CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040147

Trade Name : LEUCOVORIN CALCIUM INJECTION USP

Generic Name: Leucovorin Calcium Injection USP 10mg (base)/ml 10ml and 25ml single dose vials

Sponsor : Abbott Laboratories

Approval Date: June 25, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040147

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Bioequivalence Review(s)	X			
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040147

APPROVAL LETTER

DW

ANDA 40-147

MAY 25 1997

Abbott Laboratories
Attention: Frederick A. Gustafson
One Abbott Park Road
Abbott Park, IL 60064-3500

Dear Sir:

This is in reference to your abbreviated new drug application dated May 31, 1995 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Leucovorin Calcium Injection USP, 10 mg (base)/mL; 10 mL and 25 mL single-dose vials.

Reference is also made to your amendments dated August 30 and September 17, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Leucovorin Calcium Injection USP, 10 mg (base)/mL can be expected to have the same therapeutic effect as that of the listed drug product upon which the Agency relied as the basis of safety and effectiveness.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #40-147
ANDA #40-147/Division file
Field Copy
HFD-600/Reading file
HFD-82
HFD-610/J.Phillips
HFD-210/B.Poole

Endorsements:

HFD-625/SBrown/9-24-96
HFD-613/CHolquist/9-27-96
HFD-613/JGrace/9-27-96
HFD-625/MSmela/9-25-96
HFD-617/SO'Keefe, PM/9-25-96
X:\new\firmsam\abbott\ltrs&rev\40147r#3.apl
FT by MM June 13, 1997
Approval

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040147

FINAL PRINTED LABELING

10 mL Single-dose Fliptop Vial

LEUCOVORIN CALCIUM Inj., USP

100 mg*
(10 mg/mL)*

Protect from light.
Discard unused portion.
For I.V or I.M. use

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

NDC 0074-4541-02

*Each mL contains leucovorin calcium equivalent to 10 mg leucovorin; sodium chloride 8 mg. May contain HCl and/or NaOH for pH adjustment. pH 7.8 (6.5 to 8.5).

RAO5288-5/R2-12/95

9

25 mL Fill Single-dose Fliptop Vial

NDC 0074-4541-04

LEUCOVORIN CALCIUM

Injection, USP

250 mg*
(10 mg/mL)*

Protect from light.
Discard unused portion.
For I.V or I.M. use

*Each mL contains leucovorin calcium equivalent to 10 mg leucovorin; sodium chloride 8 mg. May contain HCl and/or NaOH for pH adjustment. pH 7.8 (6.5 to 8.5).

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

RAO5290-5/R2-12/95

9

One Unit/NDC 0074-4541-02

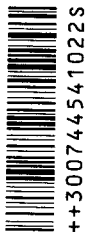
10 mL Single-dose Fliptop Vial

LEUCOVORIN CALCIUM

Injection, USP

100 mg*

(10 mg/mL)*



USE ASEPTIC TECHNIQUE

Remove cover from Fliptop Vial and cleanse stopper with antiseptic. Store in refrigerator 2° to 8°C (36° to 46°F).

One Unit/NDC 0074-4541-02

10 mL Single-dose Fliptop Vial

LEUCOVORIN CALCIUM

Injection, USP

100 mg*

(10 mg/mL)*

Protect from light.

Discard unused portion.

For I.V or I.M. use

*Each mL contains leucovorin calcium equivalent to 10 mg leucovorin; sodium chloride 8 mg. May contain hydrochloric acid and/or sodium hydroxide for pH adjustment. pH 7.8 (6.5 to 8.5).

Sterile, nonpyrogenic.

Usual dosage: See insert.

Caution: Federal (USA) law prohibits dispensing without prescription.

ABBOTT LABS., N. CHGO., IL 60064, USA

©Abbott 1995 Printed in USA

RAO5289-5/R2-12/95

One Unit/NDC 0074-4541-04

25 mL Fill Single-dose Fliptop Vial

LEUCOVORIN CALCIUM

Injection, USP

250 mg*

(10 mg/mL)*

Protect from light.

Discard unused portion.

For I.V or I.M. use

*Each mL contains leucovorin calcium equivalent to 10 mg leucovorin; sodium chloride 8 mg. May contain hydrochloric acid and/or sodium hydroxide for pH adjustment. pH 7.8 (6.5 to 8.5).

Sterile, nonpyrogenic.
Usual dosage: See insert.

Caution: Federal (USA) law prohibits dispensing without prescription.

