DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-140 **NDA APPROVAL**

Spectrum Pharmaceuticals, Inc.
Attention: Cynthia Letizia, MPH, RAC
Vice President, Regulatory Affairs
157 Technology Dr.
Irvine, CA 92618

Dear Ms. Letizia:

Please refer to your new drug application (NDA) dated December 14, 1990, received December 18, 1990, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levoleucovorin for Injection.

We acknowledge receipt of your submissions dated July 10, August 10, September 27, October 23, November 5, 12, December 12, 2007, January 4, 14, February 4, 6, 12, 16, 27, March 3, 4 and 5, 2008.

The July 10, 2007, submission constituted a complete response to our January 3, 1992, action letter.

This new drug application provides for the use of Levoleucovorin for Injection, 50 mg/10 mL or 10 mg/mL for rescue after high-dose methotrexate therapy in osteosarcoma and to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 20-140."

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission

"**Final Printed Carton and Container Labels for approved NDA 20-140**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

We remind you of your postmarketing study commitment in your submission dated March 3, 2008. This commitment is listed below.

Commitment 1:
You have agreed that the structural identity of the degradation products listed as *(b) (4)* in the drug product specifications, will be confirmed within six months from the date of approval of the NDA.

Study Start:	by March 2008
Final Report Submission:	by September 2008

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

An expiration dating period of 24 months is granted when the drug product is stored as recommended in the labeling. You may extend the expiration dating period upon accrual of real time stability data and report this in the next annual report.

A decision on the acceptability of your proposed trade name will be made by the Division of Medication Error Prevention and will be communicated to you at a later date. Accordingly, you may submit a post-approval labeling supplement with inclusion of the accepted trade name. Until then, you may not use any trade name on the labels and labeling, but may only use the established name.

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any question, call Paul Zimmerman, Regulatory Project Manager, at 301-796-1489.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Deputy Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Levoleucovorin safely and effectively. See full prescribing information for Levoleucovorin.

Levoleucovorin (for Injection) INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION for INTRAVENOUS use

Initial U.S. Approval: 1952 (d,l-leucovorin), 2008 (levoleucovorin)

----------INDICATIONS AND USAGE----------

Levoleucovorin is a folate analog. (1)

Levoleucovorin rescue is indicated after high-dose methotrexate therapy in osteosarcoma. (1)

Levoleucovorin is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists. (1)

Limitations of Use

Levoleucovorin is not approved for pernicious anemia and megaloblastic anemias. Improper use may cause a hematologic remission while neurologic manifestations continue to progress. (1.1)

----------DOSAGE AND ADMINISTRATION----------

Levoleucovorin Rescue After High-Dose Methotrexate Therapy

Do not administer intrathecally. (2.1)

Levoleucovorin is dosed at one-half the usual dose of the racemic form. (2.1)

Levoleucovorin rescue recommendations are based on a methotrexate dose of 12 grams/m^2 administered by intravenous infusion over 4 hours. Levoleucovorin rescue at a dose of 7.5 mg (approximately 5 mg/m^2) every 6 hours for 10 doses starts 24 hours after the beginning of the methotrexate infusion. Determine serum creatinine and methotrexate levels at least once daily. Continue levoleucovorin administration, hydration, and urinary alkalinization (pH of 7.0 or greater) until the methotrexate level is below 5 x 10^{-8} M (0.05 micromolar). The levoleucovorin dose may need to be adjusted. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Each 50 mg single-use vial of Levoleucovorin for Injection contains a sterile lyophilized powder consisting of 64 mg levoleucovorin calcium pentahydrate (equivalent to 50 mg levoleucovorin) and 50 mg mannitol. (16) It is intended for intravenous administration after reconstitution with 5.3 mL of sterile 0.9% Sodium Chloride for Injection, USP. (2.5, 11)

----------CONTRAINDICATIONS----------

Levoleucovorin is contraindicated for patients who have had previous allergic reactions attributed to folic acid or folinic acid. (4)

----------WARNINGS AND PRECAUTIONS----------

Due to Ca^{++} content, no more than 16 mL (160 mg) of levoleucovorin solution should be injected intravenously per minute. (5.1)

