



Rec'd 11/15/00  
H. K. H.

SERVICES TO MEDICINE

~~5786 '00 OCT -5 19:58~~

Dockets Management Branch  
Food & Drug Administration  
Department of Health and  
Human Services, Room 1061  
5630 Fishers Lane  
Rockville, MD 20657

September 7, 2000

***Suitability Petition for Cladribine-Lipomed***

Dear Sirs,

Prior to the submission of the ANDA for Cladribine-Lipomed, we hereby request a change from the listed drug by the following petition:

- Listed drug

**Leustatin** (Cladribine, 2-CDA) produced by Ortho Biotech, Raritan, NJ 08869, NDA number 02100. One ampule contains 10 mg of active ingredient in 10 ml solution, i.e. 1 mg / ml. Leustatin is approved in the US for the treatment of Hairy Cell Leucemia.

- Cladribine-Lipomed

**Cladribine-Lipomed** (Cladribine, 2-CDA) contains the identical active ingredient like the listed drug Leustatin. One ampule contains 10 mg of API, formulated in 5 ml sodium chloride solution, resulting in the double concentration of 2 mg / ml in comparison to the listed drug. The API of Cladribine-Lipomed is of the same pharmacological and therapeutic class and has the same therapeutic effect as the listed reference drug Leustatin.

00P-1621

CPI

- Requested Change

The FDA shall allow the submission of the abbreviated new drug application for Cladribine-Lipomed, injection in a strength of 10 milligrams / 5 millilitres. This corresponds to a double concentration in comparison to the listed reference drug Leustatin. Since the content of the API in one ampule is the same in both the proposed and the listed drug - 10 milligrams of Cladribine – there is no difference in the final formulation because the listed and the proposed drugs are further diluted in an infusion bag during the preparation of the solution for the intravenous infusion.

We enclose the package insert of Cladribine-Lipomed (proposed drug) as well as the label of the listed reference drug. If additional information is requested, please contact us in Cambridge, MA (phone 617 577 7222, fax 617 577 1776, email [lipomed@tiac.net](mailto:lipomed@tiac.net)).

Sincerely yours,

Lipomed Inc.



Dr. H. Hamberger  
President and CEO



Mario Pasquier  
Vice President

*enclosures:*

- package insert draft of Cladribine-Lipomed
- package insert of Leustatin

# CLADRIBINE-Lipomed

Rx ONLY.

For Intravenous Infusion Only

## WARNINGS

Cladribine Injection should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. Suppression of bone marrow function should be anticipated. This is usually reversible and appears to be dose dependent. Serious neurological toxicity (including irreversible paraparesis and quadraparesis) has been reported in patients who received cladribine injection by continuous infusion at high doses (4 to 9 times the recommended dose for Hairy Cell Leukemia). Neurologic toxicity appears to demonstrate a dose relationship; however, severe neurological toxicity has been reported rarely following treatment with standard cladribine dosing regimens. Acute nephrotoxicity has been observed with high doses of cladribine (4 to 9 times the recommended dose for Hairy Cell Leukemia), especially when given concomitantly with other nephrotoxic agents/therapies.

## DESCRIPTION

Cladribine Injection (also commonly known as 2-chloro-2'-deoxy-B-D-adenosine) is a synthetic antineoplastic agent for continuous intravenous infusion. It is a clear, colorless, sterile, preservative-free, isotonic solution. Cladribine Injection is available in single-use vials containing 10 mg (2mg / mL) of Cladribine, a chlorinated purine nucleoside analog. Each mL of Cladribine injection contains 2 mg of the active ingredient and 45 mL (0.15 mEq) of sodium chloride as an inactive ingredient. The solution has a pH range at 5.5 to 8.0. Phosphoric acid and/or dibasic sodium phosphate may have been added to adjust the pH to  $6.3 \pm 0.3$ . The chemical name for cladribine is 2-chloro-6-amino-9-(2-deoxy-B-D-erythro-pentofuranosyl) purine and the structure is represented below:

## (STRUCTURAL FORMULA)

Molecular Formula =  $C_{10}H_{12}ClN_5O_5$

Molecular Weight = 285.59

## CLINICAL PHARMACOLOGY

### Cellular Resistance and Sensitivity:

The selective toxicity of 2-chloro-2'-deoxy-B-D-adenosine towards certain normal and malignant lymphocyte and monocyte populations is based on the relative activities of deoxycytidine kinase and deoxynucleotidase. Cladribine passively crosses the cell membrane. In cells with a high ratio of deoxycytidine kinase to deoxynucleotidase, it is phosphorylated by deoxycytidine kinase to 2-chloro-2'-deoxy-B-D-adenosine monophosphate (2-CdAMP). Since 2-chloro-2'-deoxy-B-D-adenosine is resistant to deamination by adenosine deaminase and there is little deoxynucleotide deaminase in lymphocytes and monocytes, 2-CdAMP accumulates intracellularly and is subsequently converted into the active triphosphate deoxydeoxydeotide, 2-chloro-2'-deoxy-0-adenosine triphosphate (PCdATP). It is postulated that cells with high deoxycytidine kinase and low deoxynucleotidase activities will be selectively killed by 2-chloro-2'-deoxy-0-adenosine triphosphate as toxic deoxynucleotides accumulate intracellularly. Cells containing high concentrations of deoxynucleotidase are unable to properly repair single-strand DNA breaks. The broken ends at DNA activate the enzyme poly (ADP-ribose) polymerase resulting in NAD and ATP depletion and disruption of cellular metabolism. There is evidence, also, that 2-CdATP is incorporated into the DNA at dividing cells, resulting in impairment of DNA synthesis. Thus, 2-chloro-2'-deoxy-B-D-adenosine can be distinguished from other chemotherapeutic agents affecting purine metabolism in that it is cytotoxic to both actively dividing and quiescent lymphocytes and monocytes, inhibiting both DNA synthesis and repair.

## HUMAN PHARMACOLOGY

In a clinical investigation, 17 patients with Hairy Cell Leukemia and normal renal function were treated for 7 days with the recommended treatment regimen of cladribine (0.09 mg/kg/day) by continuous intravenous infusion. The mean steady-state serum concentration was estimated to be 5.7 ng/mL with an estimated systemic clearance of 663.5 mL/h/kg when cladribine was given by continuous infusion over 7 days. In Hairy Cell Leukemia patients, there does not appear to be a relationship between serum concentrations and ultimate clinical outcome. In another study, B patients with hematologic malignancies received a two (2) hour infusion of cladribine (0.12 mg/kg). The mean end-of-infusion plasma cladribine concentration was  $48 \pm 19$  ng/mL. For 5 of these patients, the disappearance of cladribine could be described by either a biphasic or triphasic decline. For these patients with normal renal function, the mean terminal half-life was 5.4 hours. Mean values for clearance and steady-state volume of distribution were  $978 \pm 422$  mL/kg and  $4.5 \pm 2.8$  L/kg, respectively. Plasma concentrations are reported to decline multi-exponentially after intravenous infusions with terminal half-lives ranging from approximately 3 to 22 hours. In general, the apparent volume of distribution of cladribine is very large (mean approximately 9 L/kg), indicating an extensive distribution of cladribine in body tissues. The mean half-life of cladribine in leukemic cells has been reported to be 23 hours. Cladribine penetrates into cerebrospinal fluid. One report indicates that concentrations are approximately 25% of those in plasma. Cladribine is bound approximately 20% to plasma proteins. Except for some understanding of the mechanism of cellular toxicity, no other information is available on the metabolism of cladribine in humans. An average of 18% of the administered dose has been reported to be excreted in urine of patients with solid tumors during a 5-day continuous intravenous infusion of 3.5 to 8.1 mg/m<sup>2</sup>/day of cladribine. The effect of renal and hepatic impairment on the elimination of cladribine has not been investigated in humans. Two single-center open label studies of cladribine have been conducted in patients with Hairy Cell Leukemia with evidence of active disease requiring therapy. In the study conducted at the Scripps Clinic and Research Foundation (Study A), 89 patients were treated with a single course of cladribine given by continuous intravenous infusion for 7 days at a dose of 0.09 mg/kg/day. In the study conducted at the M.D. Anderson Cancer Center (Study B), 35 patients were treated with a 7day continuous intravenous infusion of cladribine at a comparable dose of 3.6 mg/m<sup>2</sup>/day. A complete response (CR) required clearing of the peripheral blood and bone marrow of hairy cells and recovery of the hemoglobin to 12 g/dL, platelet count to  $100 \times 10^9/L$ , and absolute neutrophil count to  $1500 \times 10^6/L$ . A good partial response (GPR) required the same hematologic parameters as a complete response, and that fewer than 5% hairy cells (<25% of pretreatment levels) were reclassified as partial responses and were not considered to be complete responses with relapse. Among patients evaluable for efficacy (N=106), using the hematologic and bone marrow response criteria describe above, the complete response rates in patients treated with cladribine were 65% and 68% for Study B, respectively, yielding a combined overall response rate of 88% in evaluable patients treated with cladribine. Using an intent-to-treat analysis (N=123) and further requiring no evidence of splenomegaly as a criterion for CR (i.e., no palpable spleen on physical examination and <13cm on CT scan), the complete response rates for Study A and Study B were 54% and 53%, respectively, giving a combined CR rate of 54%. The overall response rates (CR + GPR + PR) were 90% and 85%, for studies A and B, respectively, yielding a combined overall response rate of 89%.

RESPONSE RATES TO CALDRIBINE TREATMENT IN PATIENTS WITH HAIRY CELL LEUKEMIA		
	CR	Overall
Evaluable Patients N=106	66%	88%
Intent-to-treat Population N=123	54%	89%

In these studies, 60% of the patients had not received prior chemotherapy for Hairy Cell Leukemia or had undergone splenectomy as the only prior treatment and were receiving cladribine as a first-line treatment. The remaining 40% of the patients received cladribine as a second-line treatment, having been treated previously with other agents, including interferon and/or deoxycoformycin. The overall response rate for patients without prior chemotherapy was 92%; compared with 84% for previously treated patients. Cladribine is active in previously treated patients; however, retrospective analysis suggests that the overall response rate is decreased in patients previously treated with splenectomy or deoxycoformycin and in patients refractory to cx-interferon.

OVERALL RESPONSE RATES (CR + GP+PR) TO CLADRIBINE TREATMENT IN PATIENTS WITH HAIRY LEUKEMIA CELL		
	OVERALL RESPONSE (N=123)	NR + RELAPSE
No Prior Chemotherapy	68/74 92%	6 + 4 14%
Any Prior Chemotherapy	41/49 84%	8 + 3 22 %
Previous Splenectomy	32/41* 78%	9 + 1 24%
Previous Interferon	40/48 83%	8 + 3 23%
Interferon Refractory	6/11* 55%	5 + 2 64%
Previous Deoxycoformycin	3/6* 50%	3 + 1 66%

NR = No Response  
\*P<0.05

After reversible decline, normalization of peripheral blood counts (Hemoglobin >12 g/dL, Platelets >100 x 10<sup>9</sup>/L, Absolute Neutrophil Count (ANC) >1500 x 10<sup>6</sup>/L) was achieved by 92% of evaluable patients. The median time to normalization of peripheral counts was 9 weeks from the start at treatment (Range: 2 to 72). The median time to normalization of Platelet Count was 2 weeks, the median time to normalization of ANC was 5 weeks and the median time to normalization of Hemoglobin was 8 weeks. With normalization of Platelet Count and Hemoglobin, requirements for platelet and RBC transfusions were abolished after Months 1 and 2, respectively, in those patients with complete response. Platelet recovery may be delayed in a minority of patients with severe baseline thrombocytopenia. Corresponding to normalization of ANC, a trend toward a reduced incidence of infection was seen after the third month, when compared to the months immediately preceding cladribine therapy. See also **WARNINGS, PRECAUTIONS** and **ADVERSE REACTIONS**.

