

Preparation and Administration Precautions: VUMON is a cytotoxic anticancer drug and as with other potentially toxic compounds, caution should be exercised in handling and preparing the solution of VUMON. Skin reactions associated with accidental exposure to VUMON may occur. The use of gloves is recommended. If VUMON solution contacts the skin, immediately wash the skin thoroughly with soap and water. If VUMON contacts mucous membranes, the membranes should be flushed thoroughly with water.

Preparation for Intravenous Administration: VUMON must be diluted with either 5 percent Dextrose Injection, USP or 0.9 percent Sodium Chloride Injection, USP, to give final teniposide concentrations of 0.1 mg/mL, 0.2 mg/mL, 0.4 mg/mL or 1.0 mg/mL. Solutions prepared in 5 percent Dextrose Injection, USP or 0.9 percent Sodium Chloride Injection, USP at teniposide concentrations of 0.1 mg/mL, 0.2 mg/mL or 0.4 mg/mL are stable at room temperature for up to 24 hours after preparation. VUMON solutions prepared at a final teniposide concentration of 1.0 mg/mL should be administered within 4 hours of preparation to reduce the potential for precipitation. Refrigeration of VUMON solutions is not recommended. Stability and use times are identical in glass and plastic parenteral solution containers.

Although solutions are chemically stable under the conditions indicated, precipitation of teniposide may occur at the recommended concentrations, especially if the diluted solution is subjected to more agitation than is recommended to prepare the drug solution for parenteral administration. In addition, storage time prior to administration should be minimized and care should be taken to avoid contact of the diluted solution with other drugs or fluids. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Precipitation has been reported during 24-hour infusions of VUMON diluted to teniposide concentrations of 0.1 to 0.2 mg/mL, resulting in occlusion of central venous access catheters in several patients. Heparin solution can cause precipitation of teniposide, therefore, the administration apparatus should be flushed thoroughly with 5 percent Dextrose Injection or 0.9 percent Sodium Chloride Injection, USP before and after administration of VUMON.

Hypotension has been reported following rapid intravenous administration; it is recommended that the VUMON solution be administered over at least a 30 to 60-minute period. VUMON should not be given by rapid intravenous injection.

In a 24-hour study under simulated conditions of actual use of the product relative to dilution strength, diluent and administration rates, dilutions at 0.1 to 1.0 mg/mL were chemically stable for at least 24 hours. Data collected for the presence of the extractable DEHP [di(2-ethylhexyl)phthalate] from PVC containers show that levels increased with time and concentration of the solutions. The data appeared similar for 0.9 percent Sodium Chloride Injection, USP, and 5 percent Dextrose Injection, USP. Consequently, the use of PVC containers is not recommended.

Similarly, the use of non-DEHP I.V. administration sets is recommended. Lipid administration sets or low DEHP containing nitroglycerin sets will keep patients' exposure to DEHP at low levels and are suitable for use. The diluted solutions are chemically and physically compatible with the recommended I.V. administration sets and LVP containers for up to 24 hours at ambient room temperature and lighting conditions. Because of the potential for precipitation, compatibility with other drugs, infusion materials or I.V. pumps cannot be assured.

Off Patent Oncology Drugs

Stability: Unopened ampules of VUMON are stable until the date indicated on the package when stored under refrigeration (2°-8°C) in the original package. Freezing does not adversely affect the product.

Off Patent Oncology Drugs

Generic Drug Name thioguanine

Commercial Drug Name THIOGUANINE

Indications and Usage

a) Acute Nonlymphocytic Leukemias: TABLOID brand Thioguanine is indicated for remission induction, remission consolidation, and maintenance therapy of acute nonlymphocytic leukemias. 8,9 The response to this agent depends upon the age of the patient (younger patients faring better than older) and whether thioguanine is used in previously treated or previously untreated patients. Reliance upon thioguanine alone is seldom justified for initial remission induction of acute nonlymphocytic leukemias because combination chemotherapy including thioguanine results in more frequent remission induction and longer duration of remission than thioguanine alone.

b) Other Neoplasms: TABLOID brand Thioguanine is not effective in chronic lymphocytic leukemia, Hodgkin's lymphoma, multiple myeloma, or solid tumors. Although thioguanine is one of several agents with activity in the treatment of the chronic phase of chronic myelogenous leukemia, more objective responses are observed with MYLERAN (busulfan), and therefore busulfan is usually regarded as the preferred drug.