USE ASEPTIC TECHNIQUE

Remove cover from Fliptop Vial and cleanse stopper with antiseptic. Store in refrigerator 2° to 8°C (36° to 46°F).

++30074454104 2U

©Abbott 1995 Printed in USA

ABBOTT LABS., NORTH CHICAGO., IL 60064,USA

RAO5291-5/R2-12/95

One Unit/NDC 0074-4541-04

25 mL Fill Single-dose Fliptop Vial

LEUCOVORIN CALCIUM

Injection, USP

250 mg*

(10 mg/mL)*

Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL solution per minute).

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

HOW SUPPLIED

Leucovorin Calcium Injection, USP 10 mg/mL is supplied in Single-Dose Fliptop Vials as follows:

List No.	Size	Total Leucovorin
4541-02	10 mL	100 mg
4541-04	25 mL	250 mg

Store in refrigerator 2° - 8°C (36° - 46°F). Protect from light.

Caution: Federal (USA) law prohibits dispensing without prescription.

REFERENCES

1. Grem JL, Shoemaker DD, Petrelli NJ, Douglas HO, "Severe and Fatal Toxic Effects Observed in Treatment with High- and Low-Dose Leucovorin Plus 5-Fluorouracil for Colorectal Carcinoma," *Cancer Treat Rep* 1987; 71:1122.
2. Link, MP, Coorin, AH, Miser, AW, *et al.* "The Effect of Adjuvant Chemotherapy on Relapse-Free Survival in Patients with Osteosarcoma of the Extremity." *N Engl J Med* 1986; 314:1600-1606.

©Abbott 1995 RAO5423-R3-Rev. Aug., 1996 Printed in USA

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

LEUCOVORIN CALCIUM
Injection, USP

100 mg TOTAL Leucovorin (10 mg/mL) Single-Dose Vial

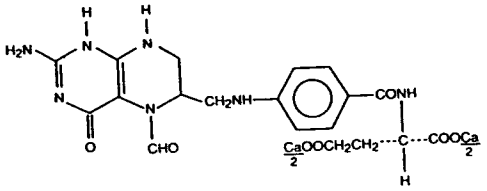
250 mg TOTAL Leucovorin (10 mg/mL) Single-Dose Vial

DESCRIPTION

Leucovorin is one of several active, chemically reduced derivatives of folic acid. It is useful as an antidote to drugs which act as folic acid antagonists.

Also known as folinic acid, Citrovorum factor, or 5-formyl-5,6,7,8-tetrahydrofolic acid, this compound has the chemical designation of *N*-[4-[[(2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)-methyl]amino]benzoyl]-L-Glutamic acid, calcium salt (1:1). The formula weight is 511.51 and the structural formula of leucovorin calcium is:

25 1997



Leucovorin Calcium is chemically designated as: $C_{20}H_{21}CaN_7O_7$

Leucovorin Calcium Injection, USP is a sterile preservative free solution available for intravenous or intramuscular

administration in 10 mL and 25 mL single-dose vials. Each mL contains leucovorin calcium equivalent to 10 mg leucovorin. In addition, each mL contains 10 mg Leucovorin, USP; sodium chloride 8 mg. Sodium Hydroxide and/or hydrochloric acid are used for pH adjustment. pH 7.8 (6.5 to 8.5). Contains 0.004 mEq of calcium per mg of leucovorin. Solution contains no bacteriostat or antimicrobial agents.

CLINICAL PHARMACOLOGY

Leucovorin is a mixture of the diasteroisomers of the 5-formyl derivative of tetrahydrofolic acid (THF). The biologically active compound of the mixture is the (-)-*l*-isomer, known as Citrovorum factor or (-)-folinic acid. Leucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates as a source of "one-carbon" moieties. *l*-Leucovorin (*l*,5-formyltetrahydrofolate) is rapidly metabolized (via 5,10-methenyltetrahydrofolate then 5, 10-methylene-tetrahydrofolate) to 1,5-methyltetrahydrofolate. 1,5-Methyl-tetrahydrofolate can in turn be metabolized via other pathways back to 5,10-methylenetetrahydrofolate, which is converted to 5-methyltetrahydrofolate by an irreversible, enzyme catalyzed reduction using the cofactors $FADH_2$ and NADPH.

Administration of leucovorin can counteract the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase.