CLADRIBINE TREATMENT IN PATIENTS WITH HAIRY CELL LEUKEMIA TIME TO NORMALIZATION OF PERIPHERAL BLOOD COUNTS	
Parameter	Median Time to Normalization of Count*
Platelet Count	2 weeks
Absolute Neutrophil Count	5 weeks
Hemoglobin	8 weeks
ANC, Hemoglobin and Platelet Count	9 weeks

\* Day 1 = First Day of infusion

For patients achieving a complete response, the median time to response (i.e., absence of hairy cells in bone marrow and peripheral blood together with normalization of peripheral blood parameters), measured from treatment start, was approximately 4 months. Since bone marrow aspiration and biopsy were frequently not performed at the time of peripheral blood normalization, the median time to complete response may actually be shorter than that which was recorded. At the time of data cut-off, the median duration of complete response was greater than 8 months and ranged to 25+ months. Among 93 responding patients, seven had shown evidence of disease progression at the time of the data cut-off. In four of these patients, disease was limited to the bone marrow without peripheral blood abnormalities (pathologic progression), while in three patients there were also peripheral blood abnormalities (clinical progression). Seven patients who did not respond to a first course of cladribine received a second course of therapy. In the five patients who had adequate follow-up, additional courses did not appear to improve their overall response.

#### INDICATIONS AND USAGE

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

#### CONTRAINDICATIONS

Cladribine is contraindicated in those patients who are hypersensitive to this drug or any of its components.

#### WARNINGS

Severe bone marrow suppression, including neutropenia, anemia and thrombocytopenia has been commonly observed in patients treated with cladribine, especially at high doses. At initiation of treatment, most patients in the clinical studies had hematologic impairment as a manifestation of active Hairy Cell Leukemia. Following treatment with cladribine, further hematologic impairment occurred before recovery of peripheral blood counts began. During the first two weeks after treatment initiation, mean Platelet Count, ANC, and Hemoglobin concentration declined and subsequently increased with normalization of mean counts by Day 12, Week 5 and Week 8, respectively. The myelosuppressive effects of cladribine were most notable during the first month following treatment. Forty-four percent (44%) of patients received transfusions with RBCs and 14% received transfusions with platelets during Month 1. Careful hematologic monitoring, especially during the first 4 to 8 weeks after treatment with cladribine, is recommended. See **PRECAUTIONS**. Fever (T P<sub>o</sub> ≥ 100°F) was associated with the use of cladribine in approximately two-thirds of patients (131/196) in the first month of therapy. Virtually all of these patients were treated empirically with parenteral antibiotics. Overall, 47% (93/196) of all patients had fever in the setting of neutropenia (ANC ≥ 1000), including 62 patients (32%) with severe neutropenia (i.e., ANC ≥ 500).

In a Phase I investigational study using cladribine in high doses (4 to 9 times the recommended dose for Hairy Cell Leukemia) as part of a bone marrow transplant conditioning regimen, which also included high dose cyclophosphamide and total body irradiation, acute nephrotoxicity and delayed onset neurotoxicity were observed. Thirty-one (31) poor-risk patients with drug-resistant acute leukemia in relapse (29 cases) or non-Hodgkins Lymphoma (2 cases) received cladribine for 7 to 14 days prior to bone marrow transplantation. During infusion, 8 patients experienced gastrointestinal symptoms. While the bone marrow was initially cleared of all hematopoietic elements, including tumor cells, leukemia eventually recurred in all treated patients. Within 7 to 13 days after starting treatment with cladribine, 6 patients (19%) developed manifestations of renal dysfunction (e.g., acidosis, anuria, elevated serum creatinine, etc.) and 5 required dialysis. Several of these patients were also being treated with other medications having known nephrotoxic potential. Renal dysfunction was reversible in 2 of these patients. In the 4 patients whose renal function had not recovered at the time of death, autopsies were performed; in 2 of these, evidence of tubular damage was noted. Eleven (11) patients (35%) experienced delayed onset neurologic toxicity. In the majority, this was characterized by progressive irreversible motor weakness (paraparesis/quadruparesis), of the upper and/or lower extremities, first noted 35 to 84 days after starting high dose therapy with cladribine. Non-invasive testing (electromyography and nerve conduction studies) was consistent with demyelinating disease. Severe neurologic toxicity has also been noted with high dosers of another drug in this class. Axonal peripheral polyneuropathy was observed in a dose escalation study at the highest dose levels (approximately 4 times the recommended dose for Hairy Cell Leukemia) in patients not receiving cyclophosphamide or total body irradiation. Severe neurological toxicity has been reported rarely following treatment with standard cladribine dosing regimens. In patients with Hairy Cell Leukemia treated with the recommended treatment regimen (0.09 mg/kg/day for 7 consecutive days), there have been no reports of nephrologic toxicities. Of the 196 Hairy Cell Leukemia patients entered in the two trials, there were 8 deaths following treatment. Of these, 6 were of infectious etiology, including 3 pneumonias, and 2 occurred in the first month following cladribine therapy. Of the 8 deaths, 6 occurred in previously treated patients who were Refractory to *interferon*. Benzyl alcohol is a constituent at the recommended diluent for the 7-day infusion solution. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. See **DOSE AND ADMINISTRATION**. *Pregnancy Category D:* Cladribine should not be given during pregnancy. Cladribine is teratogenic in mice and rabbits and consequently has the potential to cause fetal harm when administered to a pregnant woman. A significant increase in fetal variations was observed in mice receiving 1.5 mg/kg/day (4.5 mg/m<sup>2</sup>) and increased resorptions, reduced litter size and increased fetal malformations were observed when mice received 3 mg/kg/day (9 mg/m<sup>2</sup>). Fetal death and malformations were observed in rabbits that received 3 mg/kg/day

(33 mg/m<sup>2</sup>). No fetal effects were seen in mice at 0.5 mg/kg/day (1.5 mg/m<sup>2</sup>) or in rabbits at 1 mg/kg/day (11 mg/m<sup>2</sup>). Although there is no evidence of teratogenicity in humans due to cladribine, other drugs which inhibit DNA synthesis (e.g., methotrexate and aminopterin) have been reported to be teratogenic in humans. Cladribine has been shown to be embryotoxic in mice when given at doses equivalent to the recommended dose. There are no adequate and well controlled studies in pregnant women. If cladribine is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant.

## PRECAUTIONS

**General:** Cladribine is a potent antineoplastic agent with potentially significant toxic side effects. It should be administered only under the supervision of a physician experienced with the use of cancer chemotherapeutic agents. Patients undergoing therapy should be closely observed for signs of hematologic and non-hematologic toxicity. Periodic assessment or peripheral blood counts, particularly during the first 4 to 8 weeks post-treatment, is recommended to detect the development of anemia, neutropenia and thrombocytopenia and for early detection of any potential sequelae (eg., infection or bleeding). As with other potent chemotherapeutic agents, monitoring of renal and hepatic function also recommended, especially in patients with underlying kidney or liver dysfunction. See

### WARNINGS and ADVERSE REACTIONS.

Fever was a frequently observed side effect during the first month on study. Since the majority of fevers occurred in neutropenic patients, patients should be closely monitored during the first month of treatment and empiric antibiotics should be initiated as clinically indicated. Although 69% of patients developed fevers, less than 1/3 of febrile events were associated with documented infection. Given the known myelosuppressive effects of cladribine, practitioners should carefully evaluate the risks and benefits of administering this drug to patients with active infections. See **WARNINGS and ADVERSE REACTIONS.**

There are inadequate data on dosing of patients with renal or hepatic insufficiency. Development of acute renal insufficiency in some patients receiving high doses of cladribine has been described. Until more information is available, caution is advised when administering the drug to patients with known or suspected renal or hepatic insufficiency. See **WARNINGS.**

Rare cases of tumor lysis syndrome have been reported in patients treated with cladribine with other hematologic malignancies having a high tumor burden. Cladribine must be diluted in designated intravenous solutions prior to administration. See **DOSAGE AND ADMINISTRATION.**

**Laboratory Tests:** During and following treatment, the patient's hematologic profile should be monitored regularly to determine the degree of hematopoietic suppression. In the clinical studies, following reversible declines in all cell counts, the mean Platelet Count reached 100x10<sup>9</sup>/L by Day 12, the mean Absolute Neutrophil Count reached 1500 x 10<sup>6</sup>/L by Week 5 and the mean Hemoglobin reached 12 g/dL by Week 8. After peripheral counts have normalized, bone marrow aspiration and biopsy should be performed to confirm response to treatment with cladribine. Febrile events should be investigated with appropriate laboratory and radiologic studies. Periodic assessment of renal function and hepatic function should be performed as clinically indicated.

**Drug Interactions:** There are no known drug interactions with cladribine. Caution should be exercised if cladribine is administered before, after, or in conjunction with other drugs known to cause immunosuppression or myelosuppression. See **WARNINGS.**

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** No animal carcinogenicity studies have been conducted with cladribine. However, its carcinogenic potential cannot be excluded based on demonstrated genotoxicity of cladribine.

As expected for compounds in this class, the actions of cladribine yield DNA damage. In mammalian cells in culture, cladribine caused the accumulation of DNA strand breaks. Cladribine was also incorporated into DNA of human lymphoblastic leukemia cells. Cladribine was not mutagenic *in vitro* (Ames and Chinese hamster ovary cell gene mutation tests) and did not induce unscheduled DNA synthesis in primary rat hepatocyte cultures. However, cladribine was clastogenic both *in vitro* (chromosome aberrations in Chinese hamster ovary cells) and *in vivo* (mouse bone marrow micronucleus test). When administered intravenously to Cynomolgus monkeys, cladribine has been shown to cause suppression of rapidly generating cells, including testicular cells. The effect on human fertility is unknown.

**Pregnancy: Teratogenic Effects; Pregnancy Category D:** See **WARNINGS.**

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from cladribine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug for the mother.

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. In a Phase I study involving patients 1 to 21 years old with relapsed acute leukemia, cladribine was given by continuous intravenous infusion in doses ranging from 3 to 10.7 mg/m<sup>2</sup>/day for 5 days (one-half to twice the dose recommended in Hairy Cell Leukemia). In this study, the dose-limiting toxicity was severe myelosuppression with profound neutropenia and thrombocytopenia. At the highest dose (10.7 mg/m<sup>2</sup>/day), 3 of 7 patients developed irreversible myelosuppression and fatal systemic bacterial or fungal infections. No unique toxicities were noted in this study. See **WARNINGS and ADVERSE REACTIONS.**

## ADVERSE REACTIONS

Safety data are based on 196 patients with Hairy Cell Leukemia: the original cohort of 124 patients plus and additional 72 patients enrolled at the same two centers after the original enrollment cutoff. In Month 1 of the Hairy Cell Leukemia clinical trials, severe neutropenia was noted in 70% of patients, fever in 69% and infection was documented in 28%. Other adverse experiences reported frequently during the first 14 days after initiating treatment included: fatigue (45%), nausea (28%), rash (27%), headache (22%) and injection site reactions (19%). Most non-hematologic adverse experiences were mild to moderate in severity. Myelosuppression was frequently observed during the first month after starting treatment.

