CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-286

APPROVAL LETTER

ANDA 40-286

FEB 26 1999

Bigmar, Inc.
Attention: Peter Stoelzle
9711 Sportsman Club Road
Johnstown, OH 43031-2773

Dear Sir:

This is in reference to your abbreviated new drug application dated November 24, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Leucovorin Calcium for Injection, 500 mg (base)/vial, (Preservative-Free).

Reference is also made to your amendments dated January 12, April 30, and May 29, 1998; and January 20, February 1, and February 15, 1999.

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 drug product, Leucovorin Calcium for Injection, 500 mg (base)/vial, 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 and 314.98. 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-40). 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-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

D. L. Sporn 2/26/99

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-286

APPROVED DRAFT LABELING

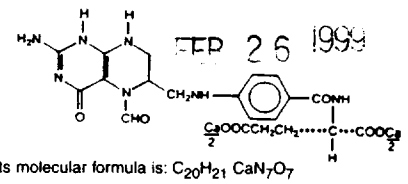
Pharmaceutech

Bigmar

LEUCOVORIN CALCIUM FOR INJECTION

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 Calcium *N*-[*p*-[[[(6*RS*)-2-amino-5-formyl-5,6,7,8-tetrahydro-4-hydroxy-6-pteridinyl]methyl]amino]benzoyl]-L-glutamate(1: 1). Leucovorin calcium has a molecular weight of 511.51 and the following structural formula:



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

Leucovorin Calcium For Injection is a sterile product indicated for intravenous or intramuscular administration and is supplied in 500 mg vials. Each vial, when reconstituted with 50 mL of sterile diluent, contains leucovorin calcium equivalent to 10 mg/mL leucovorin. The inactive ingredient is sodium chloride 450 mg/vial. Sodium hydroxide and/or hydrochloric acid may be added to adjust the pH to 7.7 to 7.9 during manufacture.

There is 0.004 mEq of calcium per mg of leucovorin.

CLINICAL PHARMACOLOGY: Leucovorin is a mixture of the diastereoisomers 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-methylenetetrahydrofolate) to *l*,5-methyltetrahydrofolate. *l*,5-Methyltetrahydrofolate 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 fluorodeoxyridylic acid to thymidylate synthase and thereby enhances the inhibition of this enzyme.

The pharmacokinetics after intravenous and intramuscular 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 to 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-methyltetrahydrofolate 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/m²) 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 to 725) and occurred at 52 minutes. Similar to IV 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 IM and IV administration in the AUC for total reduced folates, 5-formyl-THF, or 5-methyl-THF.

After oral administration of leucovorin reconstituted with aromatic elixir, the mean peak concentration of serum total reduced folates was 393 ng/mL (range 160 to 550). The mean time to peak was 2.3 hours and the terminal half-life was 5.7 hours. The major component was the metabolite 5-methyltetrahydrofolate to which leucovorin is primarily converted in the intestinal mucosa. The mean peak of 5-methyl-THF was 367 ng/mL at 2.4 hours. The peak level of the parent compound was 51 ng/mL at 1.2 hours. The AUC of total reduced folates after oral administration of the 25 mg dose was 92% of the AUC after intravenous administration.

Following oral administration, leucovorin is rapidly absorbed and expands the serum pool of reduced folates. At a dose of 25 mg, almost 100% of the *l*-isomer but only 20% of the *d*-isomer is absorbed. Oral absorption of leucovorin is saturable at doses above 25 mg. The apparent bioavailability of leucovorin was 97% for 25 mg, 75% for 50 mg, and 37% for 100 mg.

In a randomized clinical study conducted by the Mayo Clinic and the North Central Cancer Treatment Group (Mayo/NCCTG) in patients with advanced metastatic colorectal cancer three treatment regimens were compared: Leucovorin (LV) 200 mg/m² and 5-fluorouracil (5-FU) 370 mg/m² versus LV 20 mg/m² and 5-FU 425 mg/m² versus 5-FU 500 mg/m². All drugs were administered by slow intravenous infusion daily for 5 days repeated every 28 to 35 days. Response rates were 26% (p=0.04 versus 5-FU alone), 43% (p=0.001 versus 5-FU alone) and 10% for the high dose leucovorin, low dose leucovorin and 5-FU alone groups respectively. Respective median survival times were 12.2 months (p=0.037), 12 months (p=0.050), and 7.7 months. The low dose LV regimen gave a statistically significant improvement in weight gain of more than 5%, relief of symptoms, and improvement in performance status. The high dose LV regimen gave a statistically significant improvement in performance status and trended toward improvement in weight gain and in relief of symptoms but these were not statistically significant.

In a second Mayo/NCCTG randomized clinical study the 5-FU alone arm was replaced by a regimen of sequentially

administered methotrexate, 5-FU, and LV. Response rates with LV 200 mg/m^2 and 5-FU 370 mg/m^2 versus LV 20 mg/m^2 and 5-FU 425 mg/m^2 versus sequential Methotrexate and 5-FU and LV were respectively 31% (p= <.01), 42% (p=<.01), and 14%. Respective median survival times were 12.7 months (p=<.04), 12.7 months (p=<.01), and 8.4 months. No statistically significant difference in weight gain of more than 5% or in improvement in performance status was seen between the treatment arms.