Dosage and Administration

TABLOID brand Thioguanine is administered orally. The dosage which will be tolerated and effective varies according to the stage and type of neoplastic process being treated. Because the usual therapies for adult and pediatric acute nonlymphocytic leukemias involve the use of thioguanine with other agents in combination, physicians responsible for administering these therapies should be experienced in the use of cancer chemotherapy and in the chosen protocol.

Ninety-six (59%) of 163 pediatric patients with previously untreated acute nonlymphocytic leukemia obtained complete remission with a multiple-drug protocol including thioguanine, prednisone, cytarabine, cyclophosphamide, and vincristine. Remission was maintained with daily thioguanine, 4-day pulses of cytarabine and cyclophosphamide, and a single dose of vincristine every 28 days. The median duration of remission was 11.5 months. 8

Fifty-three percent of previously untreated adults with acute nonlymphocytic leukemias attained remission following use of the combination of thioguanine and cytarabine according to a protocol developed at The Memorial Sloan-Kettering Cancer Center. A median duration of remission of 8.8 months was achieved with the multiple-drug maintenance regimen which included thioguanine. 9

On those occasions when single-agent chemotherapy with thioguanine may be appropriate, the usual initial dosage for pediatric patients and adults is approximately 2 mg/kg of body weight per day. If, after 4 weeks on this dosage, there is no clinical improvement and no leukocyte or platelet depression, the dosage may be cautiously increased to 3 mg/kg per day. The total daily dose may be given at one time.

The dosage of thioguanine used does not depend on whether or not the patient is receiving ZYLOPRIM (allopurinol); this is in contradistinction to the dosage reduction which is mandatory when PURINETHOL (mercaptopurine) or IMURAN (azathioprine) is given simultaneously with allopurinol.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. 17 - 23

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Off Patent Oncology Drugs

Generic Drug Name thiotepa

Commercial Drug Name THIOPLEX

Indications and Usage

Thiotepa has been tried with varying results in the palliation of a wide variety of neoplastic diseases. However, the most consistent results have been seen in the following tumors:

1. Adenocarcinoma of the breast.
2. Adenocarcinoma of the ovary.
3. For controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities.
4. For the treatment of superficial papillary carcinoma of the urinary bladder.

While now largely superseded by other treatments, thiotepa has been effective against other lymphomas, such as lymphosarcoma and Hodgkin's disease.

Dosage and Administration

Since absorption from the gastrointestinal tract is variable, thiotepa should not be administered orally.

Dosage must be carefully individualized. A slow response to thiotepa does not necessarily indicate a lack of effect. Therefore, increasing the frequency of dosing may only increase toxicity. After maximum benefit is obtained by initial therapy, it is necessary to continue the patient on maintenance therapy (1 to 4 week intervals). In order to continue optimal effect, maintenance doses should not be administered more frequently than weekly in order to preserve correlation between dose and blood counts.

Preparation and Administration Precautions: Thiotepa is a cytotoxic anticancer drug and as with other potentially toxic compounds, caution should be exercised in handling and preparation of thiotepa. Skin reactions associated with accidental exposure to thiotepa may occur. The use of gloves is recommended. If thiotepa solution contacts the skin, immediately wash the skin thoroughly with soap and water. If thiotepa contacts mucous membranes, the membranes should be flushed thoroughly with water.

Preparation of Solution: Thioplex (thiotepa for injection) should be reconstituted with 1.5 mL of Sterile Water for Injection resulting in a drug concentration of approximately 10 mg/mL. The actual withdrawable quantities and concentration achieved are illustrated in the following table:

(See Table)

The reconstituted solution is hypotonic and should be further diluted with Sodium Chloride Injection (0.9% sodium chloride) before use.