Neutropenia (ANC < 500 x 10<sup>6</sup>/L) was noted in 70% of patients, compared with 26% in whom it was present initially. Severe anemia (Hemoglobin < 8.5 g/dL) developed in 37% of patients, compared with 10% initially and thrombocytopenia (Platelets < 20 x10<sup>9</sup>/L) developed in 12% of patients, compared to 4% in whom it was noted initially. During the first month, 54 of 196 patients (28%) exhibited documented evidence of infection. Serious infections (e.g., septicemia, pneumonia) were reported in 6% of all patients, the remainder were mild or moderate. Several deaths were attributable to infection and/or complications related to the underlying disease. During the second month, the overall rate of documented infection was 6%; these infections were mild to moderate and no severe systemic infections were seen. After the third month, the monthly incidence of infection was either less than or equal to that of the months immediately preceding cladribine therapy. During the first month, 11% of patients experienced severe fever (i.e., >104°F). Documented infections were noted in fewer than one-third of febrile episodes.

Of the 196 patients studied, 19 were noted to have a documented infection in the month prior to treatment. In the month following treatment, there were 54 episodes of documented infection: 23 (42%) were bacterial, 11 (20%) were viral and 11 (20%) were fungal. Seven (7) of 8 documented episodes of herpes zoster occurred during the month following treatment. Fourteen (14) of 16 episodes of documented fungal infections occurred in the first two months following treatment. Virtually all of these patients were treated empirically with antibiotics. See **WARNINGS and PRECAUTIONS.**

Analysis of lymphocyte subsets indicates that treatment with cladribine is associated with prolonged depression of the CD4 counts. Prior to treatment, the mean CD4 count was 766/ L. The mean CD4 count nadir, which occurred 4 to 6 months following treatment, was 272/ L. Fifteen (15) months after treatment, mean CD4 counts remained below 500/ L. CD8 counts behaved similarly, though increasing counts were observed after 9 months. The clinical significance of the prolonged CD4 lymphopenia is unclear.

Another event of unknown clinical significance includes the observation of prolonged bone marrow hypocellularity. Bone marrow cellularity of <35% was noted after 4 months in 42 of 124 patients (34%) treated in the two pivotal trials. This hypocellularity was noted as late as day 1010. It is not known whether the hypocellularity is the result of disease related marrow fibrosis or if it is the result of cladribine toxicity. There was no apparent clinical effect on the peripheral blood counts.

The vast majority of rashes were mild and occurred in patients who were receiving or had recently been treated with other medications (e.g., allopurinol or antibiotics) known to cause rash. Most episodes of nausea were mild, not accompanied by vomiting, and did not require treatment with antiemetics. In patients requiring antiemetics, nausea was easily controlled, most frequently with chlorpromazine. Adverse reactions reported during the first 2 weeks following treatment initiation (regardless of relationship to drug) by >5% of patients included:

**Body as a Whole:** fever (69%), fatigue (45%), chills (9%), asthenia (9%), diaphoresis (9%), malaise (7%), trunk pain (6%)

**Gastrointestinal:** nausea (28%), decreased appetite (17%), vomiting (13%), diarrhea (10%), constipation (9%), abdominal pain (6%)

**Hemr/Lymphatic:** purpura (10%), petechiae (8%), epistaxis (5%)

**Nervous System:** headache (22%), dizziness (9%), insomnia (7%)

**Cardiovascular System:** edema (6%), tachycardia (6%)

**Respiratory System:** abnormal breath sounds (11%), cough (10%), abnormal chest sounds (9%), shortness of breath (7%)

**Skin/Subcutaneous Tissue:** rash (27%), injection site reactions (19%), pruritis (6%), pain (6%), erythema (6%)

**Musculoskeletal System:** myalgia (7%), arthralgia (5%)

Adverse experiences related to intravenous administration included: injection site reactions (9%) (i.e., redness swelling, pain) thrombosis (2%), phlebitis (2%) and a broken catheter (1%).

These appear to be related to the infusion procedure and/or indwelling catheter, rather than the medication or the vehicle. From Day 15 to the last follow-up visit, the only events reported by >5% of patients were: fatigue (11%), rash (10%), headache (7%), cough (7%), and malaise (5%).

For a description of adverse reactions associated with use of high doses in non-Hairy Cell Leukemia patients, see **WARNINGS.**

The following additional adverse events have been reported since the drug became commercially available. These adverse events have been reported primarily in patients who received multiple courses of cladribine:

**Hematological:** bone marrow suppression with prolonged pancytopenia, including some reports of aplastic anemia; hemolytic anemia, which was reported in patients with lymphoid malignancies, occurring within the first few weeks following treatment.

**Hepatic:** reversible, generally mild increases in bilirubin and transaminases.

**Nervous System:** Neurological toxicity; however, severe neurotoxicity has been reported rarely following treatment with standard cladribine dosing regimens.  
**Respiratory System:** pulmonary interstitial infiltrates; In most cases, an infectious etiology was identified.  
**Skin/Subcutaneous:** urticaria, hypereosinophilia. In isolated cases Stevens-Johnson and toxic epidermal necrolysis have been reported in patients who were receiving or had recently been treated with other medications (e.g., allopurinol or antibiotics) known to cause these syndromes.  
 Opportunistic infections have occurred in the acute phase of treatment due to the immunosuppression mediated by cladribine.

### OVERDOSAGE

High doses of cladribine have been associated with: irreversible neurologic toxicity (paraparesis/quadruparesis), acute nephrotoxicity, and severe bone marrow suppression resulting in neutropenia, anemia and thrombocytopenia. See **WARNINGS**. There is no known specific antidote to overdosage. Treatment of overdosage consists of discontinuation of cladribine, careful observation and appropriate supportive measures. It is not known whether the drug can be removed from the circulation by dialysis or hemofiltration.

### DOSAGE AND ADMINISTRATION

**Usual Dose:** The recommended dose and schedule of cladribine for active Hairy Cell Leukemia is as a single course given by continuous infusion for 7 consecutive days at a dose of 0.09 mg/kg/day. Deviations from this dosage regimen are not advised. If the patient does not respond to the initial course of cladribine for Hairy Cell Leukemia, it is unlikely that they will benefit from additional courses. Physicians should consider delaying or discontinuing the drug if neurotoxicity or renal toxicity occurs. See **WARNINGS**. Specific risk factors predisposing to increased toxicity from cladribine have not been defined. In view of the known toxicities of agents of this class, it would be prudent to proceed carefully in patients with known or suspected renal insufficiency or severe bone marrow impairment of any etiology. Patients should be monitored closely for hematologic and non-hematologic toxicity. See **WARNINGS** and **PRECAUTIONS**.

#### Preparation and Administration of Intravenous Solutions:

Cladribine must be diluted with the designated diluent prior to administration. Since the drug product does not contain any antimicrobial preservative or bacteriostatic agent, **aseptic technique and proper environmental precautions must be observed in preparation of cladribine solutions.**

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

	Dose of Cladribine Injection	Recommended Diluent	Quantity of Diluent
24 Hour infusion method	1(day) x 0.09mg/kg	0.9% Sodium Chloride Injection	500mL

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

	Dose of Cladribine Injection	Recommended Diluent	Quantity of Diluent
7 day infusion method (use sterile 0.22 µ filter when preparing infusion solution)	7 (days) x 0.09 mg/kg	Bacteriostatic 0.9% Sodium Chloride Injection (0.9% benzyl alcohol)	q.s. to 100 mL

#### Since Limited compatibility data are available, adherence to the recommended diluents and infusion systems is advised

Solutions containing cladribine should not be mixed with other intravenous drugs or additives or infused simultaneously via a common intravenous line, since compatibility testing has not been performed. Preparations containing benzyl alcohol should not be used in neonates. See **WARNINGS**.

Care must be taken to assure the sterility of prepared solutions. Once diluted, solutions of cladribine should be administered promptly or stored in the refrigerator (2° to 8° C) for no more than 8 hours prior to start of administration. Vials of cladribine are for single-use only. Any unused portion should be discarded in an appropriate manner. See **Handling and Disposal:** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. A precipitate may occur during the exposure of cladribine to low temperatures; it may be resolubilized by allowing the solution to warm naturally to room temperature and by shaking vigorously. **DO NOT HEAT OR MICROWAVE.**

#### Chemical Stability of Vials:

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

#### Handling and Disposal:

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

### HOW SUPPLIED

Cladribine Injection is supplied as a sterile, preservative-free, isotonic solution containing 10 mg (2 mg/mL) of cladribine as 5 mL filled into a single-use clear flint glass 10 mL vial, individually boxed. NDC 55390-124-01 Store refrigerated 2° to 8° C (36° to 46°F). Protect from light during storage.

## REFERENCES

1. Santana VM, Mirro J, Harwood FC et al: A Phase I Clinical Trial of 2-Chloro-deoxyadenosine in Pediatric Patients with Acute Leukemia. *J Clin. Oncol.* 1991; 9: 416.
  2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents: US Government Printing Office, Washington, DC 20402.
  3. AMA Council Report Guidelines for Handling Parenteral Antineoplastics. *JAMA* 1985; 253 (11):1590-1592.
  4. National Study Commission on Cytotoxic Exposure-Recommendations for Handling Cytotoxic Agents. Available from Louis P Jeffrey, Chairman. National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts, 02115.
  5. Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia* 1983; 1:426-428.
  6. 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.
  7. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm* 1990; 47:1033-1049.
  8. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. *Am J Hosp Pharm* 1986; 43:1193-1204.
- † Vialflex® containers, manufactured by Baxter Healthcare Corporation Code No. 288013 (tested in 1991)  
‡MEDICATION CASSETTE™ Reservoir, manufactured by SIMS Deltec, Inc. - Reorder No. 602100A (tested in 1991)

Manufactured by:  
Lipomed AG  
Fabrikmattenweg 4  
CH-4144 Arlesheim  
Switzerland

Manufactured for:  
Lipomed Inc  
One Broadway  
Cambridge, MA 02142

(Draft, Oct. 1, 2000 MP)

**Zemuron—Cont.**

CLINICAL PHARMACOLOGY) and the associated rapid spontaneous recovery; initiation of the infusion after substantial return of neuromuscular function (more than 10% of control  $T_1$ ), may necessitate additional bolus doses to maintain adequate block for surgery.

Upon reaching the desired level of neuromuscular block, the infusion of ZEMURON™ must be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as monitored with the use of a peripheral nerve stimulator. In clinical trials, infusion rates have ranged from 0.004 to 0.016 mg/kg/min. Inhalation anesthetics, particularly enflurane and isoflurane may enhance the neuromuscular blocking action of nondepolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion by 30 to 50%, at 45–60 minutes after the intubating dose.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of ZEMURON™ infusion may be expected to proceed at rates comparable to that following comparable total doses administered by repetitive bolus injections (see Pharmacodynamics subsection of CLINICAL PHARMACOLOGY).

Infusion solutions of ZEMURON™ can be prepared by mixing ZEMURON™ with an appropriate infusion solution such as 5% glucose in water or Lactated Ringers (see Compatibility). Unused portions of infusion solutions should be discarded.