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.

Leucovorin is also indicated for use in combination with 5-fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer. Leucovorin should not be mixed in the same infusion as 5-fluorouracil because a precipitate may form.

CONTRAINDICATIONS: Leucovorin is improper therapy for pernicious anemia and other megaloblastic anemia 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 benzyl alcohol contained in certain diluents used for Leucovorin Calcium for Injection, when doses greater than 10 mg/m^2 are administered, Leucovorin Calcium for Injection should be reconstituted with Sterile Water for Injection, USP, and used immediately. (See DOSAGE AND ADMINISTRATION.)

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, in the palliative therapy of advanced colorectal cancer, the dosage of 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.

In the first Mayo/NCCTG controlled trial, toxicity, primarily gastrointestinal, resulted in 7% of patients requiring hospitalization when treated with 5-fluorouracil alone or 5-fluorouracil in combination with 200 mg/m^2 of leucovorin and 20% when treated with 5-fluorouracil in combination with 20 mg/m^2 of leucovorin. In the second Mayo/NCCTG trial, hospitalizations related to treatment toxicity also appeared to occur more often in patients treated with the low dose leucovorin/5-fluorouracil combination than in patients treated with the high dose combination - 11% versus 3%. Therapy with leucovorin /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]

Seizures and/or syncope have been reported rarely in cancer patients receiving leucovorin, usually in association with fluoropyrimidine administration, and most commonly in those with CNS metastases or other predisposing factors, however, a casual relationship has not been established.[3]

The concomitant use of 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.

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.

Since leucovorin enhances the toxicity of fluorouracil, leucovorin/5-fluorouracil combination therapy for advanced colorectal cancer should be administered under the supervision of a physician experienced in the use of antimetabolite cancer chemotherapy. Particular care should be taken in the treatment of elderly or debilitated colorectal cancer patients, as these patients may be at increased risk of severe toxicity.

Laboratory Tests:
Patients being treated with the leucovorin/5-fluorouracil combination should have a CBC with differential and platelets prior to each treatment. During the first two courses a CBC with differential and platelets has to be repeated weekly and thereafter once each cycle at the time of anticipated WBC nadir. Electrolytes and liver function tests should be performed prior to each treatment for the first three cycles then prior to every other cycle. Dosage modifications of fluorouracil should be instituted as follows, based on the most severe toxicities:

Diarrhea and/or Stomatitis	WBC/mm^3 Nadir	Platelets/mm^3 Nadir	5-FU Dose
Moderate	1,000 to 1,900	25 to 75,000	decrease 20%
Severe	<1,000	<25,000	decrease 30%

If no toxicity occurs, the 5-fluorouracil dose may increase 10%. Treatment should be deferred until WBCs are 4,000/mm^3 and platelets 130,000/mm^3. If blood counts do not reach these levels within two weeks, treatment should be discontinued. Patients should be followed up with physical examination prior to each treatment course and appropriate radiological examination as needed. Treatment should be discontinued when there is clear evidence of tumor progression.

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 to 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 PRECAUTIONS, **Drug Interactions.**

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

The following table summarizes significant adverse events occurring in 316 patients treated with the leucovorin-5-fluorouracil combinations compared against 70 patients treated with 5-fluorouracil alone for advanced colorectal carcinoma. These data are taken from the Mayo/NCCTG large multicenter prospective trial evaluating the efficacy and safety of the combination regimen.

PERCENTAGE OF PATIENTS TREATED WITH LEUCOVORIN/FLUOROURACIL FOR ADVANCED COLORECTAL CARCINOMA REPORTING ADVERSE EXPERIENCES OR HOSPITALIZED FOR TOXICITY

	(High LV) /5-FU (N=155)		(Low LV) /5-FU (N=161)		5-FU Alone (N=70)	
	Any (%)	Grade 3+ (%)	Any (%)	Grade 3+ (%)	Any (%)	Grade 3+ (%)
Leukopenia	69	14	83	23	93	48
Thrombocytopenia	8	2	8	1	18	3
Infection	8	1	3	1	7	2
Nausea	74	10	80	9	60	6
Vomiting	46	8	44	9	40	7
Diarrhea	66	18	67	14	43	11
Stomatitis	75	27	84	29	59	16
Constipation	3	0	4	0	1	-
Lethargy/ Malaise/Fatigue	13	3	12	2	6	3
Alopecia	42	5	43	6	37	7
Dermatitis	21	2	25	1	13	-
Anorexia	14	1	22	4	14	-
Hospitalization for Toxicity	5%		15%		7%	

High LV = Leucovorin 200 mg/m^2, Low LV = Leucovorin 20 mg/m^2
Any = percentage ot patients reporting toxicity of any severity
Grade 3+ = percentage of patients reporting toxicity ot Grade 3 or higher

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

DOSAGE AND ADMINISTRATION: Advanced Colorectal Cancer: Either of the following two regimens is recommended:

1. Leucovorin is administered at 200 mg/m^2 by slow intravenous injection over a minimum of 3 minutes, followed by 5-fluorouracil at 370 mg/m^2 by intravenous injection.
2. Leucovorin is administered at 20 mg/m^2 by intravenous injection followed by 5-fluorouracil at 425 mg/m^2 by intravenous injection.