In contrast, leucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy, such as 5-fluorouracil. Concurrent administration of leucovorin does not appear to alter the plasma pharmacokinetics of 5-fluorouracil. 5-Fluorouracil is metabolized to fluorodeoxyuridylic acid, which binds to and inhibits the enzyme thymidylate synthase (an enzyme important in DNA repair and replication).

Leucovorin is readily converted to another reduced folate, 5,10-methylenetetrahydrofolate, which acts to stabilize the

binding of fluorodeoxyuridylic acid to thymidylate synthase and thereby enhances the inhibition of this enzyme.

The pharmacokinetics after intravenous, intramuscular, and oral administration of a 25 mg dose of leucovorin were studied in male volunteers. After intravenous administration, serum total reduced folates (as measured by *Lactobacillus casei* assay) reached a mean peak of 1259 ng/mL (range 897-1625). The mean time to peak was 10 minutes. This initial rise in total reduced folates was primarily due to the parent compound 5-formyl-THF (measured by *Streptococcus faecalis* assay) which rose to 1206 ng/mL at 10 minutes. A sharp drop in parent compound followed and coincided with the appearance of the active metabolite 5-methyl-THF which became the predominant circulating form of the drug.

The mean peak of 5-methyl-THF was 258 ng/mL and occurred at 1.3 hours. The terminal half-life for total reduced folates was 6.2 hours. The area under the concentration versus time curves (AUCs) for *l*-leucovorin, *d*-leucovorin and 5-methyl-tetrahydrofolate were 28.4 ± 3.5, 956 ± 97 and 129 ± 12 (mg.min/L ± S.E.). When a higher dose of *d,l*-leucovorin (200 mg/m^2) was used, similar results were obtained. The *d*-isomer persisted in plasma at concentrations greatly exceeding those of the *l*-isomer.

After intramuscular injection, the mean peak of serum total reduced folates was 436 ng/mL (range 240-725) and occurred at 52 minutes. Similar to I.V. administration, the initial sharp rise was due to the parent compound. The mean peak of 5-formyl-THF was 360 ng/mL and occurred at 28 minutes. The level of the metabolite 5-methyl-THF increased subsequently over time until at 1.5 hours it represented 50% of the circulating total folates. The mean peak of 5-methyl-THF was 226 ng/mL at 2.8 hours. The terminal half-life of total reduced folates was 6.2 hours. There was no difference of statistical significance between I.M. and I.V. administration in the AUC for total reduced folates, 5-formyl-THF, or 5-methyl-THF.

INDICATIONS AND USAGE

Leucovorin calcium rescue is indicated after high-dose methotrexate therapy in osteosarcoma. Leucovorin calcium is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages of folic acid antagonists.

Leucovorin calcium is indicated in the treatment of megaloblastic anemias due to folic acid deficiency when oral therapy is not feasible.

CONTRAINDICATIONS

Leucovorin is improper therapy for pernicious anemia and other megaloblastic anemias secondary to the lack of vitamin B_{12}. A hematologic remission may occur while neurologic manifestations continue to progress.

WARNINGS

In the treatment of accidental overdosages of folic acid antagonists, leucovorin should be administered as promptly as possible. As the time interval between antifolate administration [e.g., methotrexate] and leucovorin rescue increases, leucovorin's effectiveness in counteracting toxicity decreases. Do not administer leucovorin intrathecally.

Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

Delayed methotrexate excretion may be caused by a third space fluid accumulation (i.e., ascites, pleural effusion), renal insufficiency, or inadequate hydration. Under such circumstances, higher doses of leucovorin or prolonged administration may be indicated. Doses higher than those recommended for oral use must be given intravenously.

Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL, or 8 mL of a

20 mg/mL solution per minute).

Leucovorin enhances the toxicity of 5-fluorouracil. When these drugs are administered concurrently, the dosage of the 5-fluorouracil must be lower than usually administered. Although the toxicities observed in patients treated with the combination of leucovorin plus 5-fluorouracil are qualitatively similar to those observed in patients treated with 5-fluorouracil alone, gastrointestinal toxicities (particularly stomatitis and diarrhea) are observed more commonly and may be more severe and of prolonged duration in patients treated with the combination.

