CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-379

APPROVAL LETTER

ANDA 40-379

NOV 15 2000

PD Regulatory Services Inc.
Attention: P.Diane Wood
U.S. Agent for: Bigmar, Inc.
601 Route 206, Suite 26-443
Belle Mead, NJ 08502

Dear Madam:

This is in reference to your abbreviated new drug application dated July 19, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Fluorouracil Injection USP, 50 mg/mL (100 mL Pharmacy Bulk Package Vial).

Reference is also made to your amendments dated February 11 and October 19, 2000.

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 your Fluorouracil Injection USP, 50 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Adrucil® Injection, 50 mg/mL, of Pharmacia and Upjohn Co.).

Under Section 506A of the Act, 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,

Gary Buehler 11/15/00
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
40-379

APPROVED DRAFT LABELING

FLUOROURACIL INJECTION, USP

5g/100mL
(50mg/mL)

PHARMACY BULK PACKAGE
NOT FOR DIRECT INFUSION

FOR INTRAVENOUS USE ONLY

APPROVED
NOV 15 2000

5-100mL PHARMACY BULK PACKAGES

STORE AT ROOM TEMPERATURE 15° to 30°C (59° to 86°F) **Protect from light.** Retain in carton until contents are used. Discard any unused portion.

Bigmar Pharmaceuticals

Rx Only

Manufactured by:
Bigmar Pharmaceuticals SA
Barbengo, Switzerland

Manufactured for:
Bigmar, Inc.,
Johnstown, OH 43031

Lot
Exp

Each mL contains Fluorouracil, USP 50 mg, water for injection q.s. Sodium hydroxide and if necessary hydrochloric acid may be added to adjust pH to 9.0 to 9.1 during manufacture.

If a precipitate forms due to exposure to low temperatures, resolubilize in a water bath maintained at 60°C (140°F) with vigorous shaking; allow to cool to body temperature before using.

A single entry through the vial closure should be made with a sterile dispensing set or transfer device which will accept a syringe hub. Use of a syringe needle is not recommended. Withdrew contents into syringe through the set/device. The above process should be carried out under a laminar flow hood using aseptic technique.

Date of Entry _____

Time of Entry _____

Lot
Exp

FLUOROURACIL INJECTION, USP
5g/100mL
(50mg/mL)
PHARMACY BULK PACKAGE
NOT FOR DIRECT INFUSION
FOR INTRAVENOUS USE ONLY

PROMPTLY DISPENSE CONTENTS OF THE PHARMACY BULK PACKAGE AFTER INSERTING STERILE TRANSFER DEVICE OR DISPENSING SET.

If dispensing cannot be performed promptly, DISCARD CONTENTS NO LATER THAN FOUR (4) HOURS AFTER INITIAL ENTRY. Use only if clear and seal is intact and undamaged.

Bigmar Pharmaceuticals
Rx Only
100mL Pharmacy Bulk Package

Usual Dosage: See package insert for dosage and prescribing information and for proper use of this container.

Store at room temperature 15° to 30°C (59° to 86°F). Protect from light. Retain in carton until contents are used. Discard any unused portion.

Manufactured by:
Bigmar Pharmaceuticals SA
Barbengo, Switzerland

Manufactured for:
Bigmar, Inc.,
Johnstown, OH 43031

APPROVED
NOV 15 2000

FLUOROURACIL INJECTION, USP
50mg/mL PHARMACY BULK PACKAGE

three days. *If no toxicity is observed,* 3 mg/kg/day may be given on the 5th, 7th and 9th days *unless toxicity occurs.* No therapy is given on the 4th, 6th or 8th days. The daily dose should not exceed 400 mg.

A sequence of injections on either schedule constitutes a "course of therapy".

Maintenance Therapy: In instances where toxicity has not been a problem, it is recommended that therapy be continued using either of the following schedules:

1. Repeat dosage of first course every 30 days after the last day of the previous course of treatment.
2. When toxic signs resulting from the initial course of therapy have subsided, administer a maintenance dosage of 10 to 15 mg/kg/week as a single dose. Do not exceed 1 g per week.

The patientis reaction to the previous course of therapy should be taken into account in determining the amount of the drug to be used, and the dosage should be adjusted accordingly. Some patients have received from 9 to 45 courses of treatment during periods which ranged from 12 to 60 months.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Although the Fluorouracil solution may discolor slightly during storage, the potency and safety are not adversely affected. If a precipitate occurs due to exposure to low temperatures, resolubilize by heating to 140°F and shaking vigorously; allow to cool to body temperature before using.

Directions for Proper Use of Pharmacy Bulk Package
(Not for Direct Infusion)
The 100 mL Pharmacy Bulk Package is for use in the Pharmacy Admixture Service only. It should be inserted into a plastic hanging device and suspended as a unit in a laminar flow hood. Use only if clear and seal is intact and undamaged.