5-Fluorouracil and leucovorin should be administered separately to avoid the formation of a precipitate.

Treatment is repeated daily for five days. This five-day treatment course may be repeated at 4 week (28-day) intervals, for 2 courses and then repeated at 4 to 5 week (28 to 35 day) intervals provided that the patient has completely recovered from the toxic effects of the prior treatment course.

In subsequent treatment courses, the dosage of 5-fluorouracil should be adjusted based on patient tolerance of the prior treatment course. The daily dosage of 5-fluorouracil should be reduced by 20% for patients who experienced moderate hematologic or gastrointestinal toxicity in the prior treatment course, and by 30% for patients who experienced severe toxicity (see PRECAUTIONS: Laboratory Tests.) For patients who experienced no toxicity in the prior treatment course, 5-fluorouracil dosage may be increased by 10%. Leucovorin dosages are not adjusted for toxicity.

Several other doses and schedules of leucovorin/5-fluorouracil therapy have also been evaluated in patients with advanced colorectal cancer; some of these alternative regimens may also have efficacy in the treatment of this disease. However, further clinical research will be required to confirm the safety and effectiveness of these alternative leucovorin/5-fluorouracil treatment regimens.

Leucovorin Rescue After High-Dose Methotrexate Therapy: The recommendations for leucovorin rescue are based on a methotrexate dose of 12 to 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/m^2) 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. 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 x 10^{-8} M

(0.05 micromolar). The leucovorin dose should be adjusted or leucovorin rescue extended based on the following guidelines.

GUIDELINES FOR LEUCOVORIN DOSAGE AND ADMINISTRATION
DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY

Clinical Situation: Normal Methotrexate Elimination
Laboratory Findings: 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.
Leucovorin Dosage and Duration: 15 mg IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).

Clinical Situation: Delayed Late Methotrexate Elimination
Laboratory Findings: Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration.
Leucovorin Dosage and Duration: Continue 15 mg IV q 6 hours, until methotrexate level is than 0.05 micromolar.

Clinical Situation: Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury
Laboratory Findings: 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).
Leucovorin Dosage and Duration: 150 mg IV q 3 hours, until methotrexate level is less
than 1 micromolar; then 15 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 leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved.

Some patients will have abnormalities in methotrexate elimination or renal function following methotrexate administration, which are significant but less severe than 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 a delayed excretion (see WARNINGS.) Leucovorin 10 mg/m^2 should be administered IV every 6 hours until the serum methotrexate level is less than 10^{-8}M. 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 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 x 10^{-6}M or the 48 hour level is greater than 9 x10^{-7}M, the dose of leucovorin should be increased to 100 mg/m^2 IV 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.

Instructions for Preparation: Each 500 mg vial of Leucovorin Calcium for Injection when reconstituted with 50 mL of sterile diluent yields a leucovorin concentration of 10 mg per mL. Leucovorin Calcium for Injection contains no preservative. Reconstitute with Bacteriostatic Water for Injection, USP, which contains benzyl alcohol, or with Sterile Water for Injection USP. When reconstituted with Bacteriostatic Water for Injection USP, the resulting solution must be used within 7 days. If the product is reconstituted with Sterile Water for Injection, USP, it must be used immediately.

Because of the benzyl alcohol contained in Bacteriostatic Water for Injection USP, when doses greater than 10 mg/m^2 are administered Leucovorin Calcium for Injection should be reconstituted with Sterile Water for Injection, USP, and used immediately. (See WARNINGS)

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).

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

Leucovorin should not be mixed in the same infusion as 5-fluorouracil, since this may lead to the formation of a precipitate.

HOW SUPPLIED: Leucovorin Calcium for Injection is supplied as follows:

500 mg vial.

STORAGE: Store between 15° to 30° C (59° to 86° F). PROTECT FROM LIGHT. Retain in carton until contents are used. Discard any unused portion.

Rx Only

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, Goorin AH, Miser AW, et al. "The Effect of Adjuvant Chemotherapy on Relapse-Free Survival of Patients with Osteosarcoma of the Extremity." *N Engl J Med* 1986;314:1600-1606.

3.Meropol NJ, Creaven PJ, White RM, et al, "Seizures Associated with Leucovorin Administration in Cancer Patients." *JNCL* 1995;87(1):56-58.

Manufactured by:
Bigmar Pharmaceuticals SA
Barbengo, Switzerland

Manufactured for:
Bigmar, Inc.
Johnstown, OH 43031

Rev.01, January 1999

Store between 15° to 30°C (59° to 86°F).
PROTECT FROM LIGHT.
Retain in carton until contents are used.

Manufactured by:
Bigmar Pharmaceuticals SA
Barbengo, Switzerland

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Bigmar, Inc.
Johnstown, OH 43031

LEUCOVORIN CALCIUM FOR INJECTION

Lyophilized

500 MG*

FOR INTRAVENOUS OR INTRAMUSCULAR USE

Pharmaceuticals Bigmar

Lot #

Exp. Date

Usual Dosage: Consult package insert for dosage and full prescribing information. Do not use preservative containing solution for doses greater than 10 mg/m². (See WARNINGS)

*Each vial contains Leucovorin Calcium equivalent to 500 mg leucovorin and 450 mg sodium chloride. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH to 7.7 to 7.9 during manufacture.

When reconstituted with 50 mL Sterile Water for Injection or Bacteriostatic Water for Injection (preserved with benzyl alcohol), each mL contains leucovorin calcium equivalent to 10 mg leucovorin.

Reconstitute with Bacteriostatic Water for Injection, USP (preserved with Benzyl alcohol) and use within 7 days, or with Sterile Water for Injection, USP and use immediately.

Rx Only

LEUCOVORIN CALCIUM

500 MG*

Merzo

LEUCOVORIN CALCIUM
FOR INJECTION
LYOPHILIZED

500 MG*

FOR INTRAMUSCULAR OR
INTRAVENOUS USE

Pharmaceuticals Bigmar

Rx Only

Usual Dosage:Consult package insert for dosage and full prescribing information.
Do not use preservative containing solution for doses greater than 10 mg/m². (See WARNINGS)

Store product between 15°to 30°C (59°to 86°F). PROTECT FROM LIGHT. Retain in carton until contents are used.

*Each vial contains Leucovorin Calcium equivalent to 500 mg leucovorin and 450 mg sodium chloride. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH to 7.7 to 7.9 during manufacture.

When reconstituted with 50 mL Sterile Water for Injection or Bacteriostatic Water (preserved with benzyl alcohol), each mL contains leucovorin calcium equivalent to 10 mg leucovorin.

Do not use after _____

Manufactured by:

BIGMAR PHARMACEUTICALS SA
Barbengo, Switzerland

Manufactured for:

BIGMAR, INC.
Johnstown, OH 43031

EXP DATE

LOT#

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-286

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NUMBER
2

2. ANDA NUMBER
40-286

3. NAME AND ADDRESS OF APPLICANT
Bigmar, Inc.
Attention: Marilyn A. Friedly
9711 Sportsman Club Road
Johnstown, OH 43031

4. LEGAL BASIS for ANDA SUBMISSION
The Agency approval of suitability petition, Docket No. 97P-0303/CP1 and 97P-0303/CP2, provides the basis for this ANDA submission. The petitions, submitted on July 15, 1997 and November 25, 1997, requested permission to file an ANDA for Leucovorin Calcium for Injection, 500 mg (base) single-dose vials, final concentration 10 mg/mL when reconstituted, and they were approved on October 7, 1997 and March 31, 1998, respectively. Leucovorin Calcium for Injection, 350 mg (base) single-dose vials, final concentration 20 mg/mL when reconstituted, manufactured by Immunex Corporation is the reference listed drug against which this ANDA will be evaluated.

5. SUPPLEMENT(s)
None

6. NAME OF DRUG
Leucovorin Calcium for Injection

7. NONPROPRIETARY NAME
Leucovorin Calcium for Injection

8. SUPPLEMENT(s) PROVIDE(s) FOR
None

9. AMENDMENTS AND OTHER DATES

11/24/1997	Original submission (refused to file)
1/12/1998	Correspondence
4/30/1998	Original amendment (accepted to file)
5/29/1998	Original amendment (microbiology)
1/20/1999	Facsimile amendment (labeling)
2/1/1999	Original amendment (chemistry)
2/12/1999	Telephone amendment

10. PHARMACOLOGICAL CATEGORY

Anti-anemic (folate deficiency), antidote (to folic acid antagonists)

11. HOW DISPENSED

Prescription (℞)

12. RELATED DMF(s)

Product	Holder	DMF (type)	LOA letter
▸ Leucovorin Calcium			1.1, p107
▸ Rubber stopper			4, p
▸ Testing laboratory			.1, p
▸ Testing laboratory			i.1, p
▸ Testing laboratory			1.1, p

13. DOSAGE FORM

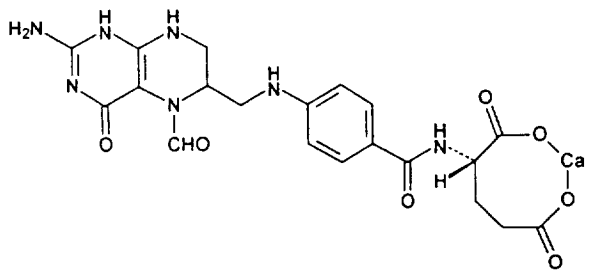
Lyophilized powder for injection

14. POTENCY

500 mg/vial

15. CHEMICAL NAME AND STRUCTURE

Leucovorin Calcium. L-Glutamic acid, *N*-[4-[[(2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- calcium salt (1:1). $C_{20}H_{21}CaN_7O_7$. 511.51. 1492-18-8.