Therapy with leucovorin and 5-fluorouracil must not be initiated or continued in patients who have symptoms of gastrointestinal toxicity of any severity, until those symptoms have completely resolved. Patients with diarrhea must be monitored with particular care until the diarrhea has resolved, as rapid clinical deterioration leading to death can occur. In a study utilizing higher weekly doses of 5-FU and leucovorin, elderly and/or debilitated patients were found to be at greater risk for severe gastrointestinal toxicity.[1]

PRECAUTIONS

General

Parenteral administration is preferable to oral dosing if there is a possibility that the patient may vomit or not absorb the leucovorin. Leucovorin has no effect on non-hematologic toxicities of methotrexate such as the nephrotoxicity resulting from drug and/or metabolite precipitation in the kidney.

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.

Preliminary animal and human studies have shown that small quantities of systemically administered leucovorin enter the CSF

primarily as 5-methyltetrahydrofolate and, in humans, remain 1-3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Leucovorin may enhance the toxicity of 5-fluorouracil (see WARNINGS).

Pregnancy: Teratogenic Effects:

"Pregnancy Category C". Adequate animal reproduction studies have not been conducted with leucovorin. It is also not known whether leucovorin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Leucovorin should be given to a pregnant woman only if clearly needed.

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 leucovorin is administered to a nursing mother.

Pediatric Use: See **Drug Interactions.**

ADVERSE REACTIONS

Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported following administration of both oral and parenteral leucovorin. No other adverse reactions have been attributed to the use of leucovorin *per se.*

OVERDOSAGE

Excessive amounts of leucovorin may nullify the chemotherapeutic effect of folic acid antagonists.

DOSAGE AND ADMINISTRATION

Leucovorin Rescue After High-Dose Methotrexate Therapy. The recommendations for leucovorin rescue are based on a methotrexate dose of 12-15 grams/m^2 administered by intravenous infusion over 4 hours (see methotrexate package insert for full prescribing information).[2]

Leucovorin rescue at a dose of 15 mg (approximately 10 mg/m²) every 6 hours for 10 doses starts 24 hours after the beginning of the methotrexate infusion. In the presence of gastrointestinal toxicity, nausea or vomiting, leucovorin should be administered parenterally. In the presence of gastrointestinal toxicity, nausea, or vomiting, leucovorin should be administered parenterally. Do not administer leucovorin intrathecally.

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

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

GUIDELINES FOR LEUCOVORIN DOSAGE AND ADMINISTRATION
DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY

Clinical Situation	Laboratory Findings	Leucovorin 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.	15 mg P.O., I.M. or I.V. 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 15 mg P.O., I.M. or I.V. 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).	150 mg I.V. q 3 hours, until methotrexate level is less than 1 micromolar; then 15 mg I.V. q 3 hours until methotrexate level is less than 0.05 micromolar.

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, leucovorin 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.

Impaired Methotrexate Elimination or Inadvertent Overdosage: Leucovorin rescue should begin as soon as possible after an inadvertent overdosage and within 24 hours of methotrexate administration when there is delayed excretion (see WARNINGS). Leucovorin 10 mg/m² should be administered I.V., I.M., or P.O. 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 leucovorin should be increased to 100 mg/m² I.V. every 3 hours until the methotrexate level is less than 10^{-8} M.

Hydration (3 L/d) and urinary alkalinization with sodium bicarbonate solution should be employed concomitantly. The bicarbonate dose should be adjusted to maintain the urine pH at 7.0 or greater.

Megaloblastic Anemia Due to Folic Acid Deficiency: Up to 1 mg daily. There is no evidence that doses greater than 1 mg/day have greater efficacy than those of 1 mg; additionally, loss of folate in urine becomes roughly logarithmic as the amount administered exceeds 1 mg.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040147

CHEMISTRY REVIEW(S)

1. **CHEMISTRY REVIEW NO. 3**

2. **ANDA #** 40-147

3. **NAME AND ADDRESS OF APPLICANT**

Abbott Laboratories
One Abbott Park Road
Abbott Park, IL 60064-3500

4. **LEGAL BASIS FOR SUBMISSION**

Accepted by OGD

5. **SUPPLEMENT(s)**

N/A

6. **PROPRIETARY NAME**

N/A

7. **NONPROPRIETARY NAME**

Leucovorin Calcium

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**

N/A

9. **AMENDMENTS AND OTHER DATES:**

May 31, 1995 - original submission
June 21, 1995 - amendment (replacement pages for page 5-169)
May 31, 1996 - amendment responding to NAL dated 11/20/95.
*August 30, 1996 -amendment responding to NAL dated 8/16/96.
*September 17, 1996 - amendment responding to telecon on 9/17/96

10. **PHARMACOLOGICAL CATEGORY**

Antidote to folic acid antagonists
Antianemic (folate deficiency)

11. **Rx or OTC**

Rx

12. **RELATED IND/NDA/DMF(s)**

(b)4 - Confidential Business

13. **DOSAGE FORM**

Injection (solution)

14. **POTENCY**

10 mg (base)/mL

15. **CHEMICAL NAME AND STRUCTURE**

See review #1.

