

Rx only

DepoCyt[®]

(cytarabine liposome injection)

For Intrathecal Use Only

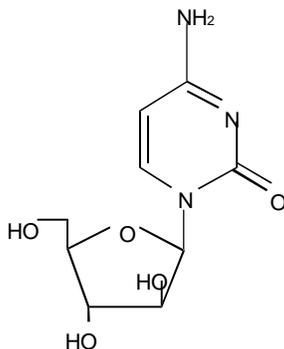
50 mg vial

WARNING

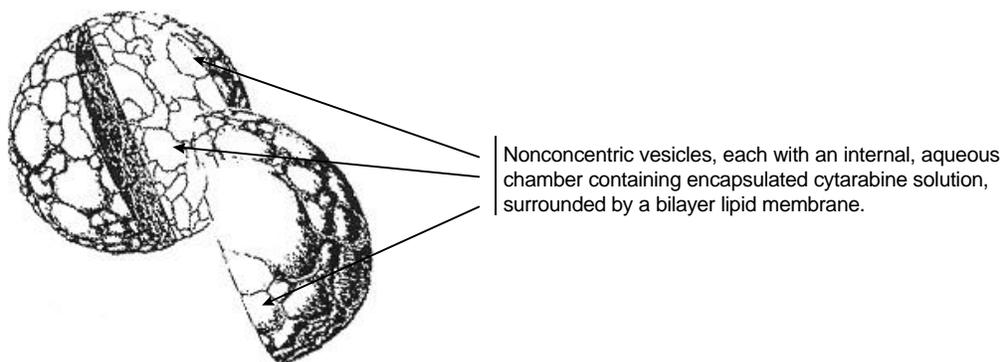
DepoCyt should be administered only under the supervision of a qualified physician experienced in the use of intrathecal cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available. In all clinical studies, chemical arachnoiditis, a syndrome manifested primarily by nausea, vomiting, headache, and fever was a common adverse event. If left untreated, chemical arachnoiditis may be fatal. The incidence and severity of chemical arachnoiditis can be reduced by coadministration of dexamethasone (see WARNINGS). Patients receiving DepoCyt should be treated concurrently with dexamethasone to mitigate the symptoms of chemical arachnoiditis (see DOSAGE AND ADMINISTRATION).

DESCRIPTION

DepoCyt is a sterile, injectable suspension of the antimetabolite cytarabine, encapsulated into multivesicular lipid-based particles. Chemically, cytarabine is 4-amino-1-β-D-arabinofuranosyl-2(1H)-pyrimidinone, also known as cytosine arabinoside (C₉H₁₃N₃O₅, molecular weight 243.22).



The following is an artist's rendition of a DepoCyt particle:



DepoCyt is available in 5 mL, ready-to-use, single-use vials containing 50 mg of cytarabine. DepoCyt is formulated as a sterile, non-pyrogenic, white to off-white suspension of cytarabine in Sodium Chloride 0.9% w/v in Water for Injection. DepoCyt is preservative-free. Cytarabine, the active ingredient, is present at a concentration of 10 mg/mL, and is encapsulated in the particles. Inactive ingredients at their respective approximate concentrations are cholesterol 4.1 mg/mL, triolein 1.2 mg/mL, dioleoylphosphatidylcholine (DOPC) 5.7 mg/mL, and dipalmitoylphosphatidylglycerol (DPPG) 1.0 mg/mL. The pH of the product falls within the range from 5.5 to 8.5.

CLINICAL PHARMACOLOGY

Mechanism of Action

DepoCyt is a sustained-release formulation of the active ingredient cytarabine designed for direct administration into the cerebrospinal fluid (CSF). Cytarabine is a cell cycle phase-specific antineoplastic agent, affecting cells only during the S-phase of cell division. Intracellularly, cytarabine is converted into cytarabine-5'-triphosphate (ara-CTP), which is the active metabolite. The mechanism of action is not completely understood, but it appears that ara-CTP acts primarily through inhibition of DNA polymerase. Incorporation into DNA and RNA may also contribute to cytarabine cytotoxicity. Cytarabine is cytotoxic to a wide variety of proliferating mammalian cells in culture.

Pharmacokinetics

The pharmacokinetics of DepoCyt administered intrathecally to patients at a 50 mg dose every 2 weeks is currently under investigation. However, preliminary analysis of the pharmacokinetic data show that following DepoCyt intrathecal administration in patients, in either the lumbar sac or by intraventricular reservoir, peak levels of free cytarabine were observed within 5 hours in both the ventricle and lumbar sac. These peak levels were followed by a biphasic elimination profile with a terminal phase half-life of 100 to 263 hours over a dose range of 12.5 mg to 75 mg. In contrast, intrathecal administration of 30 mg of free cytarabine showed a biphasic CSF concentration profile with a terminal phase half-life of 3.4 hours. Since the transfer rate of cytarabine from the CSF to plasma is slow and the conversion of cytarabine to ara-U in the plasma is fast, systemic exposure to cytarabine was negligible following intrathecal administration of DepoCyt, 50 mg or 75 mg.

Metabolism and Elimination

The primary route of elimination of cytarabine is metabolism to the inactive compound ara-U (1- β -D-arabinofuranosyluracil or uracilarabinoside), followed by urinary excretion of ara-U. In contrast to systemically administered cytarabine, which is rapidly metabolized to ara-U, conversion to ara-U in the CSF is negligible after intrathecal administration because of the significantly lower cytidine deaminase activity in the CNS tissues and CSF. The CSF clearance rate of cytarabine is similar to the CSF bulk flow rate of 0.24 mL/min.

Drug Interactions

No formal assessments of pharmacokinetic drug-drug interactions between DepoCyt and other agents have been conducted.

Special Populations

The effects of gender or race on the pharmacokinetics of DepoCyt have not been studied, nor has the effect of renal or hepatic impairment.

CLINICAL STUDIES

DepoCyt was studied in clinical trials that enrolled patients with neoplastic meningitis due to solid tumors, lymphoma, or leukemia. A randomized multi-center, multi-arm study involving a total of 99 patients compared 50 mg of DepoCyt administered every 2 weeks to standard intrathecal chemotherapy administered twice a week to patients with either solid tumors, lymphoma, or leukemia. For patients with lymphoma, standard therapy consisted of 50 mg of unencapsulated cytarabine given twice a week. Thirty-three lymphoma patients (17 DepoCyt, 16 cytarabine) were enrolled. Patients went off study if they had not achieved a complete response, defined as clearing of the CSF from all previously positive sites in the absence of progression of neurological symptoms, after four weeks of treatment with study drug. Patients were to receive concurrent treatment with dexamethasone to minimize symptoms associated with chemical arachnoiditis, a known toxicity of intrathecal cytarabine and methotrexate (see WARNINGS and DOSAGE AND ADMINISTRATION).

Lymphoma

Approval of DepoCyt for lymphomatous meningitis is based on an increased complete response rate with DepoCyt compared to control unencapsulated cytarabine. There has been no demonstration of an improved clinical outcome as a result of the increased response rate. In the controlled trial, complete response was prospectively defined as (a) conversion, confirmed by a blinded central pathologist, from a positive examination of the CSF for malignant cells to a negative examination on two separate occasions (at least 3 days apart on day 29 and later) at all initially positive sites, together with (b) an absence of neurologic progression during the treatment period.

The complete response rates in the controlled study of lymphoma are shown in Table 1, giving results for all of the 33 lymphoma patients randomized. Although there was a plan for central pathology review of

data, in four of the seven responding patients on the DepoCyt arm this was not accomplished and these cases were considered to have had a complete response based on the reading of an unblinded pathologist. The median overall survival of all treated patients was 99.5 days on the DepoCyt arm and 63 days on the cytarabine arm. In both arms the majority of patients died from progressive systemic disease, not the neoplastic meningitis.

TABLE 1: COMPLETE RESPONSES IN PATIENTS WITH LYMPHOMATOUS MENINGITIS IN THE CONTROLLED STUDY

Intent-to-treat	
DepoCyt	Cytarabine
7/17 (41%)	1/16 (6%)

INDICATIONS

Depocyt is indicated for the intrathecal treatment of lymphomatous meningitis. This indication is based on demonstration of increased complete response rate compared to unencapsulated cytarabine. There are no controlled trials that demonstrate a clinical benefit resulting from this treatment, such as improvement in disease-related symptoms, or increased time to disease progression, or increased survival.

CONTRAINDICATIONS

DepoCyt is contraindicated in patients who are hypersensitive to cytarabine or any component of the formulation, and in patients with active meningeal infection.