Infusion rates of ZEMURON™ can be individualized for each patient using the following tables as guidelines:

[See table 6 at top of previous page]

[See table 7 at top of previous page]

**Use in Pediatrics:** Initial doses of 0.6 mg/kg in pediatric patients under halothane anesthesia produce excellent to good intubating conditions within 1 minute. The median (range) time to maximum block was 1 (0.5–3.3) minute(s). This dose will provide a median (range) time of clinical relaxation of 41 (24–68) minutes in 3 months–1 year pediatric patients and 27 (17–41) minutes in 1–12 year old pediatric patients. Maintenance doses of 0.075–0.125 mg/kg, administered upon return of  $T_1$  to 25% of control, provide clinical relaxation for 7–10 minutes.

Spontaneous recovery proceeds at approximately the same rate in pediatric patients (3 months–1 year) as in adults, but is more rapid in pediatric patients (1–12 years) than adults (see Tables 2 and 4 in Pharmacodynamics subsection of CLINICAL PHARMACOLOGY). A continuous infusion of ZEMURON™ (rocuronium bromide) Injection initiated at a rate of 0.012 mg/kg/min upon return of  $T_1$  to 10% of control (one twitch present in the train-of-four), may also be used to maintain neuromuscular blockade in pediatric patients. The infusion of ZEMURON™ must be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as monitored with the use of a peripheral nerve stimulator. Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of ZEMURON™ infusion may be expected to proceed at rates comparable to that following similar total exposure to single bolus doses (see Pharmacodynamics subsection of CLINICAL PHARMACOLOGY).

**Use in Obese Patients:** An analysis across all U.S. controlled clinical studies indicates that the pharmacodynamics of ZEMURON™ (rocuronium bromide) Injection are not different between obese and non-obese patients when dosed based upon their actual body weight.

**Use in Geriatrics:** Geriatric patients ( $\geq 65$  year) exhibited a slightly prolonged median (range) clinical duration of 46 (22–73), 62 (49–75), and 94 (64–138) minutes under opioid/nitrous oxide/oxygen anesthesia following doses of 0.6, 0.9 and 1.2 mg/kg, respectively. Maintenance doses of 0.1 and 0.15 mg/kg ZEMURON™ (rocuronium bromide) Injection, administered at 25% recovery of  $T_1$ , provide approximately 13 and 33 minutes of clinical duration under opioid/nitrous oxide/oxygen anesthesia. The median (range) rate of spontaneous recovery of  $T_1$  from 25 to 75% in geriatric patients is 17 (7–56) minutes which is not different from that in other adults (see Pharmacokinetics and Pharmacodynamics subsections of CLINICAL PHARMACOLOGY).

**Compatibility:** ZEMURON™ (rocuronium bromide) Injection is compatible in solution with:

0.9% NaCl solution	Sterile water for injection
5% glucose in water	Lactated Ringers
5% glucose in saline	

Use within 24 hours of mixing with the above solutions. Parenteral drug products should be inspected visually for particulate matter and clarity prior to administration whenever solution and container permit. Do not use solution if particulate matter is present.

**Safety and Handling:** There is no specific work exposure limit for ZEMURON™ (rocuronium bromide) Injection. In case of eye contact, flush with water for at least 10 minutes.

**HOW SUPPLIED**

ZEMURON™ (rocuronium bromide) Injection is available in the following forms:

ZEMURON™ 5 mL multiple dose vials containing 50 mg rocuronium bromide injection (10 mg/mL)	
Boxes of 10	NDC No. 0052-0450-15
ZEMURON™ 10 mL multiple dose vials containing 100 mg rocuronium bromide injection (10 mg/mL)	
Boxes of 10	NDC No. 0052-0450-16

Information will be superseded by supplements and subsequent editions

**Storage:** ZEMURON™ (rocuronium bromide) Injection should be stored under refrigeration, 2 to 8°C (36 to 46°F). DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use ZEMURON™ within 60 days. Use opened vials of ZEMURON™ within 30 days.

**Caution:** Federal law prohibits dispensing without prescription.

ORGANON INC. WEST ORANGE, NEW JERSEY 07052  
5310153 7/97

Shown in Product Identification Guide, page 327

**ZYMASE®**  
(pancrelipase, USP)  
enteric coated spheres**DESCRIPTION**

Zymase® capsules contain enteric coated spheres of pancrelipase, a substance containing enzymes, principally lipase, with amylase and protease obtained from the pancreas of the hog. Each capsule contains not less than:

Lipase—12,000 USP Units  
Protease—24,000 USP Units  
Amylase—24,000 USP Units

Each capsule also contains: Gelatin, purified water, starch, talc, titanium dioxide, FD&C Green #3, FD&C Yellow #10, and other inactive ingredients.

**CLINICAL PHARMACOLOGY**

Zymase® is protected against inactivation by gastric acidity, and active enzymes are released in the duodenum. The enzymes promote hydrolysis of fats into glycerol and fatty acids, protein into proteases and derived substances, and starch into dextrans and sugars.

**INDICATIONS AND USAGE**

Zymase® is indicated in conditions where pancreatic enzymes are either absent or deficient with resultant inadequate fat digestion. Such conditions include but are not limited to chronic pancreatitis, pancreatectomy, cystic fibrosis and steatorrhea of diverse etiologies.

**CONTRAINDICATIONS**

Known hypersensitivity to pork protein.

**PRECAUTIONS**

To maintain enteric coating integrity, do not chew or crush spheres.

**ADVERSE REACTIONS**

No adverse reactions have been reported. It should be noted, however, that extremely high doses of exogenous pancreatic enzymes have been associated with hyperuricemia and hyperuricemia.

**DOSAGE AND ADMINISTRATION**

One to two capsules with each meal or snack. Individual cases may require higher dosage and dietary adjustment. Where swallowing of capsules is difficult, capsules may be opened and the spheres taken with liquids or soft foods which do not require chewing.

**STORAGE**

Not to exceed 25°C (77°F). Store in dry place when opened.

**DISPENSE**

In tight container as defined in the USP.

Revised 4/93

Shown in Product Identification Guide, page 327

**Ortho Biotech Inc.**  
RARITAN, NJ 08869-0602

Direct Inquiries to:  
(800) 325-7504  
Prompt #1, Customer Service  
Prompt #2, Medical Information  
FAX: (908) 526-9230  
(908) 526-6457

**LEUSTATIN®**  
(cladribine) Injection  
For Intravenous Infusion Only**WARNING**

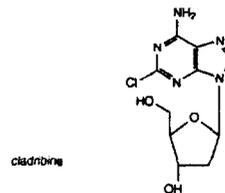
LEUSTATIN (cladribine) Injection should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. Suppression of bone marrow function should be anticipated. This is usually reversible and appears to be dose dependent. Serious neurological toxicity (including irreversible paraparesis and quadraparesis) has been reported in patients who received LEUSTATIN Injection by continuous infusion at high doses (4 to 9 times the recommended dose for Hairy Cell Leukemia). Neurologic toxicity appears to demonstrate a dose relationship; however, severe neurological toxicity has been reported rarely following treatment with standard cladribine dosing regimens.

Acute nephrotoxicity has been observed with high doses of LEUSTATIN (4 to 9 times the recommended dose for Hairy Cell Leukemia), especially when given concomitantly with other nephrotoxic agents/therapies.

**DESCRIPTION**

LEUSTATIN (cladribine) Injection (also commonly known as 2-chloro-2'-deoxy- $\beta$ -D-adenosine) is a synthetic antineoplastic agent for continuous intravenous infusion. It is a clear, colorless, sterile, preservative-free, isotonic solution. LEUSTATIN Injection is available in single-use vials containing 10 mg (1 mg/mL) of cladribine, a chlorinated purine nucleoside analog. Each milliliter of LEUSTATIN Injection contains 1 mg of the active ingredient and 9 mg (0.15 mEq) of sodium chloride as an inactive ingredient. The solution has a pH range of 5.5 to 8.0. Phosphoric acid and/or dibasic sodium phosphate may have been added to adjust the pH to 6.3±0.3.

The chemical name for cladribine is 2-chloro-6-amino-9-(2'-deoxy- $\beta$ -D-erythro-pentofuranosyl) purine and the structure is represented below:



cladribine

MW 285.7

**CLINICAL PHARMACOLOGY****Cellular Resistance and Sensitivity:**

The selective toxicity of 2-chloro-2'-deoxy- $\beta$ -D-adenosine towards certain normal and malignant lymphocyte and monocyte populations is based on the relative activities of deoxycytidine kinase and deoxynucleotidase. Cladribine passively crosses the cell membrane. In cells with a high ratio of deoxycytidine kinase to deoxynucleotidase, it is phosphorylated by deoxycytidine kinase to 2-chloro-2'-deoxy- $\beta$ -D-adenosine monophosphate (2-CdAMP). Since 2-chloro-2'-deoxy- $\beta$ -D-adenosine is resistant to deamination by adenosine deaminase and there is little deoxynucleotide deaminase in lymphocytes and monocytes, 2-CdAMP accumulates intracellularly and is subsequently converted into the active triphosphate deoxynucleotide, 2-chloro-2'-deoxy- $\beta$ -D-adenosine triphosphate (2-CdATP). It is postulated that cells with high deoxycytidine kinase and low deoxynucleotidase activities will be selectively killed by 2-chloro-2'-deoxy- $\beta$ -D-adenosine as toxic deoxynucleotides accumulate intracellularly.

Cells containing high concentrations of deoxynucleotidase are unable to properly repair single-strand DNA breaks. The broken ends of DNA activate the enzyme poly (ADP-ribose) polymerase resulting in NAD and ATP depletion and disruption of cellular metabolism. There is evidence, also, that 2-CdATP is incorporated into the DNA of dividing cells, resulting in impairment of DNA synthesis. Thus, 2-chloro-2'-deoxy- $\beta$ -D-adenosine can be distinguished from other chemotherapeutic agents affecting purine metabolism in that it is cytotoxic to both actively dividing and quiescent lymphocytes and monocytes, inhibiting both DNA synthesis and repair.

**HUMAN PHARMACOLOGY**

In a clinical investigation, 17 patients with Hairy Cell Leukemia and normal renal function were treated for 7 days with the recommended treatment regimen of LEUSTATIN Injection (0.09 mg/kg/day) by continuous intravenous infusion. The mean steady-state serum concentration was estimated to be 5.7 ng/mL with an estimated systemic clearance of 663.5 mL/h/kg when LEUSTATIN was given by continuous infusion over 7 days. In Hairy Cell Leukemia patients, there does not appear to be a relationship between serum concentrations and ultimate clinical outcome.

In another study, 8 patients with hematologic malignancies received a two (2) hour infusion of LEUSTATIN Injection (0.12 mg/kg). The mean end-of-infusion plasma LEUSTATIN concentration was 48±19 ng/mL. For 5 of these patients, the disappearance of LEUSTATIN could be described by either a biphasic or triphasic decline. For these patients with normal renal function, the mean terminal half-life was 5.4 hours. Mean values for clearance and steady-state volume of distribution were 978±422 mL/h/kg and 4.5±2.8 L/kg, respectively.

Plasma concentrations are reported to decline multi-exponentially after intravenous infusions with terminal half-lives ranging from approximately 3-22 hours. In general, the apparent volume of distribution of cladribine is very large (mean approximately 9 L/kg), indicating an extensive distribution of cladribine in body tissues. The mean half-life of cladribine in leukemic cells has been reported to be 23 hours.

Cladribine penetrates into cerebrospinal fluid. One report indicates that concentrations are approximately 25% of those in plasma.

LEUSTATIN is bound approximately 20% to plasma proteins.

Except for some understanding of the mechanism of cellular toxicity, no other information is available on the metabolism of LEUSTATIN in humans. An average of 18% of the administered dose has been reported to be excreted in urine of patients with solid tumors during a 5-day continuous intravenous infusion of 3.5-8.1 mg/m<sup>2</sup>/day of LEUSTATIN. The effect of renal and hepatic impairment on the elimination of cladribine has not been investigated in humans.

Two single-center open label studies of LEUSTATIN (cladribine) have been conducted in patients with Hairy Cell Leukemia with evidence of active disease requiring therapy. In the study conducted at the Scripps Clinic and Research Foundation (Study A), 89 patients were treated with a single course of LEUSTATIN Injection given by continuous intravenous infusion for 7 days at a dose of 0.09 mg/kg/day. In the study conducted at the M.D. Anderson Cancer Center (Study B), 35 patients were treated with a 7-day continuous intravenous infusion of LEUSTATIN Injection at a comparable dose of 3.6 mg/m<sup>2</sup>/day. A complete response (CR) required clearing of the peripheral blood and bone marrow of hairy cells and recovery of the hemoglobin to 12 g/dL, platelet count to 100 × 10<sup>9</sup>/L, and absolute neutrophil count to 1500 × 10<sup>6</sup>/L. A good partial response (GPR) required the same hematologic parameters as a complete response, and that fewer than 5% hairy cells remain in the bone marrow. A partial response (PR) required that hairy cells in the bone marrow be decreased by at least 50% from baseline and the same response for hematologic parameters as for complete response. A pathologic relapse was defined as an increase in bone marrow hairy cells to 25% of pretreatment levels. A clinical relapse was defined as the recurrence of cytopenias, specifically, decreases in hemoglobin ≥ 2 g/dL, ANC ≥ 25% or platelet counts ≥ 50,000. Patients who met the criteria for a complete response but subsequently were found to have evidence of bone marrow hairy cells (<25% of pretreatment levels) were reclassified as partial responses and were not considered to be complete responses with relapse.

Among patients evaluable for efficacy (N=106), using the hematologic and bone marrow response criteria described above, the complete response rates in patients treated with LEUSTATIN Injection were 65% and 68% for Study A and Study B, respectively, yielding a combined complete response rate of 66%. Overall response rates (i.e., Complete plus Good Partial plus Partial Responses) were 89% and 86% in Study A and Study B, respectively, for a combined overall response rate of 88% in evaluable patients treated with LEUSTATIN Injection.

Using an intent-to-treat analysis (N=123) and further requiring no evidence of splenomegaly as a criterion for CR (i.e., no palpable spleen on physical examination and ≤13 cm on CT scan), the complete response rates for Study A and Study B were 54% and 53%, respectively, giving a combined CR rate of 54%. The overall response rates (CR + GPR + PR) were 90% and 85%, for Studies A and B, respectively, yielding a combined overall response rate of 89%.

**RESPONSE RATES TO LEUSTATIN TREATMENT IN PATIENTS WITH HAIRY CELL LEUKEMIA**

	CR	Overall
Evaluable Patients N=106	66%	88%
Intent-to-treat Population N=123	54%	89%

In these studies, 60% of the patients had not received prior chemotherapy for Hairy Cell Leukemia or had undergone splenectomy as the only prior treatment and were receiving LEUSTATIN as a first-line treatment. The remaining 40% of the patients received LEUSTATIN as a second-line treatment, having been treated previously with other agents, including α-interferon and/or deoxycoformycin. The overall response rate for patients without prior chemotherapy was 92%, compared with 84% for previously treated patients. LEUSTATIN is active in previously treated patients; however, retrospective analysis suggests that the overall response rate is decreased in patients previously treated with splenectomy or deoxycoformycin and in patients refractory to α-interferon.

**OVERALL RESPONSE RATES (CR + GPR + PR) TO LEUSTATIN TREATMENT IN PATIENTS WITH HAIRY CELL LEUKEMIA**

	OVERALL RESPONSE (N=123)	NR + RELAPSE
No Prior Chemotherapy	68/74 92%	6 + 4 14%
Any Prior Chemotherapy	41/49 84%	8 + 3 22%
Previous Splenectomy	32/41* 78%	9 + 1 24%
Previous Interferon	40/48 83%	8 + 3 23%

Interferon Refractory	6/11* 55%	5 + 2 64%
Previous Deoxycoformycin	3/6* 50%	3 + 1 66%

NR = No Response  
\* P < 0.05

After a reversible decline, normalization of peripheral blood counts (Hemoglobin >12.0 g/dL, Platelets >100 × 10<sup>9</sup>/L, Absolute Neutrophil Count (ANC) >1500 × 10<sup>6</sup>/L) was achieved by 92% of evaluable patients. The median time to normalization of peripheral counts was 9 weeks from the start of treatment (Range: 2 to 72). The median time to normalization of Platelet Count was 2 weeks, the median time to normalization of ANC was 5 weeks and the median time to normalization of Hemoglobin was 8 weeks. With normalization of Platelet Count and Hemoglobin, requirements for platelet and RBC transfusions were abolished after Months 1 and 2, respectively, in those patients with complete response. Platelet recovery may be delayed in a minority of patients with severe baseline thrombocytopenia. Corresponding to normalization of ANC, a trend toward a reduced incidence of infection was seen after the third month, when compared to the months immediately preceding LEUSTATIN therapy. (see also WARNINGS, PRECAUTIONS and ADVERSE REACTIONS)

**LEUSTATIN TREATMENT IN PATIENTS WITH HAIRY CELL LEUKEMIA TIME TO NORMALIZATION OF PERIPHERAL BLOOD COUNTS**

Parameter	Median Time to Normalization of Count*
Platelet Count	2 weeks
Absolute Neutrophil Count	5 weeks
Hemoglobin	8 weeks
ANC, Hemoglobin and Platelet Count	9 weeks

\*Day 1 = First day of infusion

For patients achieving a complete response, the median time to response (i.e., absence of hairy cells in bone marrow and peripheral blood together with normalization of peripheral blood parameters), measured from treatment start, was approximately 4 months. Since bone marrow aspiration and biopsy were frequently not performed at the time of peripheral blood normalization, the median time to complete response may actually be shorter than that which was recorded. At the time of data cut-off, the median duration of complete response was greater than 8 months and ranged to 25+ months. Among 93 responding patients, seven had shown evidence of disease progression at the time of the data cut-off. In four of these patients, disease was limited to the bone marrow without peripheral blood abnormalities (pathologic progression), while in three patients there were also peripheral blood abnormalities (clinical progression). Seven patients who did not respond to a first course of LEUSTATIN received a second course of therapy. In the five patients who had adequate follow-up, additional courses did not appear to improve their overall response.

**INDICATIONS FOR USE**

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

**CONTRAINDICATIONS**

LEUSTATIN is contraindicated in those patients who are hypersensitive to this drug or any of its components.

**WARNINGS**

Severe bone marrow suppression, including neutropenia, anemia and thrombocytopenia, has been commonly observed in patients treated with LEUSTATIN, especially at high doses. At initiation of treatment, most patients in the clinical studies had hematologic impairment as a manifestation of active Hairy Cell Leukemia. Following treatment with LEUSTATIN, further hematologic impairment occurred before recovery of peripheral blood counts began. During the first two weeks after treatment initiation, mean Platelet Count, ANC, and Hemoglobin concentration declined and subsequently increased with normalization of mean counts by Day 12, Week 5 and Week 8, respectively. The myelosuppressive effects of LEUSTATIN were most notable during the first month following treatment. Forty-four percent (44%) of patients received transfusions with RBCs and 14% received transfusions with platelets during Month 1. Careful hematologic monitoring, especially during the first 4 to 8 weeks after treatment with LEUSTATIN Injection, is recommended. (see PRECAUTIONS)

Fever (T ≥ 100°F) was associated with the use of LEUSTATIN in approximately two-thirds of patients (13/196) in the first month of therapy. Virtually all of these patients were treated empirically with parenteral antibiotics.

Overall, 47% (93/196) of all patients had fever in the setting of neutropenia (ANC ≤ 1000), including 62 patients (32%) with severe neutropenia (i.e., ANC ≤ 500).

In a Phase I investigational study using LEUSTATIN in high doses (4 to 9 times the recommended dose for Hairy Cell Leukemia) as part of a bone marrow transplant conditioning regimen, which also included high dose cyclophosphamide and total body irradiation, acute nephrotoxicity and delayed onset neurotoxicity were observed. Thirty-one (31) poor-risk patients with drug-resistant acute leukemia in relapse (29 cases) or non-Hodgkins Lymphoma (2 cases) received LEUSTATIN for 7 to 14 days prior to bone marrow transplantation. During infusion, 8 patients experienced gastrointestinal symptoms. While the bone marrow was initially cleared of all hematopoietic elements, including tumor cells, leukemia eventually recurred in all treated patients. Within 7 to 13 days after starting treatment with LEUSTATIN, 6 patients (19%) developed manifestations of renal dysfunction (e.g., acidosis, anuria, elevated serum creatinine, etc.) and 5 required dialysis. Several of these patients were also being treated with other medications having known nephrotoxic potential. Renal dysfunction was reversible in 2 of these patients. In the 4 patients whose renal function had not recovered at the time of death, autopsies were performed; in 2 of these, evidence of tubular damage was noted. Eleven (11) patients (35%) experienced delayed onset neurologic toxicity. In the majority, this was characterized by progressive irreversible motor weakness (paraparesis/quadruparesis), of the upper and/or lower extremities, first noted 35 to 84 days after starting high dose therapy with LEUSTATIN. Non-invasive testing (electromyography and nerve conduction studies) was consistent with demyelinating disease. Severe neurologic toxicity has also been noted with high doses of another drug in this class.

Axonal peripheral polyneuropathy was observed in a dose escalation study at the highest dose levels (approximately 4 times the recommended dose for Hairy Cell Leukemia) in patients not receiving cyclophosphamide or total body irradiation. Severe neurological toxicity has been reported rarely following treatment with standard cladribine dosing regimens.

In patients with Hairy Cell Leukemia treated with the recommended treatment regimen (0.09 mg/kg/day for 7 consecutive days), there have been no reports of nephrologic toxicities.

Of the 196 Hairy Cell Leukemia patients entered in the two trials, there were 8 deaths following treatment. Of these, 6 were of infectious etiology, including 3 pneumonias, and 2 occurred in the first month following LEUSTATIN therapy. Of the 8 deaths, 6 occurred in previously treated patients who were Refractory to α-interferon.

Benzyl alcohol is a constituent of the recommended diluent for the 7-day infusion solution. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. (see DOSAGE AND ADMINISTRATION)

**Pregnancy Category D:** LEUSTATIN Injection should not be given during pregnancy.

Cladribine is teratogenic in mice and rabbits and consequently has the potential to cause fetal harm when administered to a pregnant woman. A significant increase in fetal variations was observed in mice receiving 1.5 mg/kg/day (4.5 mg/m<sup>2</sup>) and increased resorptions, reduced litter size and increased fetal malformations were observed when mice received 3.0 mg/kg/day (9 mg/m<sup>2</sup>). Fetal death and malformations were observed in rabbits that received 3.0 mg/kg/day (33.0 mg/m<sup>2</sup>). No fetal effects were seen in mice at 0.5 mg/kg/day (1.5 mg/m<sup>2</sup>) or in rabbits at 1.0 mg/kg/day (11.0 mg/m<sup>2</sup>).