16. **RECORDS AND REPORTS**

N/A

17. **COMMENTS**

As requested applicant noted and acknowledged that an acceptable compliance evaluation is required prior to approval, and that we have requested an evaluation from our Office of Compliance.

18. CONCLUSIONS AND RECOMMENDATIONS

Application is approvable pending satisfactory EER.

ESTABLISHMENT INSPECTION

EER dated 10/10/95 - acceptable 4/4/96 for the following facilities:

Abbott Laboratories
Hospital Products Division
Highway 31 North
P.O. Drawer 2226
Rocky Mount, NC 27801

Abbott Laboratories
Hospital Products Division
14th and Sheridan Road
North Chicago, IL 60064

and **unacceptable for the manufacturer of the active ingredient:**

(b)4 - Confidential Business

FUR dated 8/13/96 - Pending.

19. **REVIEWER:**	**DATE COMPLETED:**
Shirley S. Brown	September 12, 1996 September 24, 1996 (revised per 9/17/96 amendment)

cc: ANDA #40-147
ANDA #40-147/Division File
Field Copy

Endorsements:

HFD-625/S.Brown/9-24-96

HFD-625/K.Furnkranz for M.Smela/9-25-96

X:\NEW\FIRMSAM\ABBOTT\LTRS&REV\40147R#3.APL
F/T MM October 7, 1996
Approval Letter

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040147

BIOEQUIVALENCE REVIEW(S)

AADA 40-147

Abbott Laboratories
Attention: Frederick A. Gustafson
One Abbott Park Road
Abbott Park IL 60064-3500

NOV 21 1995

Dear Sir:

Reference is made to your abbreviated new drug application dated May 31, 1995, submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Leucovorin Calcium Injection USP, 10 mg (base) / mL, 100 mg and 250 mg vials.

The following comments pertain only to bioequivalency issues in the May 31, 1995 submission.

> The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

18 June 1997

MEMORANDUM TO ANDA 40-147 (Leucovorin Calcium Injection solution, Abbott)

I have reviewed the justification for granting the waiver of in vivo bioequivalence studies for the drug product which is the subject of this ANDA. I fully concur with the granting of the waiver based on 21 CFR 320.22(b)(1) as recommended in Dr. Makary's review dated 16 Nov 1995.

The drug product is a parenteral solution intended solely for administration by injection. It contains the same active and inactive ingredients in the same **concentration** as a drug product that is the subject of an approved full new drug application.

The reference listed drug (RLD) is available as a lyophilized powder which must be reconstituted with a diluent before it can be administered. Therefore, it must be in solution before it becomes usable. The labeling for the RLD indicates reconstitution with 10 ml of diluent and no other volume. The drug product in this ANDA is already in solution form, ready to be administered. From a bioequivalence perspective, and since the inactive ingredients are in the same concentration in both the lyophilized (RLD, after reconstitution) and solution products (ANDA), the difference of lyophilization versus ready solution is not of significance.

This ANDA requests approval of two sizes of product, 100 mg/10 ml and 250 mg/25 ml. There is no RLD for the 250 mg size, however, this also is not of concern from a bioequivalence perspective since the concentration in both ANDA products and the RLD are identical, i.e. 10 mg/ml.

/S/ 6/18/97

Nicholas M. Fleischer, R.Ph.,M.S.,Ph.D.
Director, Division of Bioequivalence

CC: ANDA #40-147, original, HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Makary), Drug file, Division file, HFD-650 (Director)

NOV 16 1995

Leucovorin Calcium Injection
10 mg/mL Leucovorin, Solution
100 mg & 250 mg/Vial, Single Dose Vial
ANDA #40-147
Reviewer: Moheb H. Makary
WP. 40147W.595