16. RECORDS AND REPORTS

None

17. COMMENTS

The following section is currently pending:

33. Establishment inspection - EER

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable pending an acceptable EER.

19. REVIEWER AND DATE COMPLETED

Naiqi Ya, Ph.D./February 22, 1999

Page(s) 17

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Chem Rev 2
2/22/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-286

MICROBIOLOGY REVIEW

3.1

OFFICE OF GENERIC DRUGS

Microbiologists Review #1
February 10, 1999

A. 1. ANDA: **40-286**
APPLICANT: Bigmar Inc.
9711 Sportsman Club Road
Johnstown, Ohio 43031-1941

2. PRODUCT NAME: **Leucovorin Calcium for Injection**
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 500 mg/vial, lyophilized powder for IV and IM injection.
4. METHOD(S) OF STERILIZATION:
5. PHARMACOLOGICAL CATEGORY: Misc. Used for rescue after high dosage methotrexate treatment for osteosarcoma.

B. 1. DATE OF INITIAL SUBMISSION: **November 24, 1997.**
Accepted to File 4/30/98. -Subject of this Review.

2. DATE OF AMENDMENT:
April 30 1998. Subject of this Review.
May 29, 1998. Subject of this Review.
January 20, 1999. Subject of this Review.
Labeling deficiencies response. No Sterility Assurance data for review.
February 1, 1999. Subject of this Review. A gratuitous Amendment with Chemistry information. No Sterility Assurance review needed.

3. RELATED DOCUMENTS: DMFs not reviewed.
4. ASSIGNED FOR REVIEW: February 9, 1999.

C. REMARKS: This review relied on previously reviewed ANDA 40-258, the 200 mg/vial version of this product and the responses give to concerns in that review.

D. CONCLUSIONS: The submission is **recommended for approval** on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiologist's Draft of Letter to Applicant".

James L. McVey 2/11/98

James L. McVey

initialed by M. Fanning, M.D. 2/17/99

cc:

Page(s) 17

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Micro Review 1

2/10/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-286

Bioequivalence Review(s)

1.60.12

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-286 APPLICANT: Bigmar, Inc.

DRUG PRODUCT: Leucovorin Calcium Injection

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

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Leucovorin Calcium Injection, USP
500 mg vial
ANDA #40-286
Reviewer: Carol Y. Kim
x:\new\firmsam\bigmar\ltrs&rev\40286w.498.doc

Bigmar, Inc.
Johnstown, Ohio
Submission Date:
April 30, 1998

REVIEW OF A WAIVER REQUEST

I. Background

1. The firm has requested a waiver of an in vivo bioequivalence study requirement for its proposed product, Leucovorin Calcium Injection, USP, 500 mg vial. The reference listed product is Immunex [R] (Leucovorin Calcium) Injection 350 mg vial. When the proposed product is reconstituted with sterile diluent of 50 ml, the final leucovorin concentration is 10 mg per ml. Each 350 mg vial of the reference listed product, Immunex [R] (Leucovorin Calcium) Injection, reconstituted with sterile diluent of 17 ml, yields leucovorin concentration of 20 mg per ml.

2. Leucovorin Calcium Injection is indicated in combination with high dose methotrexate therapy for treatment of osteosarcoma, diminishing toxicity and counteracting the effects of inadvertent overdosages of folic acid antagonists, and in combination with 5-fluorouracil in the palliative treatment of patients with advanced colorectal cancer.

3. The reference product Immnex [R] (Leucovorin Calcium) Injection is to be administered by either intravenous or intramuscular route. The same routes of administration apply for the proposed product, Leucovorin Calcium Injection, USP.

II. Formulation comparison

As shown in the table below, the test product contains excess amount of inactive ingredient, sodium chloride, compared to the RLD (450 mg vs 140 mg). However, Bedford Laboratories' Leucovorin Calcium Injection 200 mg/vial (the RLD for Leucovorin Calcium Injection 200 mg per vial, ANDA #40056), yields the same reconstituted concentration of sodium chloride (9 mg/ml) as the test product. The table below compares mg per vial and reconstituted concentrations of active and inactive ingredients for the test product, reference product (Immunex), and Bedford Laboratories' product:

Ingredient	Leucovorin Calcium for Injection, 500 mg/vial, Bigmar (test product)		Leucovorin Calcium for Injection, 350 mg/vial, Immunex (RLD)		Leucovorin Calcium for Injection, 200 mg/vial, Bedford	
	per vial	reconstituted	per vial	reconstituted	per vial	reconstituted
Leucovorin	500 mg	10 mg/ml	350 mg	20 mg/ml	200 mg	10 mg/ml
Sodium Chloride	450 mg	9 mg/ml	140 mg	8.2 mg/ml	180 mg	9 mg/ml
NaOH and/or HCl	to pH 7.7-7.9	NA	to pH 8.1	NA	to pH 8.1	NA
Sterile water for Injection	QS	50 ml	QS	17 ml	QS	20 ml

III. Comments

1. The change in strength from 350 mg/vial to 500 mg/vial Leucovorin Calcium (base) is authorized under section 505 (j) (2) (C) (I) of the Food Drug and Cosmetic Act. The change in strength (total drug content) for the specific proposed drug product does not pose questions of safety or effectiveness because the uses, dosage form, and route of administration of the proposed drug product are the same as that of the listed drug product.