WARNINGS (see boxed WARNING)

DepoCyt should be administered only under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available. Chemical arachnoiditis, a syndrome manifested primarily by nausea, vomiting, headache, and fever, has been a common adverse event in all studies. If left untreated, chemical arachnoiditis may be fatal. The incidence and severity of chemical arachnoiditis can be reduced by coadministration of dexamethasone. Patients receiving DepoCyt should be

treated concurrently with dexamethasone to mitigate the symptoms of chemical arachnoiditis (see DOSAGE AND ADMINISTRATION).

During the clinical studies, 2 deaths related to DepoCyt were reported. One patient died after developing encephalopathy 36 hours after an intraventricular dose of DepoCyt, 125 mg. This patient was receiving concurrent whole-brain irradiation and had previously received systemic chemotherapy with cyclophosphamide, doxorubicin, and fluorouracil, as well as intraventricular methotrexate. The other patient received DepoCyt 50 mg by the intraventricular route and developed focal seizures progressing to status epilepticus. This patient died approximately 8 weeks after the last dose of study medication. The death of one additional patient was considered “possibly” related to DepoCyt. He was a 63 year old with extensive lymphoma involving the nasopharynx, brain, and meninges with multiple neurologic deficits who died of apparent disease progression 4 days after his second dose of DepoCyt.

After intrathecal administration of free cytarabine the most frequently reported reactions are nausea, vomiting and fever. Intrathecal administration of free cytarabine may cause myelopathy and other neurologic toxicity and can rarely lead to a permanent neurologic deficit. Administration of intrathecal cytarabine in combination with other chemotherapeutic agents or with cranial/spinal irradiation may increase this risk of neurotoxicity.

Blockage to CSF flow may result in increased free cytarabine concentrations in the CSF and an increased risk of neurotoxicity.

Pregnancy Category D.

There are no studies assessing the reproductive toxicity of DepoCyt. Cytarabine, the active component of DepoCyt, can cause fetal harm if a pregnant woman is exposed to the drug systemically. Three anecdotal cases of major limb malformations have been reported in infants after their mothers received intravenous cytarabine, alone or in combination with other agents, during the first trimester. The concern for fetal harm following intrathecal DepoCyt administration is low, however, because systemic exposure to cytarabine is negligible. Cytarabine was teratogenic in mice (cleft palate, phocomelia, deformed appendages, skeletal abnormalities) when doses ≥ 2 mg/kg/day were administered i.p. during the period of organogenesis (about 0.2 times the recommended human dose on mg/m² basis), and in rats (deformed appendages) when 20 mg/kg was administered as a single i.p. dose on day 12 of gestation (about 4 times the recommended human dose on mg/m² basis). Single i.p. doses of 50 mg/kg in rats (about 10 times the recommended human dose on mg/m² basis) on day 14 of gestation also cause reduced prenatal and postnatal brain size and permanent

impairment of learning ability. Cytarabine was embryotoxic in mice when administered during the period of organogenesis. Embryotoxicity was characterized by decreased fetal weight at 0.5 mg/kg/day (about 0.05 times the recommended human dose on mg/m² basis), and increased early and late resorptions and decreased live litter sizes at 8 mg/kg/day (approximately equal to the recommended human dose on mg/m² basis). There are no adequate and well controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Despite the low apparent risk for fetal harm, women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General Precautions

DepoCyt has the potential of producing serious toxicity (see boxed WARNING). All patients receiving DepoCyt should be treated concurrently with dexamethasone to mitigate the symptoms of chemical arachnoiditis (see DOSAGE AND ADMINISTRATION). Toxic effects may be related to a single dose or to cumulative administration. Because toxic effects can occur at any time during therapy(although they are most likely within 5 days of drug administration), patients receiving intrathecal therapy with DepoCyt should be monitored continuously for the development of neurotoxicity. If patients develop neurotoxicity, subsequent doses of DepoCyt should be reduced, and DepoCyt should be discontinued if toxicity persists.

Some patients with neoplastic meningitis receiving treatment with DepoCyt may require concurrent radiation or systemic therapy with other chemotherapeutic agents; this may increase the rate of adverse events.

Anaphylactic reactions following intravenous administration of free cytarabine have been reported.

Although significant systemic exposure to free cytarabine following intrathecal treatment is not expected, some effect on bone marrow function cannot be excluded. Systemic toxicity due to intravenous administration of cytarabine consists primarily of bone marrow suppression with leukopenia, thrombocytopenia, and anemia. Accordingly, careful monitoring of the hematopoietic system is advised.

Transient elevations in CSF protein and white blood cells have been observed in patients following DepoCyt administration and have also been noted after intrathecal treatment with methotrexate or cytarabine.

Information for the Patient

Patients should be informed about the expected adverse events of headache, nausea, vomiting, and fever, and about the early signs and symptoms of neurotoxicity. The importance of concurrent dexamethasone administration should be emphasized at the initiation of each cycle of DepoCyt treatment. Patients should be instructed to seek medical attention if signs or symptoms of neurotoxicity develop, or if oral dexamethasone is not well tolerated (see DOSAGE AND ADMINISTRATION).

Drug Interactions

No formal drug interaction studies of DepoCyt and other drugs were conducted. Concomitant administration of DepoCyt with other antineoplastic agents administered by the intrathecal route has not been studied. With intrathecal cytarabine and other cytotoxic agents administered intrathecally, enhanced neurotoxicity has been associated with co-administration of drugs.

Laboratory Test Interactions

Since DepoCyt particles are similar in size and appearance to white blood cells, care must be taken in interpreting CSF examinations following DepoCyt administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, mutagenicity or impairment of fertility studies have been conducted with DepoCyt. The active ingredient of DepoCyt, cytarabine, was mutagenic in *in vitro* tests and was clastogenic *in vitro* (chromosome aberrations and SCE in human leukocytes) and *in vivo* (chromosome aberrations and SCE assay in rodent bone marrow, mouse micronucleus assay). Cytarabine caused the transformation of hamster embryo cells and rat H43 cells *in vitro*. Cytarabine was clastogenic to meiotic cells; a dose-dependent increase in sperm-head abnormalities and chromosomal aberrations occurred in mice given i.p. cytarabine. Impairment of Fertility: No studies assessing the impact of cytarabine on fertility are available in the literature. Because the systemic exposure to free cytarabine following intrathecal treatment with DepoCyt was negligible, the risk of impaired fertility after intrathecal DepoCyt is likely to be low.

Pregnancy

Pregnancy Category D (see WARNINGS).

Nursing Mothers

It is not known whether cytarabine is excreted in human milk following intrathecal DepoCyt administration. The systemic exposure to free cytarabine following intrathecal treatment with DepoCyt was negligible. Despite the low apparent risk, because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, the use of DepoCyt is not recommended in nursing women.

Pediatric Use

The safety and efficacy of DepoCyt in pediatric patients has not been established.

ADVERSE REACTIONS

The toxicity database consists of the observations made during an early uncontrolled study and the controlled multi-arm study described above. In the early study, patients received DepoCyt at doses ranging from 12.5 mg to 125 mg. In the randomized multi-arm study DepoCyt was administered at a dose of 50 mg every two weeks and was compared to standard intrathecal chemotherapy (cytarabine or methotrexate) in patients with lymphoma, leukemia and solid tumors; twenty-eight lymphoma patients, 5 leukemia patients and 59 solid tumor patients received study drug.

Arachnoiditis is an expected and well-documented side effect of both neoplastic meningitis and of intrathecal chemotherapy. For clinical studies of DepoCyt, chemical arachnoiditis was defined as the occurrence of any one of the symptoms of neck rigidity, neck pain, meningism, or any two of the symptoms of nausea, vomiting, headache, fever, back pain, or CSF pleocytosis; the grade assigned to an episode of chemical arachnoiditis was the highest severity grade of its component symptoms. Since most of the adverse events reported in the trials were transient episodes associated with drug exposure, the incidence of these events is best expressed by drug cycle. A cycle of treatment for all treatment groups was defined as the 14-day period between DepoCyt doses. The duration of reported symptoms was from 1 to 5 days. Although it was sometimes difficult to distinguish between drug-related chemical arachnoiditis, infectious meningitis, or disease progression, >90% of the chemical arachnoiditis cases reported occurred within 48 hours of the administration of intrathecal drug, indicating a drug etiology. The incidence and severity of chemical arachnoiditis by cycle in patients with lymphomatous meningitis in the controlled study are shown in Figure 3.

In the early study, chemical arachnoiditis was observed in 100% of cycles without dexamethasone prophylaxis; with concurrent administration of dexamethasone, chemical arachnoiditis was observed in 33% of cycles. Patients receiving DepoCyt should be treated concurrently with dexamethasone to mitigate the symptoms of chemical arachnoiditis (see DOSAGE AND ADMINISTRATION).

Figure 3: Incidence and Severity of Chemical Arachnoiditis by Cycle in Patients with Lymphomatous Meningitis in the Randomized Study

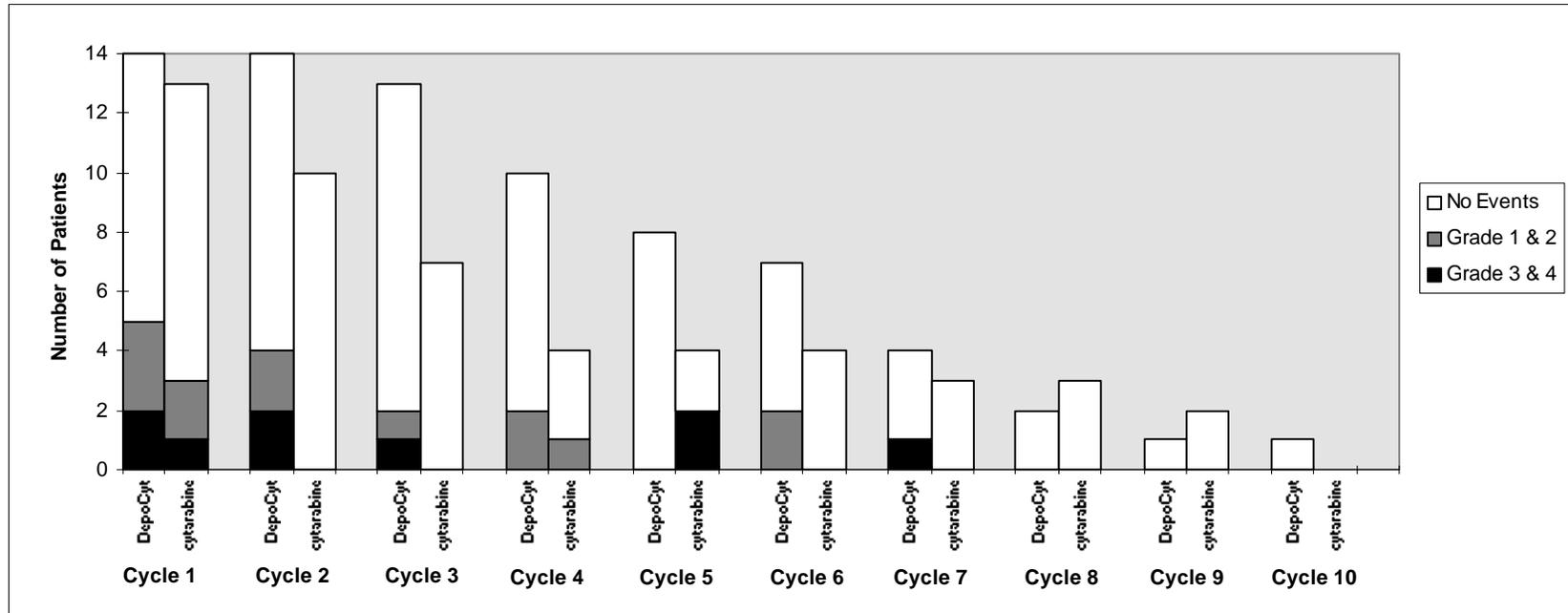


Table 2 shows the rate of all adverse events occurring in $\geq 10\%$ of patients, as a rate per cycle, in the lymphoma randomized study.