Abbott Laboratories
Abbott Park, Illinois
Submission date
May 31, 1995

Review a Request for Waivers

I. Objective:

The firm requested waivers of bioequivalence study requirements for its products Leucovorin Calcium Injection, 10 mg/mL, (ready-to-use solution), 250 mg single-dose vial and 100 mg single-dose vial. Innovator product is Leucovorin Calcium® for Injection (lyophilized) 100 mg/vial, manufactured by Immunex. The firm submitted two petitions. The first petition requested a change in dosage form that of the listed drug product (i.e., from a lyophilized powder for reconstitution to a ready-to-use solution) and a change in the strength (i.e., from a 100 mg single-dose vial to a 250 mg single-dose vial) which represents the addition of intermediate strength. The second petition requested a change in dosage form for the 100 mg single dose vial, from that of the listed drug product (i.e., from a lyophilized powder for reconstitution to a ready-to-use solution). The Agency approved these two petitions on January 19, 1995. The firm included a copy of the FDA approval letter in the submission.

Leucovorin is one of several active, chemically reduced derivatives of folic acid. It is useful as an antidote to drugs which act as folic acid antagonists. Leucovorin Calcium for Injection is indicated for intravenous or intramuscular administration.

II. Formulations:

The formulations of the proposed test products and reference product are shown below:

	Reference Product Leucovorin Calcium for Injection* 100 mg/Vial 10 mg/mL (Lyophilized)	Proposed Test Products Leucovorin Calcium Injection 100 mg/Vial & 250 mg/Vial 10 mg/mL (Solution)
Contents per mL		
Leucovorin (Leucovorin Calcium, USP)	10 mg	10 mg

Sodium Chloride	8 mg**	8 mg**
Sodium Hydroxide	qs to pH adjust	qs to pH adjust
Hydrochloric Acid	qs to pH adjust	qs to pH adjust
Water for Injection	qs	qs
Nitrogen	qs	qs

* Upon reconstitution with sterile water for injection.
** For isotonicity.

III. Comments:

1. As shown above, the proposed test products, Leucovorin Calcium Injection, 10 mg/mL, 100 mg/Vial and 250 mg/Vial contain the same active and inactive ingredients in the same quantities per mL as the reference product, Leucovorin Calcium® for Injection, 10 mg/mL, 100 mg/Vial.

2. The reference product, Leucovorin Calcium® for Injection 100 mg/Vial is marketed as a lyophilized powder. The proposed test drug, Leucovorin Calcium Injection, 10 mg/mL leucovorin, is a ready-to-use solution. The test products will be packaged in 10 mL/10 mL vial and 25 mL/30 mL vial containing 100 mg and 250 mg of leucovorin, respectively. The ready-to-use product is the subject of approved petitions, Docket #93P-0427/CP2 and 93P-0427/CP3, dated January 19, 1995. Waivers of in vivo bioequivalence study requirements may be granted based on 21 CFR 320.22 (b)(1).

IV. Recommendation:

The Division of Bioequivalence agrees that the information submitted by Abbott Laboratories, demonstrates that Leucovorin Calcium Injection 10 mg /mL, 100 mg/Vial and 250 mg/Vial, fall under Section 320.22 (b)(1) of Bioavailability/Bioequivalence Regulations. Waivers of in vivo bioequivalence study for the test products are granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation, Leucovorin Calcium Injection 10 mg /mL, 100 mg/Vial, manufactured by Abbott Laboratories, to be bioequivalent to Leucovorin Calcium® for Injection 100 mg/Vial manufactured by Immunex.

The firm should be informed of the above recommendation.

/S/
Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE /S/
FT INITIALLED RMHATRE Date: 10/13/95

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 40-147 SPONSOR: Abbott Laboratories
DRUG: Leucovorin calcium, solution
DOSAGE FORM: 10 mg/mL, 100 mg & 250 mg/vial single dose vial
STRENGTH(s): Injection
TYPE OF STUDY: Single/Multiple Fasting/Fed
STUDY SITE:

STUDY SUMMARY:
Leucovorin Calcium Injection 10 mg/mL, 100 mg/vial and 250 mg/vial, fall under Section 320.22(b)(5) of Bioequivalence/Bioavailability Regulation. Waivers are granted.

DISSOLUTION:
N/A

PRIMARY REVIEWER: [redacted] /S/ BRANCH: ~~HT~~
INITIAL: [redacted] /S/ DATE: 11/16/95

BRANCH CHIEF: BRANCH:
INITIAL: [redacted] /S/ DATE: 11/16/95

DIRECTOR
DIVISION OF BIOEQUIVALENCE
INITIAL: [redacted] /S/ DATE: 11/16/95

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL: Waiver/Signature not needed DATE: