

Approved Oncology Drugs with Pediatric Labeling

Generic Drug Name asparaginase

Commercial Drug Name ELSPAR

Indications and Usage

ELSPAR is indicated in the therapy of patients with acute lymphocytic leukemia. This agent is useful primarily in combination with other chemotherapeutic agents in the induction of remissions of the disease in pediatric patients. ELSPAR should not be used as the sole induction agent unless combination therapy is deemed inappropriate. ELSPAR is not recommended for maintenance therapy.

Dosage and Administration

This drug may have toxic properties and must be handled and administered with care. Special handling procedures should be reviewed prior to handling and followed diligently during reconstitution and administration. Inhalation of dust or aerosols and contact with skin or mucous membranes, especially those of the eyes, must be avoided. (See DOSAGE AND ADMINISTRATION; Special Handling.)

As a component of selected multiple agent induction regimens, ELSPAR may be administered by either the intravenous or the intramuscular route. When administered intravenously this enzyme should be given over a period of not less than thirty minutes through the side arm of an already running infusion of Sodium Chloride Injection or Dextrose Injection 5% (D₅W). ELSPAR has little tendency to cause phlebitis when given intravenously. Anaphylactic reactions require the immediate use of epinephrine, oxygen, and intravenous steroids.

When administering ELSPAR intramuscularly, the volume at a single injection site should be limited to 2 mL. If a volume greater than 2 mL is to be administered, two injection sites should be used.

Unfavorable interactions of ELSPAR with some antitumor agents have been demonstrated. It is recommended therefore, that ELSPAR be used in combination regimens only by physicians familiar with the benefits and risks of a given regimen. During the period of its inhibition of protein synthesis and Cell replication, ELSPAR may interfere with the action of drugs such as methotrexate which require Cell replication for their lethal effect. ELSPAR may interfere with the enzymatic detoxification of other drugs, particularly in the liver.

Recommended Induction Regimens:

When using chemotherapeutic agents in combination for the induction of remissions in patients with acute lymphocytic leukemia, regimens are sought which provide maximum chance of success while avoiding excessive cumulative toxicity or negative drug interactions.

One of the following combination regimens incorporating ELSPAR is recommended for acute lymphocytic leukemia in pediatric patients:

In the regimens below, Day 1 is considered to be the first day of therapy.

Regimen I3:

Prednisone 40 mg/Square meter of body surface area per day orally in three divided doses for 15 days, followed by tapering of the dosage as follows:

20 mg/square meter for 2 days, 10 mg/square meter for 2 days, 5 mg/square meter for 2 days, 2.5 mg/square meter for 2 days and then discontinue.

Vincristine sulfate 2 mg/square meter of body surface area intravenously once weekly on Days 1, 8, and 15 of the treatment period. The maximum single dose should not exceed 2.0 mg.

Asparaginase 1,000 I.U./kg/day intravenously for ten successive days beginning on Day 22 of the treatment period.

Regimen II4

Prednisone 40 mg/square meter of body surface area per day orally in three divided doses for 28 days (the total daily dose should be to the nearest 2.5 mg), following which the dosage of prednisone should be discontinued gradually over a 14 day period.

Vincristine sulfate 1.5 mg/square meter of body surface area intravenously weekly for four doses, on Days 1, 8, 15, and 22 of the treatment period. The maximum single dose should not exceed 2.0 mg.

Asparaginase 6,000 I.U./square meter of body surface area intramuscularly on Days 4, 7, 10, 13, 16, 19, 22, 25, and 28 of the treatment period. When a remission is obtained with either of the above regimens, appropriate maintenance therapy must be instituted. ELSPAR should not be used as part of a maintenance regimen. The above regimens do not preclude a need for special therapy directed toward the prevention of central nervous system leukemia.

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It should be noted that ELSPAR has been used in combination regimens other than those recommended above. It is important to keep in mind that ELSPAR administered intravenously concurrently with or immediately before a course of vincristine and prednisone may be associated with increased toxicity. Physicians using a given regimen should be thoroughly familiar with its benefits and risks. Clinical data are insufficient for a recommendation concerning the use of combination regimens in adults. Asparaginase toxicity is reported to be greater in adults than in pediatric patients.