Table 2: Comparison of Adverse Events Occurring in $\geq 10\%$ of Patients, by Cycle

**Patients with Lymphomatous Meningitis Receiving
DepoCyt or Cytarabine (ara-C) in the Randomized Study**

Number of Cycles	All Adverse Events %		Grade 3 or 4 Adverse Events %	
	n = 74	n = 45	n = 74	n = 45
Body System/Adverse Event	DepoCyt	ara-C	DepoCyt	Ara-C
Body as a Whole	53	60	18	22
Headache*	28	9	5	2
Asthenia	19	33	5	9
Fever*	11	24	4	0
Back Pain*	7	11	0	2
Pain	11	20	3	0
Nervous System	45	53	18	18
Confusion	14	7	4	2
Somnolence	12	11	4	2
Abnormal Gait	4	11	1	2
Digestive System	27	44	7	9
Nausea*	11	16	0	4
Vomiting*	12	18	3	2
Constipation	7	11	0	0
Metabolic and Nutritional Disorders	16	24	0	0
Peripheral Edema	7	11	0	0
Hematologic	19	22	11	13
Neutropenia	9	11	8	11
Thrombocytopenia	8	16	5	11
Anemia	1	13	1	4
Urogenital System	11	20	3	2
Urinary Incontinence	3	11	0	0
Special Senses	16	18	1	2

*Components of Chemical Arachnoiditis.

There is no antidote for overdose of intrathecal DepoCyt or unencapsulated cytarabine released from DepoCyt. Exchange of CSF with isotonic saline has been carried out in a case of intrathecal overdose of free cytarabine, and such a procedure may be considered in the case of DepoCyt overdose. Management of overdose should be directed at maintaining vital functions.

DOSAGE AND ADMINISTRATION

Preparation of DepoCyt

DepoCyt is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be used in handling DepoCyt. The use of gloves is recommended. If DepoCyt suspension contacts the skin, wash immediately with soap and water. If it contacts mucous membranes, flush thoroughly with water (see HANDLING AND DISPOSAL). DepoCyt particles are more dense than the diluent and have a tendency to settle with time. Vials of DepoCyt should be allowed to warm to room temperature and gently agitated or inverted to re-suspend the particles immediately prior to withdrawal from the vial. Avoid aggressive agitation. No further reconstitution or dilution is required.

DepoCyt Administration

DepoCyt should be withdrawn from the vial immediately before administration. DepoCyt is a single-use vial and does not contain any preservative; DepoCyt should be used within 4 hours of withdrawal from the vial. Unused portions of each vial should be discarded properly (see HANDLING AND DISPOSAL). Do not save any unused portions for later administration. Do not mix DepoCyt with any other medications.

In-line filters must not be used when administering DepoCyt. DepoCyt is administered directly into the CSF via an intraventricular reservoir or by direct injection into the lumbar sac. DepoCyt should be injected slowly over a period of 1-5 minutes. Following drug administration by lumbar puncture, the patient should be instructed to lie flat for one hour. Patients should be observed by the physician for immediate toxic reactions.

Patients should be started on dexamethasone 4 mg bid either PO or IV for 5 days beginning on the day of DepoCyt injection.

DepoCyt must only be administered by the intrathecal route.

Further dilution of DepoCyt is not recommended.

Dosing Regimen

For the treatment of lymphomatous meningitis, DepoCyt 50 mg (one vial of DepoCyt) is recommended to be given according to the following schedule:

Induction therapy: DepoCyt, 50 mg, administered intrathecally (intraventricular or lumbar puncture) every 14 days for 2 doses (weeks 1 and 3).

Consolidation therapy: DepoCyt, 50 mg, administered intrathecally (intraventricular or lumbar puncture) every 14 days for 3 doses (weeks 5, 7 and 9) followed by 1 additional dose at week 13.

Maintenance: DepoCyt, 50 mg, administered intrathecally (intraventricular or lumbar puncture) every 28 days for 4 doses (weeks 17, 21, 25 and 29).

If drug related neurotoxicity develops, the dose should be reduced to 25 mg. If it persists, treatment with DepoCyt should be discontinued.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.^(1,2,3,4,5,6,7) There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

DepoCyt (cytarabine liposome injection) is supplied as a sterile, white to off-white suspension in 5 ml glass, single use vials.

Refrigerate at 2-8°C. Protect from freezing and avoid aggressive agitation.

Available as individual carton containing one ready to use vial. NDC 53905-331-01. Do not use beyond expiration date printed on the label.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing office, Washington, DC 20402.
2. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics. JAMA, 1985; 2.53(11):1590-1592.
3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia, 1983; 1:426-428.
5. Jones RB, et al: Safe Handling Of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA - A Cancer Journal for Clinicians, 1983; (Sept/Oct) 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J. Hosp Pharm, 1990; 47:1033-1049.
7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines), Am J Health-Syst Pharm, 1996; 53:1669-1685.