When reconstituted with Sterile Water for Injection, solutions of Thioplex should be stored in a refrigerator and used within 8 hours. Reconstituted solutions further diluted with Sodium Chloride Injection should be used immediately.

In order to eliminate haze, filter solutions through a 0.22 micron filter* prior to administration. Filtering does not alter solution potency. Reconstituted solutions should be clear. Solutions that remain opaque or precipitate after filtration should not be used.

* Polysulfone membrane (Gelman's Sterile Acrodisc, Single Use) or triton-free mixed ester of cellulose/PVC (Millipore's MILLEX-GS Filter Unit).

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

Initial and Maintenance Doses: Initially the higher dose in the given range is commonly administered. The maintenance dose should be adjusted weekly on the basis of pretreatment control blood counts and subsequent blood counts.

Intravenous Administration: Thiotepa may be given by rapid intravenous administration in doses of 0.3 to 0.4 mg/kg. Doses should be given at 1 to 4 week intervals.

Intracavitary Administration: The dosage recommended is 0.6 - 0.8 mg/kg. Administration is usually effected through the same tubing which is used to remove the fluid from the cavity involved.

Off Patent Oncology Drugs

Intravesical Administration: Patients with papillary carcinoma of the bladder are dehydrated for 8 to 12 hours prior to treatment. Then 60 mg of thiotepa in 30 - 60 mL of Sodium Chloride Injection is instilled into the bladder by catheter. For maximum effect, the solution should be retained for 2 hours. If the patient finds it impossible to retain 60 mL for 2 hours, the dose may be given in a volume of 30 mL. If desired, the patient may be positioned every 15 minutes for maximum area contact. The usual course of treatment is once a week for 4 weeks. The course may be repeated if necessary, but second and third courses must be given with caution since bone-marrow depression may be increased. Deaths have occurred after intravesical administration, caused by bone-marrow depression from systemically absorbed drug.

Handling and Disposal: Follow safe cytotoxic agent handling procedures. Several guidelines on this subject have been published.¹⁻⁶ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Off Patent Oncology Drugs

Generic Drug Name vincristine

Commercial Drug Name

VELBAN

Indications and Usage

Vincristine sulfate is indicated in acute leukemia.

Vincristine sulfate has also been shown to be useful in combination with other oncolytic agents in Hodgkin's disease, non-Hodgkin's malignant lymphomas (lymphocytic, mixed-cell, histiocytic, undifferentiated, nodular, and diffuse types), rhabdomyosarcoma, neuroblastoma, and Wilms' tumor.

Dosage and Administration

This preparation is for intravenous use only (see WARNINGS).

Neurotoxicity appears to be dose related. Extreme care must be used in calculating and administering the dose of vincristine sulfate, since overdosage may have a very serious or fatal outcome.

The concentration of vincristine contained in all vials of Vincristine Sulfate Injection, USP is 1 mg/mL. Do not add extra fluid to the vial prior to removal of the dose. Withdraw the solution of vincristine sulfate into an accurate dry syringe, measuring the dose carefully. Do not add extra fluid to the vial in an attempt to empty it completely.

Caution—It is extremely important that the intravenous needle or catheter be properly positioned before any vincristine sulfate injection, usp is injected. Leakage into surrounding tissue during intravenous administration of vincristine sulfate may cause considerable irritation. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage will help disperse the drug and may minimize discomfort and the possibility of cellulitis.

Vincristine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken that there is no leakage or swelling occurring during administration (see boxed WARNINGS).

The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion (see Drug Interactions below). Injection of vincristine sulfate should be accomplished within 1 minute.

The drug is administered intravenously at weekly intervals.

The usual dose of vincristine sulfate for pediatric patients is 2 mg/m². For pediatric patients weighing 10 kg or less, the starting dose should be 0.05 mg/kg, administered once a week. The usual dose of vincristine sulfate for adults is 1.4 mg/m². A 50% reduction in the dose of vincristine sulfate is recommended for patients having a direct serum bilirubin value above 3 mg/100 mL.