Although there is no evidence of teratogenicity in humans due to LEUSTATIN, other drugs which inhibit DNA synthesis (e.g., methotrexate and aminopterin) have been reported to be teratogenic in humans. LEUSTATIN has been shown to be embryotoxic in mice when given at doses equivalent to the recommended dose.

There are no adequate and well controlled studies in pregnant women. If LEUSTATIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant.

**PRECAUTIONS**

**General:** LEUSTATIN Injection is a potent antineoplastic agent with potentially significant toxic side effects. It should be administered only under the supervision of a physician experienced with the use of cancer chemotherapeutic agents. Patients undergoing therapy should be closely observed for signs of hematologic and non-hematologic toxicity. Periodic assessment of peripheral blood counts, particularly during the first 4 to 8 weeks post-treatment, is recommended to detect the development of anemia, neutropenia and thrombocytopenia and for early detection of any potential sequelae (e.g., infection or bleeding). As with other potent chemotherapeutic agents, monitoring of renal and hepatic function is also recommended, especially in patients with underlying kidney or liver dysfunction. (see WARNINGS and ADVERSE REACTIONS)

Fever was a frequently observed side effect during the first month on study. Since the majority of fevers occurred in neutropenic patients, patients should be closely monitored during the first month of treatment and empiric antibiotics

Continued on next page

## Leustatin—Cont.

should be initiated as clinically indicated. Although 69% of patients developed fevers, less than 1/3 of febrile events were associated with documented infection. Given the known myelosuppressive effects of LEUSTATIN, practitioners should carefully evaluate the risks and benefits of administering this drug to patients with active infections. (see WARNINGS and ADVERSE REACTIONS)

There are inadequate data on dosing of patients with renal or hepatic insufficiency. Development of acute renal insufficiency in some patients receiving high doses of LEUSTATIN has been described. Until more information is available, caution is advised when administering the drug to patients with known or suspected renal or hepatic insufficiency. (see WARNINGS)

Rare cases of tumor lysis syndrome have been reported in patients treated with cladribine with other hematologic malignancies having a high tumor burden.

LEUSTATIN Injection must be diluted in designated intravenous solutions prior to administration. (see DOSAGE AND ADMINISTRATION)

**Laboratory Tests:** During and following treatment, the patient's hematologic profile should be monitored regularly to determine the degree of hematopoietic suppression. In the clinical studies, following reversible declines in all cell counts, the mean Platelet Count reached  $100 \times 10^9/L$  by Day 12, the mean Absolute Neutrophil Count reached  $1500 \times 10^6/L$  by Week 5 and the mean Hemoglobin reached 12 g/dL by Week 8. After peripheral counts have normalized, bone marrow aspiration and biopsy should be performed to confirm response to treatment with LEUSTATIN. Febrile events should be investigated with appropriate laboratory and radiologic studies. Periodic assessment of renal function and hepatic function should be performed as clinically indicated.

**Drug Interactions:** There are no known drug interactions with LEUSTATIN Injection. Caution should be exercised if LEUSTATIN Injection is administered before, after, or in conjunction with other drugs known to cause immunosuppression or myelosuppression. (see WARNINGS)

**Carcinogenesis:** No animal carcinogenicity studies have been conducted with cladribine. However, its carcinogenic potential cannot be excluded based on demonstrated genotoxicity of cladribine.

**Mutagenesis:** As expected for compounds in this class, the actions of cladribine yield DNA damage. In mammalian cells in culture, cladribine caused the accumulation of DNA strand breaks. Cladribine was also incorporated into DNA of human lymphoblastic leukemia cells. Cladribine was not mutagenic *in vitro* (Ames and Chinese hamster ovary cell gene mutation tests) and did not induce unscheduled DNA synthesis in primary rat hepatocyte cultures. However, cladribine was clastogenic both *in vitro* (chromosome aberrations in Chinese hamster ovary cells) and *in vivo* (mouse bone marrow micronucleus test).

**Impairment of Fertility:** When administered intravenously to Cynomolgus monkeys, cladribine has been shown to cause suppression of rapidly generating cells, including testicular cells. The effect on human fertility is unknown.

**Pregnancy:** Pregnancy Category D. (see WARNINGS)

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from cladribine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug for the mother.

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. In a Phase I study involving patients 1–21 years old with relapsed acute leukemia, LEUSTATIN was given by continuous intravenous infusion in doses ranging from 3 to  $10.7 \text{ mg/m}^2/\text{day}$  for 5 days (one-half to twice the dose recommended in Hairy Cell Leukemia). In this study, the dose-limiting toxicity was severe myelosuppression with profound neutropenia and thrombocytopenia. At the highest dose ( $10.7 \text{ mg/m}^2/\text{day}$ ), 3 of 7 patients developed irreversible myelosuppression and fatal systemic bacterial and fungal infections. No unique toxicities were noted in this study.<sup>11</sup> (see WARNINGS and ADVERSE REACTIONS)

## ADVERSE REACTIONS

Safety data are based on 196 patients with Hairy Cell Leukemia: the original cohort of 124 patients plus an additional 72 patients enrolled at the same two centers after the original enrollment cutoff. In Month 1 of the Hairy Cell Leukemia clinical trials, severe neutropenia was noted in 70% of patients, fever in 69%, and infection was documented in 28%. Other adverse experiences reported frequently during the first 14 days after initiating treatment included: fatigue (45%), nausea (28%), rash (27%), headache (22%) and injection site reactions (19%). Most non-hematologic adverse experiences were mild to moderate in severity.

Myelosuppression was frequently observed during the first month after starting treatment. Neutropenia (ANC  $< 500 \times 10^6/L$ ) was noted in 70% of patients, compared with 26% in whom it was present initially. Severe anemia (Hemoglobin  $< 8.5 \text{ g/dL}$ ) developed in 37% of patients, compared with 10% initially and thrombocytopenia (Platelets  $< 20 \times 10^9/L$ ) developed in 12% of patients, compared to 4% in whom it was noted initially.

During the first month, 54 of 196 patients (28%) exhibited documented evidence of infection. Serious infections (e.g.,

septicemia, pneumonia) were reported in 6% of all patients; the remainder were mild or moderate. Several deaths were attributable to infection and/or complications related to the underlying disease. During the second month, the overall rate of documented infection was 6%; these infections were mild to moderate and no severe systemic infections were seen. After the third month, the monthly incidence of infection was either less than or equal to that of the months immediately preceding LEUSTATIN therapy.

During the first month, 11% of patients experienced severe fever (i.e.,  $\geq 104^\circ\text{F}$ ). Documented infections were noted in fewer than one-third of febrile episodes. Of the 196 patients studied, 19 were noted to have a documented infection in the month prior to treatment. In the month following treatment, there were 54 episodes of documented infection: 23 (42%) were bacterial, 11 (20%) were viral and 11 (20%) were fungal. Seven (7) of 8 documented episodes of herpes zoster occurred during the month following treatment. Fourteen (14) of 16 episodes of documented fungal infections occurred in the first two months following treatment. Virtually all of these patients were treated empirically with antibiotics. (see WARNINGS and PRECAUTIONS)

Analysis of lymphocyte subsets indicates that treatment with cladribine is associated with prolonged depression of the CD4 counts. Prior to treatment, the mean CD4 count was  $766/\mu\text{L}$ . The mean CD4 count nadir, which occurred 4 to 6 months following treatment, was  $272/\mu\text{L}$ . Fifteen (15) months after treatment, mean CD4 counts remained below  $500/\mu\text{L}$ . CD8 counts behaved similarly, though increasing counts were observed after 9 months. The clinical significance of the prolonged CD4 lymphopenia is unclear.

Another event of unknown clinical significance includes the observation of prolonged bone marrow hypocellularity. Bone marrow cellularity of  $< 35\%$  was noted after 4 months in 42 of 124 patients (34%) treated in the two pivotal trials. This hypocellularity was noted as late as day 1010. It is not known whether the hypocellularity is the result of disease related marrow fibrosis or if it is the result of cladribine toxicity. There was no apparent clinical effect on the peripheral blood counts.

The vast majority of rashes were mild and occurred in patients who were receiving or had recently been treated with other medications (e.g., allopurinol or antibiotics) known to cause rash.

Most episodes of nausea were mild, not accompanied by vomiting, and did not require treatment with antiemetics. In patients requiring antiemetics, nausea was easily controlled, most frequently with chlorpromazine.

Adverse reactions reported during the first 2 weeks following treatment initiation (regardless of relationship to drug) by  $> 5\%$  of patients included:

**Body as a Whole:** fever (69%), fatigue (45%), chills (9%), asthenia (9%), diaphoresis (9%), malaise (7%), trunk pain (6%)

**Gastrointestinal:** nausea (28%), decreased appetite (17%), vomiting (13%), diarrhea (10%), constipation (9%), abdominal pain (6%)

**Hemic/Lymphatic:** purpura (10%), petechiae (8%), epistaxis (5%)

**Nervous System:** headache (22%), dizziness (9%), insomnia (7%)

**Cardiovascular System:** edema (6%), tachycardia (6%)

**Respiratory System:** abnormal breath sounds (11%), cough (10%), abnormal chest sounds (9%), shortness of breath (7%)

**Skin/Subcutaneous Tissue:** rash (27%), injection site reactions (19%), pruritus (6%), erythema (6%)

**Musculoskeletal System:** myalgia (7%), arthralgia (5%)

Adverse experiences related to intravenous administration included: injection site reactions (9%) (i.e., redness, swelling, pain), thrombosis (2%), phlebitis (2%) and a broken catheter (1%). These appear to be related to the infusion procedure and/or indwelling catheter, rather than the medication or the vehicle.

From Day 15 to the last follow-up visit, the only events reported by  $> 5\%$  of patients were: fatigue (11%), rash (10%), headache (7%), cough (7%), and malaise (5%).

For a description of adverse reactions associated with use of high doses in non-Hairy Cell Leukemia patients, see WARNINGS.

The following additional adverse events have been reported since the drug became commercially available. These adverse events have been reported primarily in patients who received multiple courses of LEUSTATIN Injection:

**Hematologic:** bone marrow suppression with prolonged pancytopenia, including some reports of aplastic anemia; pancytopenia, which was reported in patients with lymphoid malignancies, occurring within the first few weeks following treatment.

**Hepatic:** reversible, generally mild increases in bilirubin and transaminases.

**Nervous System:** Neurological toxicity; however, severe neurotoxicity has been reported rarely following treatment with standard cladribine dosing regimens.

**Respiratory System:** pulmonary interstitial infiltrates; in most cases, an infectious etiology was identified.

**Skin/Subcutaneous:** urticaria, hypersensitivity. In isolated cases Stevens-Johnson and toxic epidermal necrolysis have been reported in patients who were receiving or had recently been treated with other medications (e.g., allopurinol or antibiotics) known to cause these syndromes.

Opportunistic infections have occurred in the acute phase of treatment due to the immunosuppression mediated by LEUSTATIN Injection.

## OVERDOSAGE

High doses of LEUSTATIN have been associated with: irreversible neurologic toxicity (paraparesis/quadruparesis), acute nephrotoxicity, and severe bone marrow suppression resulting in neutropenia, anemia and thrombocytopenia. (see WARNINGS) There is no known specific antidote to overdosage. Treatment of overdosage consists of discontinuation of LEUSTATIN, careful observation and appropriate supportive measures. It is not known whether the drug can be removed from the circulation by dialysis or hemofiltration.