Use of ELSPAR as the sole induction agent should be undertaken only in an unusual situation when a combined regimen is inappropriate because of toxicity or other specific patient-related factors, or in cases refractory to other therapy. When ELSPAR is to be used as the sole induction agent for pediatric patients or adults, the recommended dosage regimen is 200 IU/kg/day intravenously for 28 days. When complete remissions were obtained with this regimen, they were of short duration, 1 to 3 months. ELSPAR has been used as the sole induction agent in other regimens.^{6-21,24} Physicians using a given regimen should be thoroughly familiar with its benefits and risks.

Patients undergoing induction therapy must be carefully monitored and the therapeutic regimen adjusted according to response and toxicity.

Such adjustments should always involve decreasing dosages of one or more agents or discontinuation depending on the degree of toxicity. Patients who have received a course of ELSPAR, if retreated, have an increased risk of hypersensitivity reactions. Therefore, retreatment should be undertaken only when the benefit of such therapy is weighed against the increased risk.

Intradermal Skin Test:

Because of the occurrence of allergic reactions, an intradermal skin test should be performed prior to the initial administration of ELSPAR and when ELSPAR is given after an interval of a week or more has elapsed between doses. The skin test solution may be prepared as follows: Reconstitute the contents of a 10,000 I.U. vial with 5.0 mL of diluent. From this solution (2,000 I.U./mL) withdraw 0.1 mL and inject it into another vial containing 9.9 mL of diluent, yielding a skin test solution of approximately 20.0 I.U./mL. Use 0.1 mL of this solution (about 2.0 I.U.) for the intradermal skin test. The skin test site should be observed for at least one hour for the appearance of a wheal or erythema either of which indicates a positive reaction. An allergic reaction even to the skin test dose in certain sensitized individuals may rarely occur. A negative skin test reaction does not preclude the possibility of the development of an allergic reaction.

(TABLE)

Directions for Reconstitution

This drug may have toxic properties and must be handled and administered with care. Inhalation of dust or aerosols and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Appropriate protective equipment should be worn when handling ELSPAR. (See Special Handling.)

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. When reconstituted, ELSPAR should be a clear, colorless solution. If the solution becomes cloudy, discard.

For Intravenous Use

Reconstitute with Sterile Water for Injection or with Sodium Chloride Injection. The volume recommended for reconstitution is 5 mL for the 10,000 unit vials. Ordinary shaking during reconstitution does not inactivate the enzyme. This solution may be used for direct intravenous administration within an eight hour period following restoration. For administration by infusion, solutions should be diluted with the isotonic solutions, Sodium Chloride Injection or Dextrose Injection 5%. These solutions should be infused within eight hours and only if clear.

Occasionally, a very small number of gelatinous fiber-like particles may develop on standing. Filtration through a 5.0 micron filter during administration will remove the particles with no resultant loss in potency. Some loss of potency has been observed with the use of a 0.2 micron filter.

For Intramuscular Use

When ELSPAR is administered intramuscularly according to the schedule cited in the induction regimen, reconstitution is carried out by adding 2 mL Sodium Chloride Injection to the 10,000 unit vial. The resulting solution should be used within eight hours and only if clear.

Special Handling

L-asparaginase may be irritating to eyes, skin and the upper respiratory tract. It has also been shown to be embryotoxic and teratogenic by the intravenous route in animal studies. Due to the drug's potential toxic properties, appropriate precautions including the use of appropriate safety equipment are recommended for the preparation of ELSPAR for administration. Inhalation of dust or aerosols and contact with skin or mucous membranes, especially those of the eyes, must be avoided. The

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National Institutes of Health presently recommends that the preparation of injectable antineoplastic drugs should be performed in a Class II laminar flow biological safety cabinet. Personnel preparing drugs of this class should wear chemical resistant, impervious gloves, safety goggles, outer garments and shoe covers. Additional body garments should be used based upon the task being performed (e.g., sleevelets, apron, gauntlets, disposable suits) to avoid exposed skin surfaces and inhalation of vapors and dust. Appropriate techniques should be used to remove potentially contaminated clothing.

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

Accidental Contact Measures

Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part should be washed immediately with soap and water. Medical attention should be sought. If inhaled, remove from exposure and seek medical attention. (See PRECAUTIONS, General and DOSAGE AND ADMINISTRATION.)