2. The firm has demonstrated the safety of the inactive ingredient, sodium chloride.

3. A waiver is granted.

IV. Recommendation

The Division of Bioequivalence agrees that the information submitted by Bigmar Inc. on its drug product, Leucovorin Calcium Injection, 500 mg/vial, falls under 21 CFR section 320.24 (b) (6) of the Bioavilability/Bioequivalence Regulations. The waiver of an in vivo bioequivalence study for the drug is granted. The Division of Bioequivalence deems the test product, Leucovorin Calcium Injection, USP, 500 mg/vial, bioequivalent to the reference product, Leucovorin Calcium Injection, 350 mg/vial, manufactured by Immunex.

The firm should be informed of the recommendation.

Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

BM D 8/13/98

RD INITIALLED BY BDAVIT
FT INITIALLED BY BDAVIT Barbara Davit Date: 8/14/98

Concur: Dale P. Conner Date: 8/26/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-286

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA:	CHEMIST:	DATE:
40-286	Naiqi Ya, Ph. D.	February 22, 1999

DRUG PRODUCT:
Leucovorin Calcium for Injection

FIRM:
Bigmar, Inc.

DOSAGE FORM:	STRENGTH:
Lyophilized powder for injection	500 mg/vial

cGMP:
The EERs are pending.

BIO:
The bio wavier was requested by the applicant and found to be acceptable by Carol. Y. Kim on August 14, 1998.

VALIDATION - *(Description of dosage form same as firm's):*
The analytical method for 500 mg/vial is identical to that of 200 mg/vial. The method validation was performed by Philadelphia District on July 10, 1998 and found to be suitable for regulatory control.

STABILITY:
The containers in the stability studies are identical to those in the container section.

LABELING:
Container, carton, and insert labeling were approved by L. Golson on February 2, 1999.

STERILIZATION VALIDATION *(If applicable)*:
Reviewed by Jame L. McVey on February 11, 1999 and found to be satisfactory.

SIZE OF BIO BATCH *(Firm's source of NDS ok?)*:
The bio batch size was ter.

SIZE OF STABILITY BATCHES *(If different from bio batch, were they Manufactured via the same process?):*
The stability batch and the bio batch are identical.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:
The proposed maximum production batch size is er.

Signature of chemist:	Signature of supervisor:
2/24/99	PS 2/22/99

X:\NEW\FIRMSAM\BIGMAR\LTRS&REV\40286SUM.WPD

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-286

CORRESPONDENCE

Pharmaceuticals
Bigmar

9711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 740-966-5800
Fax: 740-966-5801

February 1, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 40-286
Leucovorin Calcium for Injection, 500 mg/vial
Gratuitous Amendment: Chemistry

Dear Sir or Madam:

The purpose of this correspondence is to amend the above referenced application. Specifically, we wish to provide additional information which complement completed process validation studies.

Bigmar has performed a compounded bulk solution hold time evaluation as part of its comprehensive process validation study for Leucovorin Calcium for Injection. It was concluded, following a review of the study data, that the established in-process fill volume adjustment range should be revised. This process improvement has been implemented.

The *In-Process Chemical Test Summary* document for Leucovorin Calcium Bulk Solution, QC-555, has been modified to complement the validation study results. The criteria under which a fill volume adjustment is allowed has been expanded within the established potency range of mg/mL, which remains unchanged. A copy of the updated In-Process Chemical Test Summary document, QC-555, is provided under Attachment Ia of this correspondence. It replaces an earlier version found on page 262 of the original application. A copy of the earlier document is provided under Attachment Ib.

The Fill Volume Requirement Form for Leucovorin Calcium for Injection, document FVFI20500, has also been revised to complement the change made to QC-555. A copy of the updated form FVFI20500 is provided under Attachment IIa. It replaces an earlier version found on page 269 of the original application. A copy of the earlier document is provided under Attachment IIb.

If you have any questions or comments concerning this amendment, please contact me at the above address or at (740) 966-5800.

FEB 0 2 1999

In accordance with 21 CFR, Part 314.96(b), Bigmar, Inc, certifies that a true copy of the information contained in the amendment submitted to the Office of Generic Drugs has been forwarded to the FDA's Cincinnati District Office.