Only a single entry through the vial closure should be made. Swab vial stopper with an antiseptic solution. Insert a sterile dispensing set or transfer device into the vial which allows measured distribution of the contents. AFTER PIERCING THE STOPPER PROMPTLY DISPENSE CONTENTS OF THE PHARMACY BULK PACKAGE THROUGH THE STERILE TRANSFER DEVICE OR DISPENSING SET. If dispensing cannot be performed promptly, discard contents no later than four (4) hours after initial entry.

The above process should be carried out under a laminar flow hood using aseptic technique. Care should be exercised to protect personnel from aerosolized drug (see **DOSAGE and ADMINISTRATION, REFERENCES**).

HOW SUPPLIED: Fluorouracil Injection is available for intravenous use in 100 mL vials. Each vial contains 5 g fluorouracil in a colorless to faint yellow aqueous solution. Sodium hydroxide and if necessary hydrochloric acid may be added to adjust pH to 9.0 - 9.1 during manufacture.

50mg/mL in 100 mL vials (5 g Pharmacy Bulk Package), in boxes of 5

STORAGE: Store at room temperature 15° to 30°C (59° to 86°F). **Protect from light.** Retain in carton until contents are used. Discard any unused portion.

REFERENCES:

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.
2. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics. *JAMA*, 1985; 253 (ii):1590-1592.
3. National Study Commission on Cytotoxic Exposure- Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia*, 1983; 1:426-428.
5. Jones RB, et al: Safe Handling of Chemotherapeutic Agents: A report from the Mount Sinai Medical Center, CA-*A Cancer Journal for Clinicians*, 1983; (Sept/Oct), 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm*, 1990; 47:1033-1049.
7. OSHA Work Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. *Am J Hosp Pharm*, 1986; 43:1193-1204.

Manufactured by:
Bigmar Pharmaceuticals SA
Barbengo, Switzerland

Manufactured for:
Bigmar, Inc.
Johnstown, OH USA

Rev: February 2000

Bigmar Pharmaceuticals

FLUOROURACIL INJECTION, USP
Rx Only

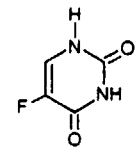
PHARMACY BULK PACKAGE— NOT FOR DIRECT INFUSION

WARNING
It is recommended that Fluorouracil Injection be given only by or under the supervision of a qualified physician who is experienced in cancer chemotherapy and who is well versed in the use of potent antimetabolites. Because of the possibility of severe toxic reactions, it is recommended that patients be hospitalized at least during the initial course of therapy. These instructions should be thoroughly reviewed before administration of Fluorouracil.

DESCRIPTION: Fluorouracil Injection, USP, an antineoplastic antimetabolite, is a colorless to faint yellow aqueous, sterile, nonpyrogenic injectable solution available in 100 mL Pharmacy Bulk Package for intravenous administration. Each mL contains 50 mg of fluorouracil in water for injection, USP. Sodium hydroxide and if necessary hydrochloric acid may be added to adjust pH to 9.0 to 9.1 during manufacture.

Chemically, fluorouracil, a fluorinated pyrimidine, is 5-fluoro-2,4 (1 *H*,3 *H*)- pyrimidinedione. It is a white to practically white crystalline powder which is sparingly soluble in water.

The molecular weight of fluorouracil is 130.08.
Molecular formula of fluorouracil is: $C_4H_3FN_2O_2$
The structural formula is:



A **Pharmacy Bulk Package** is a container of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for intravenous infusion.

CLINICAL PHARMACOLOGY: There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. In this manner, fluorouracil interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA). Since DNA and RNA are essential for cell division and growth, the effect of fluorouracil may be to create a thymine deficiency which provokes unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked on those cells which grow more rapidly and

Following intravenous injection, fluorouracil distributes into tumors, intestinal mucosa, bone marrow, liver and other tissues throughout the body. In spite of its limited lipid solubility, fluorouracil diffuses readily across the blood-brain barrier and distributes into cerebrospinal fluid and brain tissue.

Seven percent to twenty percent of the parent drug is excreted unchanged in the urine in six hours; of this over 90% is excreted in the first hour. The remaining percentage of the administered dose is metabolized, primarily in the liver. The catabolic metabolism of fluorouracil results in degradation products (e.g., CO_2, urea and α-fluoro-β-alanine) which are inactive. The inactive metabolites are excreted in the urine over the next 3 to 4 hours. When fluorouracil is labeled in the six carbon position, thus preventing the ^{14}C metabolism to CO_2, approximately 90% of the total radioactivity is excreted in the urine. When fluorouracil is labeled in the two carbon position approximately 90% of the total radioactivity is excreted in expired CO_2. Ninety percent of the dose is accounted for during the first 24 hours following intravenous administration.

Following intravenous administration of fluorouracil, the mean half-life of elimination from plasma is approximately 16 minutes, with a range of 8 to 20 minutes and is dose dependent. No intact drug can be detected in the plasma three hours after an intravenous injection.