Vincristine sulfate should not be given to patients while they are receiving radiation therapy through ports that include the liver. When vincristine sulfate is used in combination with L-asparaginase, vincristine sulfate should be given 12 to 24 hours before administration of the enzyme in order to minimize toxicity; administering L-asparaginase before vincristine sulfate may reduce hepatic clearance of vincristine sulfate.

Drug Interactions—Vincristine sulfate should not be diluted in solutions that raise or lower the pH outside the range of 3.5 to 5.5. It should not be mixed with anything other than normal saline or glucose in water.

Whenever solution and container permit, parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.¹⁻⁷ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Special Dispensing Information—WHEN DISPENSING VINCRIStINE IN OTHER THAN THE ORIGINAL CONTAINER, IT IS IMPERATIVE THAT IT BE PACKAGED IN THE PROVIDED OVERWRAP WHICH BEARS THE FOLLOWING STATEMENT: "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY" (see WARNINGS). A syringe containing a specific dose must be labeled, using the auxiliary sticker provided, to state: "FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY."

Off Patent Oncology Drugs

Generic Drug Name vincristine

Commercial Drug Name ONCOVIN

Indications and Usage

Vincristine sulfate injection is indicated in acute leukemia.

Vincristine sulfate injection has also been shown to be useful in combination with other oncolytic agents in Hodgkin's disease³, non-Hodgkin's malignant lymphomas 4-6 (lymphocytic, mixed cell, histiocytic, undifferentiated, nodular and diffuse types), rhabdomyosarcoma 7, neuroblastoma 8, and Wilms' tumor 9.

Dosage and Administration

This preparation is for intravenous use only (See WARNINGS).

Neurotoxicity appears to be dose related. Extreme care must be used in calculating and administering the dose of vincristine sulfate injection since overdosage may have a very serious or fatal outcome.

Special Dispensing INFORMATION

WHEN DISPENSING VINCRIStINE SULFATE INJECTION IN OTHER THAN THE ORIGINAL CONTAINER, IT IS IMPERATIVE THAT IT BE PACKAGED IN THE PROVIDED OVERWRAP WHICH BEARS THE FOLLOWING STATEMENT. "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY" (See WARNINGS). A syringe containing a specific dose must be labeled, using the auxiliary sticker provided, to state. "FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY."

The concentration of Vincristine Sulfate Injection is 1 mg/mL. Do not add extra fluid to the vial prior to removal of the dose. Withdraw the solution of Vincristine Sulfate Injection into an accurate dry syringe, measuring the dose carefully. Do not add extra fluid to the vial in an attempt to empty it completely.

Caution: It is extremely important that the intravenous needle or catheter be properly positioned before any vincristine is injected. Leakage into surrounding tissue during intravenous administration of vincristine sulfate injection may cause considerable irritation. If extravasation occurs, the injection should be discontinued immediately and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage will help disperse the drug and may minimize discomfort and the possibility of cellulitis.

Vincristine sulfate injection must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken that there is no leakage or swelling occurring during administration (See DESCRIPTION : BOXED WARNINGS and WARNINGS: BOXED WARNINGS.)

The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion (See Drug Interactions below) Injection of vincristine sulfate injection should be accomplished within 1 minute. The drug is administered intravenously at weekly intervals.

The usual dose of vincristine injection for children is 2 mg/m². For children weighing 10 kg or less, the starting dose should be 0.05 mg/kg, administered once a week. The usual dose of vincristine sulfate injection for adults is 1.4 mg/m². A 50% reduction in the dose of vincristine sulfate injection is recommended for patients having a direct serum bilirubin value above 3 mg/100 mL.¹⁹

Vincristine sulfate injection should not be given to patients while they are receiving radiation therapy through ports that include the liver. When vincristine sulfate injection is used in combination with L-asparaginase, vincristine sulfate injection should be given 12 to 24 hours before administration of the enzyme in order to minimize toxicity; administering L-asparaginase before vincristine sulfate injection may reduce hepatic clearance of vincristine.

Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.²⁰⁻²⁵ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.