Sincerely,

Heather L. Munsell FOR:

Peter Stoelzle
Executive Vice President
Bigmar Incorporated

enclosure

Pharmaceuticals
Bigmar

9711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 740-966-5800
Fax: 740-966-5801

January 20, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/A

RE: ANDA 40-286
Leucovorin Calcium for Injection, 500 mg/vial
Facsimile Amendment Response: Labeling Deficiencies

Dear Sir or Madam:

The purpose of this correspondence is to amend the above referenced application. Specifically, we wish to provide revised product labeling in response to Agency comments received via facsimile on December 21, 1998. The revised labeling is provided as an attachment to this correspondence.

In accordance with 21 CFR, Part 314.96(b), Bigmar, Inc, certifies that a true copy of the information contained in the amendment submitted to the Office of Generic Drugs has been forwarded to the FDA's Cincinnati District Office.

If you have any questions or comments concerning this amendment, please contact me at the above address or at (740) 966-5800.

Sincerely,

Peter Stoelzle
Executive Vice President
Bigmar Incorporated

enclosure

RECEIVED
JAN 21 1999
GENERIC DRUGS

1-22-99

Pharmaceuticals
Bigmar

9711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 740-966-5800
Fax: 740-966-5801

May 29, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North
7500 Standish Place, Room 113
Rockville, MD 20855

[illegible] AMENDMENT
N/AS

Re: ANDA 40-286
Leucovorin Calcium for Injection, 500mg/vial
Gratuitous Microbiology Amendment

Dear Sir or Madam:

The purpose of this correspondence is to amend the above referenced abbreviated new drug application (ANDA). Specifically, we wish to provide additional information, which may aid in the review process.

Bigmar Inc. has received directives following the Agency's Microbiology review of ANDA 40-258. Relevant questions and observations have been applied to the above referenced ANDA. Each observation and its corresponding response are enclosed.

In accordance with 21 CFR Part 314.96 (b), we certify that a true copy of the information contained in the amendment submitted to the Office of Generic Drugs has been forwarded to the FDA's Cincinnati District Office.

If you have any questions regarding this amendment, please contact me at the above address or at (740) 966-5800.

Sincerely,

Peter Stoelzle
Executive Vice President
Bigmar Incorporated

enclosure

RECEIVED
JUN 0 2 1998
GENERIC DRUGS

ANDA 40-286

Bigmar, Inc.
Attention: Peter Stoelzle
9711 Sportsman Club Road
Johnstown, OH 43031

MAY 12 1998

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated December 24, 1997, and your amendment dated January 12, 1998 and your new correspondence dated April 30, 1998.

NAME OF DRUG: Leucovorin Calcium for Injection, 500 mg (base)/vial

DATE OF APPLICATION: November 24, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 5, 1998

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Joe Buccine
Project Manager
(301) 827-5848

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program
Support Office of Generic Drugs
Center for Drug Evaluation and Research

Pharmaceuticals

Bigmar

9711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 740-966-5800
Fax: 740-966-5801

OC fax 5/7/98
Filing
S Middleton

BIOAVAILABILITY
ORIG AMENDMENT

April 30, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North
7500 Standish Place, Room 113
Rockville, MD 20855

RECEIVED
MAY 05 1998
GENERIC DRUGS

Re: ANDA 40-286
Leucovorin Calcium for Injection, 500mg (base)/vial
Amendment Correspondence

Dear Sir or Madam:

The purpose of this correspondence is to respond to a letter received from the Office of Generic Drugs, dated December 24, 1997, regarding the above referenced application. In that letter the Agency indicated that ANDA 40-286 was not sufficiently complete to merit review. Among other things, it was noted that the concentration of the inactive ingredient sodium chloride in Bigmar's proposed product exceeds the maximum concentration of this ingredient previously approved by the Agency. Bigmar was asked to direct questions related to that correspondence to Saundra T. Middleton, Project Manager.

In a letter sent to Ms. Middleton on January 12, 1998, Bigmar indicated that it wished to pursue approval of the lyophilized dosage form presented within ANDA 40-286. A copy of that correspondence is provided under Attachment A, beginning on page 004 of this correspondence. It was concluded that an increase in the reconstituted dilution volume of the lyophilized dosage form from 25mL to 50mL would lower the sodium chloride concentration to an acceptable level, enabling ANDA 40-286 to be accepted for further review. A suitability petition which outlined the proposed change was filed by Bigmar Inc. on November 25, 1997, under Docket No. 97P-0303/CP2. It was agreed that the status of ANDA 40-286 would remain unchanged until approval of the petition was received.

Suitability petition 97P-0303/CP2 was approved by the Agency on March 31, 1998. A copy of that approval letter is provided under Attachment B, beginning on page 007 of this correspondence. Approval of this suitability petition enables Bigmar Inc. to revise ANDA 40-286 so that the review process may proceed.

Documents within ANDA 40-286 which refer to the reconstituted drug product formula have been revised to complement the concentration identified within petition 97P-0303/CP2. Copies of the revised pages are identified and provided under Attachment C, beginning on page 011 of this correspondence.