Levoleucovorin enhances the toxicity of fluorouracil. (5.2,7)

Concomitant use of *d,l*-leucovorin with trimethoprim-sulfamethoxazole for Pneumocystis carinii pneumonia in HIV patients was associated with increased rates of treatment failure in a placebo-controlled study. (5.3)

----------ADVERSE REACTIONS----------

Allergic reactions were reported in patients receiving levoleucovorin. (6.2)

Vomiting (38%), stomatitis (38%) and nausea (19%) were reported in patients receiving levoleucovorin as rescue after high dose methotrexate therapy. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Spectrum Pharmaceuticals, Inc. at 1-866-473-4936 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

Levoleucovorin may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible patients. (7)

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

- Levoleucovorin is a folate analog.
- Levoleucovorin rescue is indicated after high-dose methotrexate therapy in osteosarcoma.
- Levoleucovorin is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists.

1.1 Limitations of Use

- Levoleucovorin is not approved for pernicious anemia and megaloblastic anemias secondary to the lack of vitamin B_{12}. Improper use may cause a hematologic remission while neurologic manifestations continue to progress.

2 DOSAGE AND ADMINISTRATION

2.1 Administration Guidelines

Levoleucovorin is dosed at **one-half** the usual dose of the racemic form.

Levoleucovorin is indicated for intravenous administration only**. Do not administer intrathecally.**

2.2 Co-administration of levoleucovorin with other agents

Due to the risk of precipitation, do not co-administer levoleucovorin with other agents in the same admixture.

2.3 Levoleucovorin Rescue After High-Dose Methotrexate Therapy

The recommendations for levoleucovorin rescue are based on a methotrexate dose of 12 grams/m^2 administered by intravenous infusion over 4 hours (see methotrexate package insert for full prescribing information). Levoleucovorin rescue at a dose of 7.5 mg (approximately 5 mg/m^2) every 6 hours for 10 doses starts 24 hours after the beginning of the methotrexate infusion.

Serum creatinine and methotrexate levels should be determined at least once daily. Levoleucovorin administration, hydration, and urinary alkalinization (pH of 7.0 or greater) should be continued until the methotrexate level is below 5 x 10^{-8} M (0.05 micromolar). The levoleucovorin dose should be adjusted or rescue extended based on the following guidelines.

Table 1 Guidelines for Levoleucovorin Dosage and Administration

Clinical Situation	Laboratory Findings	Levoleucovorin Dosage and Duration
Normal Methotrexate Elimination	Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0.2 micromolar at 72 hours	7.5 mg IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).
Delayed Late Methotrexate Elimination	Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration.	Continue 7.5 mg IV q 6 hours, until methotrexate level is less than 0.05 micromolar.
Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury	Serum methotrexate level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR; a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administration (e.g., an increase from 0.5 mg/dL to a level of 1 mg/dL or more).	75 mg IV q 3 hours until methotrexate level is less than 1 micromolar; then 7.5 mg IV q 3 hours until methotrexate level is less than 0.05 micromolar.

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

Some patients will have abnormalities in methotrexate elimination or renal function following methotrexate administration, which are significant but less severe than the abnormalities described in the table above. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed,

levoleucovorin rescue should be extended for an additional 24 hours (total of 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (e.g., medications which may interfere with methotrexate elimination or binding to serum albumin) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

Delayed methotrexate excretion may be caused by accumulation in a third space fluid collection (i.e., ascites, pleural effusion), renal insufficiency, or inadequate hydration. Under such circumstances, higher doses of levoleucovorin or prolonged administration may be indicated.

Although levoleucovorin may ameliorate the hematologic toxicity associated with high dose methotrexate, levoleucovorin has no effect on other established toxicities of methotrexate such as the nephrotoxicity resulting from drug and/or metabolite precipitation in the kidney.

2.4 Dosing Recommendations for Inadvertent Methotrexate Overdosage

Levoleucovorin rescue should begin as soon as possible after an inadvertent overdosage and within 24 hours of methotrexate administration when there is delayed excretion. As the time interval between antifolate administration [e.g., methotrexate] and levoleucovorin rescue increases, levoleucovorin's effectiveness in counteracting toxicity may decrease. Levoleucovorin 7.5 mg (approximately 5 mg/m^2) should be administered IV every 6 hours until the serum methotrexate level is less than 10^{-8} M.