## DOSAGE AND ADMINISTRATION

## Usual Dose:

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

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

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

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

	Dose of LEUSTATIN Injection	Recommended Diluent	Quantity of Diluent
24-hour infusion method	1 (day) $\times$ $0.09 \text{ mg/kg}$	$0.9\%$ Sodium Chloride Injection, USP	$500 \text{ mL}$

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

	Dose of LEUSTATIN Injection	Recommended Diluent	Quantity of Diluent
7-day infusion method (use sterile $0.22\mu$ filter when preparing infusion solution)	7 (days) $\times$ $0.09 \text{ mg/kg}$	Bacteriostatic $0.9\%$ Sodium Chloride Injection, USP ( $0.9\%$ benzyl alcohol)	q.s. to $100 \text{ mL}$

Since limited compatibility data are available, adherence to the recommended diluents and infusion systems is ad-

vised. Solutions containing LEUSTATIN Injection should not be mixed with other intravenous drugs or additives or infused simultaneously via a common intravenous line, since compatibility testing has not been performed. Preparations containing benzyl alcohol should not be used in neonates. (see WARNINGS)

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

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. A precipitate may occur during the exposure of LEUSTATIN Injection to low temperatures; it may be resolubilized by allowing the solution to warm naturally to room temperature and by shaking vigorously. **DO NOT HEAT OR MICROWAVE.**

**Chemical Stability of Vials:**

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

**Handling and Disposal:**

The potential hazards associated with cytotoxic agents are well established and proper precautions should be taken when handling, preparing, and administering LEUSTATIN Injection. The use of disposable gloves and protective garments is recommended. If LEUSTATIN Injection contacts the skin or mucous membranes, wash the involved surface immediately with copious amounts of water. Several guidelines on this subject have been published.<sup>1,2-6</sup> There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate. Refer to your Institution's guidelines and all applicable state/local regulations for disposal of cytotoxic waste.

**HOW SUPPLIED**

LEUSTATIN Injection is supplied as a sterile, preservative-free, isotonic solution containing 10 mg (1 mg/mL) of cladribine as 10 mL filled into a single-use clear flint glass 20 mL vial. LEUSTATIN Injection is supplied in 10 mL (1 mg/mL) single-use vials (NDC 59676-201-01) available in a treatment set (case) of seven vials.

Store refrigerated 2° to 8°C (36° to 46°F). Protect from light during storage.

**References:**

1. Santana VM, Mirro J, Harwood FC, et al: A phase I clinical trial of 2-Chloro-deoxyadenosine in pediatric patients with acute leukemia. *J. Clin. Onc.* 9: 416 (1991).
2. 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, D.C. 20402.
3. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*. March 15 (1985).
4. National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission of Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
5. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med. J. Australia* 1:425 (1983).
6. Jones RB, et al. Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. *Ca—A Cancer Journal for Clinicians*, Sept/Oct. 258—263 (1983).
7. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic Drugs in Hospitals. *Am. J. Hosp. Pharm.*, 42:131 (1985).
8. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (antineoplastic) Drugs. *Am. J. Hosp. Pharm.*, 43:1193 (1986).

**CAUTION:** Federal law prohibits dispensing without prescription.

† Vialflex® containers, manufactured by Baxter Healthcare Corporation - Code No. 2B8013 (testing in 1991)

‡ MEDICATION CASSETTE™ Reservoir, manufactured by SIMS Deltec, Inc. - Reorder No. 602100A (tested in 1991)

ORTHO BIOTECH INC  
Raritan, New Jersey 08869

ORTHO BIOTECH

COBI 1996

638-10-940-5

Revised December 1996

LEU-533

Shown in Product Identification Guide, page 724

**ORTHOCLONE OKT® 3 Sterile Solution**  
(muromonab-CD3)  
For Intravenous Use Only

**WARNING:**

Only physicians experienced in immunosuppressive therapy and management of solid organ transplant patients should use ORTHOCLONE OKT3 (muromonab-CD3). Patients treated with ORTHOCLONE OKT3 must be managed in a facility equipped and staffed for cardiopulmonary resuscitation and where the patient can be closely monitored for an appropriate period based on his or her health status.

Anaphylactic and anaphylactoid reactions may occur following administration of any dose or course of ORTHOCLONE OKT3. In addition, serious, occasionally life-threatening or lethal, systemic, cardiovascular, and central nervous system reactions have been reported following administration of ORTHOCLONE OKT3. These have included: pulmonary edema, especially in patients with volume overload; shock, cardiovascular collapse, cardiac or respiratory arrest, seizures, coma, cerebral edema, cerebral herniation, blindness, and paralysis. Fluid status should be carefully monitored prior to and during ORTHOCLONE OKT3 administration. Pretreatment with methylprednisolone is recommended to minimize symptoms of Cytokine Release Syndrome. (See: WARNINGS: Cytokine Release Syndrome, Central Nervous System Events, Anaphylactic Reactions; DOSAGE AND ADMINISTRATION)

**DESCRIPTION**

ORTHOCLONE OKT3 (muromonab-CD3) Sterile Solution is a murine monoclonal antibody to the CD3 antigen of human T cells which functions as an immunosuppressant. It is for intravenous use only. The antibody is a biochemically purified IgG<sub>2b</sub> immunoglobulin with a heavy chain of approximately 50,000 daltons and a light chain of approximately 25,000 daltons. It is directed to a glycoprotein with a molecular weight of 20,000 in the human T cell surface which is essential for T cell functions. Because it is a monoclonal antibody preparation, ORTHOCLONE OKT3 Sterile Solution is a homogeneous, reproducible antibody product with consistent, measurable reactivity to human T cells. Each 5 mL ampule of ORTHOCLONE OKT3 Sterile Solution contains 5 mg (1 mg/mL) of muromonab-CD3 in a clear colorless solution which may contain a few fine translucent protein particles. Each ampule contains a buffered solution (pH 7.0 ± 0.5) of monobasic sodium phosphate (2.25 mg), dibasic sodium phosphate (9.0 mg), sodium chloride (43 mg), and polysorbate 80 (1.0 mg) in water for injection. The proper name, muromonab-CD3, is derived from the descriptive term murine monoclonal antibody. The CD3 designation identifies the specificity of the antibody as the Cell Differentiation (CD) cluster 3 defined by the First International Workshop on Human Leukocyte Differentiation Antigens.

**CLINICAL PHARMACOLOGY**

ORTHOCLONE OKT3 reverses graft rejection, probably by blocking the function of T cells which play a major role in acute allograft rejection. ORTHOCLONE OKT3 reacts with and blocks the function of a 20,000 dalton molecule (CD3) in the membrane of human T cells that has been associated *in vitro* with the antigen recognition structure of T cells and is essential for signal transduction. *In vitro* cytolytic assays. ORTHOCLONE OKT3 blocks both the generation and function of effector cells. Binding of ORTHOCLONE OKT3 to T lymphocytes results in early activation of T cells, which leads to cytokine release, followed by blocking T cell functions. After termination of ORTHOCLONE OKT3 therapy, T cell function usually returns to normal within one week. *In vivo*, ORTHOCLONE OKT3 reacts with most peripheral blood T cells and T cells in body tissues, but has not been found to react with other hematopoietic elements or other tissues of the body.

A rapid and concomitant decrease in the number of circulating CD3 positive cells, including those that are CD2, CD4, or CD8 positive has been observed in patients studied within minutes after the administration of ORTHOCLONE OKT3. This decrease in the number of CD3 positive T cells results from the specific interaction between ORTHOCLONE OKT3 and the CD3 antigen on the surface of all T lymphocytes. T cell activation results in the release of numerous cytokines/lymphokines, which are felt to be responsible for many of the acute clinical manifestations seen following ORTHOCLONE OKT3 administration. (See: WARNINGS: Cytokine Release Syndrome, Central Nervous System Events)

While CD3 positive cells are not detectable between days two and seven, increasing numbers of circulating CD2, CD4, and CD8 positive cells have been observed. The presence of these CD2, CD4, and CD8 positive cells has not been shown to affect reversal of rejection. After termination of ORTHOCLONE OKT3 therapy, CD3 positive cells reappear rapidly and reach pre-treatment levels within a week. In some patients however, increasing numbers of CD3 positive cells have been observed prior to termination of ORTHOCLONE OKT3 therapy. This reappearance of CD3 positive cells has been attributed to the development of neutralizing antibodies to ORTHOCLONE OKT3, which in turn block its ability to bind to the CD3 antigen on T lymphocytes. (See: PRECAUTIONS: Sensitization)

Pediatric patients are known to have higher CD3 lymphocyte counts than adults. Pediatric patients receiving ORTHOCLONE OKT3 therapy often require progressively higher doses of ORTHOCLONE OKT3 to achieve depletion of CD3 positive cells (<25 cells/mm<sup>3</sup>) and ensure therapeutic ORTHOCLONE OKT3 serum concentrations (>800 ng/mL). (See: DOSAGE AND ADMINISTRATION; PRECAUTIONS: Laboratory Tests)

Serum levels of ORTHOCLONE OKT3 are measurable using an enzyme-linked immunosorbent assay (ELISA). During the initial clinical trials in renal allograft rejection, in patients treated with 5 mg per day for 14 days, mean serum trough levels of the drug rose over the first three days and then averaged 900 ng/mL on days 3 to 14. Serum concentrations measured daily during treatment with ORTHOCLONE OKT3 in renal, hepatic, and cardiac allograft recipients revealed that pediatric patients less than 10 years of age have higher levels than patients 10–50 years of age. Subsequent clinical experience has demonstrated that serum levels greater than or equal to 800 ng/mL of ORTHOCLONE OKT3 blocks the function of cytotoxic T cells *in vitro* and *in vivo*. Reduced T cell clearance or low plasma ORTHOCLONE OKT3 levels provide a basis for adjusting ORTHOCLONE OKT3 dosage or for discontinuing therapy. (See: WARNINGS: Anaphylactic Reactions; PRECAUTIONS: Laboratory Tests; ADVERSE EVENTS: Hypersensitivity Reactions; DOSAGE AND ADMINISTRATION) Following administration of ORTHOCLONE OKT3 *in vivo*, leukocytes have been observed in cerebrospinal and peritoneal fluids. The mechanism for this effect is not completely understood, but probably is related to cytokines altering membrane permeability, rather than an active inflammatory process. (See: WARNINGS: Cytokine Release Syndrome, Central Nervous System Events)

**CLINICAL STUDIES**

**Acute Renal Rejection:**

In a controlled randomized clinical trial, ORTHOCLONE OKT3 was compared with conventional high-dose steroid therapy in reversing acute renal allograft rejection. In this trial, 122 evaluable patients undergoing acute rejection of cadaveric renal transplants were treated either with ORTHOCLONE OKT3 daily for a mean of 14 days, with concomitant lowering of the dosage of azathioprine and maintenance steroids (62 patients), or with conventional high-dose steroids (60 patients). ORTHOCLONE OKT3 reversed 94% of the rejections compared to a 75% reversal rate obtained with conventional high-dose steroid treatment (p=0.006). The one year Kaplan-Meier (actuarial) estimates of graft survival rates for these patients who had acute rejection were 62% and 45% for ORTHOCLONE OKT3 and steroid-treated patients, respectively (p=0.04). At two years the rates were 56% and 42%, respectively (p=0.06). One- and two-year patient survivals were not significantly different between the two groups, being 85% and 75% for ORTHOCLONE OKT3 treated patients and 90% and 55% for steroid-treated patients.