The Agency noted in its letter of December 24th that the original application referred to the incorrect route of administration. The correct route of administration is **intravenous and intramuscular.** All related references have been corrected and are provided under Attachment D, beginning on page 044 of this correspondence. Form 356h, provided at the beginning of this correspondence, also refers to the corrected route of administration.

Bigmar proposed labeling, provided on pages 0021-0073A of the original application, has been revised to complement the change in reconstitution volume and the corrected route of administration noted earlier. A copy of the revised pages is provided under Attachment E, beginning on page 048 of this correspondence.

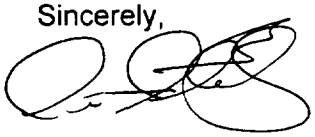
An English translation for the Nitrogen NF certificate of analysis included within ANDA 40-286 (page 197) was inadvertently omitted. The translation is provided under Attachment F, beginning on page 105 of this correspondence. Translations of all other pages that are not in English were included as part of the original application.

As requested, Bigmar Inc. shall refer to Policy and Procedure Guides #30-91, section 9 and 12; and #41-95, section 3(B)(6) for guidance in assembling future submissions.

In accordance with 21 CFR Part 314.96(b), Bigmar Inc. certifies that a true copy of the information contained in the amendment submitted to the Office of Generic Drugs has been forwarded to FDA's Cincinnati District Office.

We believe this correspondence provides a thorough response to the Agency's letter dated December 24, 1997. Please contact me at the above address or at (740) 966-5800 if you have any questions regarding this correspondence.

Sincerely,



Peter Stoelzle
Executive Vice President
Bigmar Incorporated

enclosure

Bigmar Inc.

9711 Sportsman Club Road
Johnstown, Ohio 43031-9141
Tel.: 614-966-5800
Fax: 614-966-5801

NEW CORR.

NAT 1/29/98

January 12, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Metro Park North II
7500 Standish Place, Room 615
Rockville, MD 20855

Re: ANDA 40-286
Leucovorin Calcium for Injection, 500 mg (base)/vial
Additional Correspondence

Dear Ms. Middleton,

The purpose of this correspondence is to respond to a letter received from the Office of Generic Drugs, dated December 24, 1997. In that letter, the Agency indicated that the above referenced abbreviated application could not be accepted for technical review because the sodium chloride concentration of the proposed product exceeds the maximum allowable ingredient concentration established within the Agency's Inactive Ingredient Guide (IIG).

Bigmar wishes to pursue approval of the lyophilized dosage form presented within ANDA 40-286. In a telephone conversation of January 06, 1998, we discussed how that might be accomplished. It was agreed that an increase in the reconstituted dilution volume of the lyophilized dosage form would address the Agency's concern regarding sodium chloride concentration and enable ANDA 40-286 to be accepted for further review. Such a revision would provide a reconstituted formula which compares favorably to an alternate Reference Listed Drug product, Leucovorin Calcium for Injection, 100 mg (base)/vial manufactured by and provides a sodium chloride concentration which falls within the criteria established by the current Inactive Ingredients Policy.

You noted that approval of a suitability petition would be required before the agreed upon revision could be made. Bigmar has recently submitted such a petition, under docket number 97P-0303/CP2. You also indicated that the status of ANDA 40-286 will be allowed to remain unchanged until the approval of the petition is received. A response to the petition is expected within the next 60 days. I will plan to call you at that time with an update regarding the review status of the petition.

If you have any questions or comments regarding this correspondence, please contact me at the above address or at (614) 966-5800.

Sincerely,

Marilyn A. Friedly

Marilyn A. Friedly
Manager
Regulatory Affairs

ANDA 40-286

Bigmar, Inc.
Attention: Marilyn A. Friedly
9711 Sportsman Club Road
Johnstown, OH 43031

DEC 24 1997

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated November 24, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Leucovorin Calcium for Injection, 500 mg (base)/vial.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

> The concentration of the inactive ingredient sodium chloride in your proposed product exceeds the maximum concentration of this inactive ingredient previously approved by the Agency. FDA will consider the inactive ingredients or composition of a drug product unsafe and refuse to approve an ANDA under 21 CFR 314.127(a)(8)(I) if, on the basis of information available to the agency, there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raise serious questions of safety. Examples of the changes that may raise serious questions of safety include, but are not limited to the following: a change in the composition to include a significantly greater content of an inactive ingredient than previously approved by the agency [21 CFR 314.127(a)(8)(I)]. Therefore, you are advised to reformulate your drug product.
>
> You have referred to the incorrect route of administration throughout your application. The correct route of administration should be **intravenous and intramuscular.** Please correct your form FDA 356h and other references throughout your application to reflect the correct route of administration.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

You have failed to provide English translation for the Nitrogen NF, certificate of analysis. Please review your application and provide translations of all pages that are not in English as per 21 CFR 314.50(g)(2).

In the future submissions, please refer to Policy and Procedure Guides #30-91, section 9 and 12; and #41-95, section 3(B)(6) for guidance on ANDA tabulation and a summary table of the executed batch record.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call.

Saundra T. Middleton
Project Manager
(301) 827-5862

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research