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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 "Minimal Change" 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 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

Approved Oncology Drugs with Pediatric Labeling

Generic Drug Name imatinib mesylate

Commercial Drug Name GLEEVEC

Indications and Usage

Gleevec™ (imatinib mesylate) is indicated for the treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in chronic phase. Follow-up is limited. Gleevec is also indicated for the treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Gleevec is also indicated for the treatment of pediatric patients with Ph+ chronic phase CML whose disease has recurred after stem cell transplant or who are resistant to interferon alpha therapy. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). (See CLINICAL STUDIES: Gastrointestinal Stromal Tumors.) The effectiveness of Gleevec in GIST is based on objective response rate (see CLINICAL STUDIES). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Dosage and Administration

Therapy should be initiated by a physician experienced in the treatment of patients with chronic myeloid leukemia or gastrointestinal stromal tumors.

The recommended dosage of Gleevec™ (imatinib mesylate) is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis. The recommended Gleevec dosage is 260 mg/m²/day for children with Ph+ chronic phase CML recurrent after stem cell transplant or who are resistant to interferon alpha therapy. The recommended dosage of Gleevec is 400 mg/day or 600 mg/day for adult patients with unresectable and/or metastatic, malignant GIST.

The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day.

In children Gleevec treatment can be given as a once daily dose or alternatively the daily dose may be split into two - once in the morning and once in the evening. There is no experience with Gleevec treatment in children under 3 years of age. For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass

of water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 ml for a 100 mg tablet, and 200 ml for a 400 mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory hematologic response after at least 3 months of treatment; failure to achieve a cytogenetic response after 6-12 months of treatment; or loss of a previously achieved hematologic or cytogenetic response. In children with chronic phase CML, daily doses can be increased under circumstances similar to those leading to an increase in adult chronic phase disease, from 260 mg/m²/day to 340 mg/m²/day, as clinically indicated.

Dosage of Gleevec should be increased by at least 50%, and clinical response should be carefully monitored, in patients receiving Gleevec with a potent CYP3A4 inducer such as rifampin or phenytoin.

Approved Oncology Drugs with Pediatric Labeling

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.

Approved Oncology Drugs with Pediatric Labeling

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.

Approved Oncology Drugs with Pediatric Labeling

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.

Approved Oncology Drugs with Pediatric Labeling

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.

Approved Oncology Drugs with Pediatric Labeling

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)phtalate], 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)phtalate] 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.

Approved Oncology Drugs with Pediatric Labeling

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.

Approved Oncology Drugs with Pediatric Labeling

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.

Approved Oncology Drugs with Pediatric Labeling

Generic Drug Name tretinoin

Commercial Drug Name VESANOID

Indications and Usage

VESANOID (tretinoin) capsules are indicated for the induction of remission in patients with acute promyelocytic leukemia (APL), French-American-British (FAB) classification M3 (including the M3 variant), characterized by the presence of the t(15;17) translocation and/or the presence of the PML/RARalpha gene who are refractory to, or who have relapsed from, anthracycline chemotherapy, or for whom anthracycline-based chemotherapy is contraindicated. VESANOID is for the induction of remission only. The optimal consolidation or maintenance regimens have not been defined, but all patients should receive an accepted form of remission consolidation and/or maintenance therapy for APL after completion of induction therapy with VESANOID.

Dosage and Administration

The recommended dose is 45 mg/m²/ day administered as two evenly divided doses until complete remission is documented. Therapy should be discontinued 30 days after achievement of complete remission or after 90 days of treatment, whichever occurs first.

If after initiation of treatment of VESANOID the presence of the t(15;17) translocation is not confirmed by cytogenetics and/or by polymerase chain reaction studies and the patient has not responded to VESANOID, alternative therapy appropriate for acute myelogenous leukemia should be considered.

VESANOID is for the induction of remission only. Optimal consolidation or maintenance regimens have not been determined. All patients should, therefore, receive a standard consolidation and/or maintenance chemotherapy regimen for APL after induction therapy with VESANOID, unless otherwise contraindicated.

Approved Oncology Drugs with Pediatric Labeling

Generic Drug Name vinblastine

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."

Approved Oncology Drugs with Pediatric Labeling

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.