Serum creatinine and methotrexate levels should be determined at 24 hour intervals. If the 24 hour serum creatinine has increased 50% over baseline or if the 24 hour methotrexate level is greater than 5×10^{-6} M or the 48 hour level is greater than 9×10^{-7} M, the dose of levoleucovorin should be increased to 50 mg/m^2 IV every 3 hours until the methotrexate level is less than 10^{-8} M. Hydration (3 L/day) and urinary alkalinization with $NaHCO_3$ should be employed concomitantly. The bicarbonate dose should be adjusted to maintain the urine pH at 7.0 or greater.

2.5 Reconstitution and Infusion Instructions

- Prior to intravenous injection, the 50 mg vial of Levoleucovorin for Injection is reconstituted with 5.3 mL of 0.9% Sodium Chloride Injection, USP to yield a levoleucovorin concentration of 10 mg per mL. Reconstitution with Sodium Chloride solutions with preservatives (e.g. benzyl alcohol) has not been studied. The use of solutions other than 0.9% Sodium Chloride Injection, USP is not recommended.
- The reconstituted 10 mg per mL levoleucovorin contains no preservative. Observe strict aseptic technique during reconstitution of the drug product.
- Saline reconstituted levoleucovorin solutions may be further diluted, immediately, to concentrations of 0.5 mg/mL to 5 mg/mL in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Initial reconstitution or further dilution using 0.9% Sodium Chloride Injection, USP may be held at room temperature for not more than a total of 12 hours. Dilutions in 5% Dextrose Injection, USP may be held at room temperature for not more than 4 hours.
- Visually inspect the reconstituted solution for particulate matter and discoloration, prior to administration. CAUTION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if cloudiness or precipitate is observed.
- No more than 16 mL of reconstituted solutions (160 mg of levoleucovorin) should be injected intravenously per minute, because of the calcium content of the levoleucovorin solution.

3 DOSAGE FORMS AND STRENGTHS

Levoleucovorin for Injection is supplied in sterile, single-use vials containing 64 mg levoleucovorin calcium pentahydrate (equivalent to 50 mg levoleucovorin) and 50 mg mannitol.

4 CONTRAINDICATIONS

Levoleucovorin is contraindicated for patients who have had previous allergic reactions attributed to folic acid or folinic acid.

5 WARNINGS AND PRECAUTIONS

5.1 Rate of Administration

Because of the Ca^{++} content of the levoleucovorin solution, no more than 16 mL (160 mg of levoleucovorin) should be injected intravenously per minute.

5.2 Potential for Enhanced Toxicity with 5-Fluorouracil

Levoleucovorin enhances the toxicity of 5-fluorouracil. Deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly *d,l*-leucovorin and 5-fluorouracil.

5.3 Potential for interaction with trimethoprim-sulfamethoxazole

The concomitant use of *d,l*-leucovorin with trimethoprim-sulfamethoxazole for the acute treatment of Pneumocystis carinii pneumonia in patients with HIV infection was associated with increased rates of treatment failure and morbidity in a placebo-controlled study.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Since clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The following table presents the frequency of adverse reactions which occurred during the administration of 58 courses of high dose methotrexate 12 grams/m^2 followed by levoleucovorin rescue for osteosarcoma in 16 patients age 6-21. Most patients received levoleucovorin 7.5 mg every 6 hours for 60 hours or longer beginning 24 hours after completion of methotrexate.

Table 2 Adverse Reactions

Body System/Adverse Reactions	Number (%) of Patients with Adverse Reactions (N =16)		Number (%) of Courses with Adverse Reactions (N = 58)	
	All	Grade 3+	All	Grade 3+
Gastrointestinal				
Stomatitis	6 (37.5)	1 (6.3)	10 (17.2)	1 (1.7)
Vomiting	6 (37.5)	0	14 (24.1)	0
Nausea	3 (18.8)	0	3 (5.2)	0
Diarrhea	1 (6.3)	0	1 (1.7)	0
Dyspepsia	1 (6.3)	0	1 (1.7)	0
Typhlitis	1 (6.3)	1 (6.3)	1 (1.7)	1 (1.7)
Respiratory				
Dyspnea	1 (6.3)	0	1 (1.7)	0
Skin and Appendages				
Dermatitis	1 (6.3)	0	1 (1.7)	0
Other				
Confusion	1 (6.3)	0	1 (1.7)	0
Neuropathy	1 (6.3)	0	1 (1.7)	0
Renal function abnormal	1 (6.3)	0	3 (5.2)	0
Taste perversion	1 (6.3)	0	1 (1.7)	0
Total number of patients	9 (56.3)		2 (12.5)	

Total number of courses	25 (43.1)	2 (3.4)

The incidence of adverse reactions may be underestimated because not all patients were fully evaluable for toxicity for all cycles in the clinical trials. Leukopenia and thrombocytopenia were observed, but could not be attributed to high dose methotrexate with levoleucovorin rescue because patients were receiving other myelosuppressive chemotherapy.

6.2 Postmarketing Experience

Since adverse reactions from spontaneous reports are provided voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Spontaneously reported adverse reactions collected by the WHO Collaborating Center for International Drug Monitoring in Uppsala Sweden have yielded seven cases where levoleucovorin was administered with a regimen of methotrexate. The events were dyspnea, pruritus, rash, temperature change and rigors. For 217 adverse reactions (108 reports) where levoleucovorin was a suspected or interacting medication, there were 40 occurrences of "possible allergic reaction."

7 DRUG INTERACTIONS

Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible children. It is not known whether folinic acid has the same effects. However, both folic and folinic acids share some common metabolic pathways. Caution should be taken when taking folinic acid in combination with anticonvulsant drugs.

Preliminary human studies have shown that small quantities of systemically administered leucovorin enter the CSF, primarily as its major metabolite, 5-methyltetrahydrofolate (5-MTHFA). In humans, the CSF levels of 5-MTHFA remain 1-3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration.

Levoleucovorin increases the toxicity of 5-fluorouracil *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. It is not known whether levoleucovorin can cause fetal harm when administered to a pregnant woman or if it can affect reproduction capacity. Animal reproduction studies have not been conducted with levoleucovorin. Levoleucovorin should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when levoleucovorin is administered to a nursing mother.

8.4 Pediatric Use

[See Clinical Studies (14)]

8.5 Geriatric Use

Clinical studies of levoleucovorin in the treatment of osteosarcoma did not include subjects aged 65 and over to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

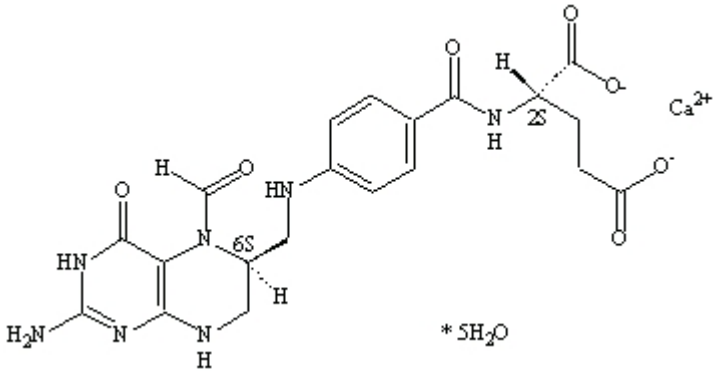
No data are available for overdosage with levoleucovorin.

11 DESCRIPTION

Levoleucovorin is the levo isomeric form of racemic *d,l*-leucovorin, present as the calcium salt. Levoleucovorin is the pharmacologically active isomer of leucovorin [(6-S)-leucovorin].

Levoleucovorin for injection contains levoleucovorin calcium, which is one of several active, chemically reduced derivatives of folic acid. It is useful as antidote to the inhibition of dihydrofolate reductase by methotrexate. This

compound has the chemical designation calcium (6S)-N-{4-[[(2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl] amino]benzoyl-L-glutamate pentahydrate. The molecular weight is 601.6 and the structural formula is:



Its molecular formula is: $C_{20}H_{21}CaN_7O_7$ 5 H_2O.

Levoleucovorin for injection is supplied as a sterile lyophilized powder consisting of 64 mg levoleucovorin calcium pentahydrate (equivalent to 50 mg levoleucovorin) and 50 mg mannitol per 50 mg vial.

Sodium hydroxide and/or hydrocholoric acid are used to adjust the pH during manufacture. It is intended for intravenous administration after reconstitution with 5.3 mL of sterile 0.9% Sodium Chloride Injection, USP [*See Dosage and Administration (2.5)*]

12 CLINICAL PHARMACOLOGY

12.1 Mechanism Of Action

Levoleucovorin is the pharmacologically active isomer of 5-formyl tetrahydrofolic acid. Levoleucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates as a source of "one-carbon" moieties. Administration of levoleucovorin can counteract the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase.

12.2 Pharmacodynamics

Levoleucovorin is actively and passively transported across cell membranes. In vivo, levoleucovorin is converted to 5-methyltetrahydrofolic acid (5-methyl-THF), the primary circulating form of active reduced folate. Levoleucovorin and 5-methyl-THF are polyglutamated intracellularly by the enzyme folylpolyglutamate synthetase. Folylpolyglutamates are active and participate in biochemical pathways that require reduced folate.

12.3 Pharmacokinetics

The pharmacokinetics of levoleucovorin after intravenous administration of a 15 mg dose was studied in healthy male volunteers. After rapid intravenous administration, serum total tetrahydrofolate (total-THF) concentrations reached a mean peak of 1722 ng/mL. Serum (6S)-5-methyl-5,6,7,8-tetrahydrofolate concentrations reached a mean peak of 275 ng/mL and the mean time to peak was 0.9 hours. The mean terminal half-life for total-THF and (6S)-5-methyl-5,6,7,8-tetrahydrofolate was 5.1 and 6.8 hours, respectively.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment Of Fertility

No studies have been conducted to evaluate the potential of levoleucovorin for carcinogenesis, mutagenesis and impairment of fertility.

13.2 Animal Toxicology And/Or Pharmacology

The acute intravenous LD_{50} values in adult mice and rats were 575 mg/kg (1725 mg/m^2) and 378 mg/kg (2268 mg/m^2), respectively. Signs of sedation, tremors, reduced motor activity, prostration, labored breathing, and/or convulsion were observed in these studies. Anticipated human dose for each administration is approximately 5 mg/m^2, which represents a 3-log safety margin.

14 CLINICAL STUDIES

The safety and efficacy of levoleucovorin rescue following high-dose methotrexate were evaluated in 16 patients age 6-21 who received 58 courses of therapy for osteogenic sarcoma. High-dose methotrexate was one component of several different combination chemotherapy regimens evaluated across several trials. Methotrexate 12 g/m^2 IV over 4 hours was administered to 13 patients, who received levoleucovorin 7.5 mg every 6 hours for 60 hours or longer beginning 24 hours after completion of methotrexate. Three patients received methotrexate 12.5 g/m^2 IV over 6 hours, followed by levoleucovorin 7.5 mg every 3 hours for 18 doses beginning 12 hours after completion of methotrexate. The mean number of levoleucovorin doses per course was 18.2 and the mean total dose per course was 350 mg. The efficacy of levoleucovorin rescue following high-dose methotrexate was based on the adverse reaction profile. *[See Adverse Reactions (6)]*

16 HOW SUPPLIED/STORAGE AND HANDLING

Each 50 mg single-use vial of Levoleucovorin for Injection contains a sterile lyophilized powder consisting of 64 mg levoleucovorin calcium pentahydrate (equivalent to 50 mg levoleucovorin) and 50 mg mannitol.

50 mg vial of freeze-dried powder – NDC 68152-101-00.

Store at 25° C (77 °F) in carton until contents are used. Excursions permitted from 15-30° C (59-86 °F). [See USP Controlled Room Temperature]. Protect from light.

Manufactured for Spectrum Pharmaceuticals, Inc.

Irvine, CA 92618

Manufactured by Chesapeake Biological Laboratories, Inc.

Baltimore, MD 21230

Spectrum Pharmaceuticals, Inc.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ann Farrell

3/7/2008 03:51:56 PM