In additional open clinical trials, the observed rate of reversal of acute renal allograft rejection was 92% (n=126) for ORTHOCLONE OKT3 therapy. ORTHOCLONE OKT3 was also effective in reversing acute renal allograft rejections in 65% (n=225) of cases where steroids and lymphocyte immune globulin preparations were contraindicated or were not successful.

The effectiveness of ORTHOCLONE OKT3 for prophylaxis of renal allograft rejection has not been established.

**Acute Cardiac or Hepatic Allograft Rejection:**

ORTHOCLONE OKT3 was studied for use in reversing acute cardiac and hepatic allograft rejection in patients who are unresponsive to high-doses of steroids. The rate of reversal in acute cardiac allograft rejection was 90% (n = 61) and was 83% for hepatic allograft rejection (n = 124) in patients unresponsive to treatment with steroids.

Controlled randomized trials have not been conducted to evaluate the effectiveness of ORTHOCLONE OKT3 compared to conventional therapy as first line treatment for acute cardiac and hepatic allograft rejection.

**INDICATIONS AND USAGE**

ORTHOCLONE OKT3 is indicated for the treatment of acute allograft rejection in renal transplant patients.

ORTHOCLONE OKT3 is indicated for the treatment of steroid-resistant acute allograft rejection in cardiac and hepatic transplant patients.

The dosage of other immunosuppressive agents used in conjunction with ORTHOCLONE OKT3 should be reduced to the lowest level compatible with an effective therapeutic response. (See: WARNINGS and ADVERSE EVENTS: Infections, Neoplasia; DOSAGE AND ADMINISTRATION)

**CONTRAINDICATIONS**

ORTHOCLONE OKT3 should not be given to patients who:

- are hypersensitive to this or any other product of murine origin;
- have anti-mouse antibody titers ≥1:1000;
- are in (uncompensated) heart failure or in fluid overload, as evidenced by chest X-ray or a greater than 3 percent weight gain within the week prior to planned ORTHOCLONE OKT3 administration;
- have uncontrolled hypertension;
- have a history of seizures, or are predisposed to seizures;
- are determined or suspected to be pregnant, or who are breast-feeding. (See: PRECAUTIONS: Pregnancy, Nursing Mothers)

Continued on next page



4 3 5 8 '00 NOV 15 A9:11

FDA / Dockets Management Branch  
Attn. Ms. Helen Harris  
HFA-305, Room 1061  
5630 Fischers Lane

Rockville, MD 20852

November 14, 2000

***Suitability Petition for Cladribine-Lipomed /  
our letter dated September 7, 2000***

Dear Ms. Harris

As per our recent phone call, we send you hereby the completion of the petition

1. Environmental Impact Statement

The Lipomed, Switzerland facility meets all the requirements of the relevant national and local authorities with respect to any environmental impact from the production of 2-chloro-2'-deoxyadenosine (2-CDA, Cladribine). Production areas in which manufactured materials can be exposed to the environment are designed to minimize the risk of contamination.

2. Certification statement

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

We look forward to hearing from you soon and remain,

sincerely yours

Lipomed Inc.

Mario Pasquier  
Vice President



**Shipment Airwaybill**  
 1-800-CALL-DHL (Non negotiable) in USA only  
 WEB ADDRESS: <http://www.dhl.com>

8904981024

Quote this shipment number in an inquiry

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MD	GA

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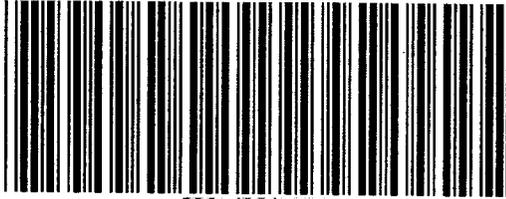
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Attention <b>BRANCH / FDA</b>	
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Zip/Postcode (required) <b>20857</b>	Phone/Fax/E-mail <b>301 827 5711</b>

**5 Shipper's authorization and signature**

I/we agree that DHL's standard terms apply to this shipment and limit DHL's liability for loss or damage to 12.5 x 100. The Warsaw Convention may also apply (see reverse). I/we authorize DHL to complete other documents necessary to export this shipment. I/we understand that insurance is available on request, for an extra charge. I/we agree to pay all charges if the recipient or third party does not pay. I/we understand that DHL DOES NOT TRANSPORT CASH.

Signature (required) <b>[Signature]</b>	Date <b>10/2/00</b>
--	------------------------



890 4981 024

**3 Shipment details**

<b>Domestic Services</b> <input checked="" type="checkbox"/> USA OVERNIGHT <b>International Services</b> <input type="checkbox"/> INT'L DOCUMENT EXPRESS <input type="checkbox"/> WORLDWIDE PRIORITY EXPRESS <input type="checkbox"/> WORLDFREIGHT <b>WorldMail Services</b> <input type="checkbox"/> APM <input type="checkbox"/> 2nd class <input type="checkbox"/> Other <b>Special Services</b> <input type="checkbox"/> SATURDAY DELIVERY <input type="checkbox"/> POD <input type="checkbox"/> OTHER	<b>Payment Options not all options available to all countries</b> <input checked="" type="checkbox"/> Shipper's account <input type="checkbox"/> Recipient <input type="checkbox"/> Third party Acct. No.
---	--

Full description of contents  
**Business documents**

**International non document shipments only**  
 Attach original and four copies of a Commercial Invoice

Declared value for customs (in US \$):	Export license No./Symbol (if applicable)
Harmonized Sched. B No. (if applicable)	Type of export <input checked="" type="checkbox"/> Permanent <input type="checkbox"/> Temporary <input type="checkbox"/> Repair/Return
Shipper's EIN/SSN	<small>These commodities, technology or software were exported from the United States in accordance with the export administration regulations. Diversion contrary to U.S. law prohibited.</small>
Destination duties/taxes If left blank recipient pays duties/taxes <input type="checkbox"/> Recipient <input type="checkbox"/> Shipper <input type="checkbox"/> Other	

**4 Pcs/Weight/Size**

No. of pieces
Weight if DHL Express Document packaging is used, enter XD <b>XD</b>
Dimensions in inches
Pieces length width height

DIMENSIONAL/CHARGED WEIGHT

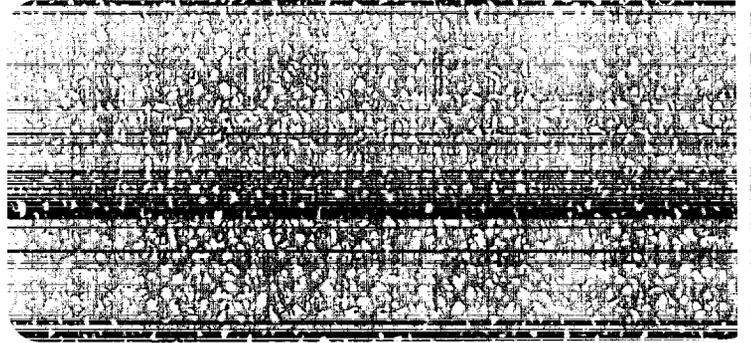
CODES	CHARGES Services
	Special services
	Insurance
	Drop Box/ Exp. Center
<b>TOTAL</b>	

TRANSPORT COLLECT STICKER No.

PICKED UP BY  
**10/4 W**

Time  
Date

AIRWAYS, INC. • 333 IWIN DOLPHIN DRIVE, REDWOOD CITY, CA 94065  
 Recipient's Copy



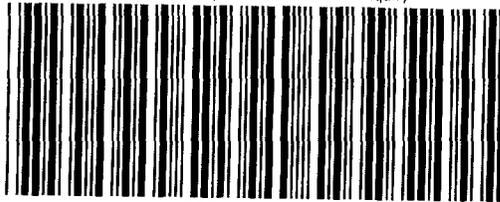


Shipment Airwaybill  
1-800-CALL-DHL (N/A negotiable)  
in USA only  
WEB ADDRESS: http://www.dhl.com

PPF  
PPF

8290164772

Quote this shipment number in an inquiry



829 0164 772

ORIGIN <b>BOS</b>	DESTINATION <b>GAI</b>
----------------------	---------------------------

**1 From (Shipper)**

Account no. **753843442** Shipper's reference **ADDA FDA**

Company name **LIPOMED**

Shipper's name **MARIO PASQUINI**

Address  
**1 BEDADWAY  
CAMBRIDGE MA**

Zip code (required) **021421100** Phone/Fax/E-mail **(617)577-7222**

**2 To (Recipient)**

Company name **FDA/Dockets Management Branch**

Attention **Ms. Helen Harris**

Delivery address  
**MFA - 305 Room 1061  
5630 Fishers Lane  
Rockville, MD**

Zip/Postcode (required) **20852** Phone/Fax/E-mail **301 827 6861**

**5 Shipper's authorization and signature**

I hereby authorize that DHL's standard terms apply to this shipment and limit DHL's liability for loss or damage to the extent of the Warsaw Convention. I agree to pay all charges if the recipient or third party does not pay.

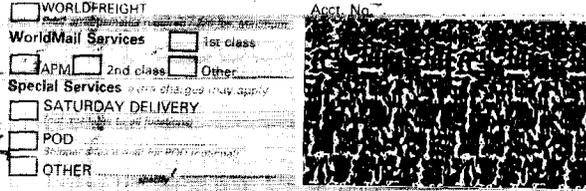
Signature (required) **[Signature]** Date **11/14/00**

**3 Shipment details**

- Domestic Services**
- USA OVERNIGHT
- International Services**
- INT'L DOCUMENT EXPRESS
  - WORLDWIDE PRIORITY EXPRESS
  - WORLDFREIGHT
- WorldMail Services**
- 1st class
  - AFM  2nd class  Other
- Special Services**
- SATURDAY DELIVERY
  - POD
  - OTHER

**Payment Options** not all options available to all countries

- Shipper's account
- Recipient
- Third party



Full description of contents  
**Business literature**

**International non document shipments only**  
Attach original and four copies of a Commercial Invoice

Declared value for customs (in US \$) \_\_\_\_\_ Export license No./Symbol (if applicable) \_\_\_\_\_

Harmonized Sched. B No. (if applicable) \_\_\_\_\_ Type of export  Permanent  Temporary  Repair/Return

Shipper's EIN/SSN \_\_\_\_\_ These commodities, technology or software were exported from the United States in accordance with the export administration regulations. Diversion contrary to U.S. law prohibited.

Destination duties/taxes If left blank recipient pays duties/taxes

- Recipient
- Shipper
- Other

**4 Pcs/Weight/Size**

No. of pieces **21**

Weight if DHL Express Document packaging is used, enter XD **XD**

Dimensions in inches

Pieces length width height

**DIMENSIONAL/CHARGED WEIGHT**

CODES CHARGES

Insurance

Drop Box/ Exp. Center

TOTAL

TRANSPORT COLLECT STICKER No.

PICKED UP BY **54**

Time \_\_\_\_\_ Date \_\_\_\_\_

DHL AIRWAYS, INC. • 333 TWIN DOLLAR DRIVE • BETHesda, MD 20814 • CA 94085 Recipient's Copy