INDICATIONS AND USAGE: Fluorouracil is effective in the palliative management of carcinoma of the colon, rectum, breast, stomach and pancreas.

CONTRAINDICATIONS: Fluorouracil therapy is contraindicated for patients in a poor nutritional state, those with depressed bone marrow function, those with potentially serious infections or those with a known hypersensitivity to fluorouracil.

WARNINGS: THE DAILY DOSE OF FLUOROURACIL IS NOT TO EXCEED 800 MG. IT IS RECOMMENDED THAT PATIENTS BE HOSPITALIZED DURING THEIR FIRST COURSE OF TREATMENT.

Fluorouracil should be used with extreme caution in poor risk patients with a history of high-dose pelvic irradiation or previous use of alkylating agents, those who have a widespread involvement of bone marrow by metastatic tumors or those with impaired hepatic or renal function.

Rarely, unexpected, severe toxicity (e.g., stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to deficiency of dipyrimidine dehydrogenase activity. A few patients have been rechallenged with 5- fluorouracil and despite 5-fluorouracil dose lowering, toxicity recurred and progressed with worse morbidity. Absence of this catabolic enzyme appears to result in prolonged clearance of 5-fluorouracil.

Pregnancy: Teratogenic Effects: Pregnancy Category D. Fluorouracil may cause fetal harm when administered to pregnant women. Fluorouracil has been shown to be teratogenic in laboratory animals.

given to mice as single intraperitoneal injections of 10 to 40 mg/kg on day 10 or 12 of gestation. Similarly, intraperitoneal doses of 12 to 37 mg/kg given to rats between days 9 and 12 of gestation and intramuscular doses of 3 to 9 mg given to hamsters between days 8 and 11 of gestation were teratogenic. Malformations included cleft palates, skeletal defects and deformed appendages, paws and tails. The dosages which were teratogenic in animals are 1 to 3 times the maximum recommended human therapeutic dose. In monkeys, divided doses of 40 mg/kg given between days 20 and 24 of gestation were not teratogenic.

There are no adequate and well-controlled studies with fluorouracil in pregnant women. While there is no evidence of teratogenicity in humans due to fluorouracil, it should be kept in mind that other drugs which inhibit DNA synthesis (e.g., methotrexate and aminopterin) have been reported to be teratogenic in humans. Women of childbearing potential should be advised to avoid becoming pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be told of the potential hazard to the fetus. Fluorouracil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Combination Therapy: Any form of therapy which adds to the stress of the patient, interferes with nutrition or depresses bone marrow function will increase the toxicity of fluorouracil.

PRECAUTIONS: *General:* Fluorouracil is a highly toxic drug with a narrow margin of safety. Therefore, patients should be carefully supervised, since therapeutic response is unlikely to occur without some evidence of toxicity. Severe hematological toxicity, gastrointestinal hemorrhage and even death may result from the use of fluorouracil despite meticulous selection of patients and careful adjustment of dosage. Although severe toxicity is more likely in poor risk patients, fatalities may be encountered occasionally even in patients in relatively good condition.

Therapy is to be discontinued promptly whenever one of the following signs of toxicity appears:

1. Stomatitis or esophagopharyngitis, at the first visible sign.
2. Leukopenia (WBC under 3500) or a rapidly falling white blood count.
3. Vomiting, intractable.
4. Diarrhea, frequent bowel movements or watery stools.
5. Gastrointestinal ulceration and bleeding.
6. Thrombocytopenia (platelets under 100,000).
7. Hemorrhage from any site.

The administration of 5-fluorouracil has been associated with the occurrence of palmar-plantar erythrodysesthesia syndrome, also known as hand-foot syndrome. This syndrome has been characterized as a tingling sensation of hands and feet which may [illegible] days to pain when holding objects or walking. The palms and soles become symmetrically swollen and erythematous with tenderness of the distal phlanges, possibly accompanied by desquamation. Interruption of therapy is followed by gradual resolution over 5 to 7 days. Although pyridoxine has been reported to ameliorate the palmar-plantar erythrodysesthesia syndrome, its safety and effectiveness have not been established.

Information for Patients: Patients should be informed of expected toxic effects, particularly oral manifestations. Patients should be alerted to the possibility of alopecia as a result of therapy and should be informed that it is usually a transient effect.

Laboratory Tests: White blood counts with differential are recommended before each dose.

Drug Interactions: Leucovorin calcium may enhance the toxicity of fluorouracil.

Also see WARNINGS section.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: Long-term studies in animals to evaluate the carcinogenic potential of fluorouracil have not been conducted. However, there was no evidence of carcinogenicity in small groups of rats given fluorouracil orally at doses of 0.01, 0.3, 1 or 3 mg per rat 5 days per week for 52 weeks, followed by a six month observation period. Also, in other studies, 33 mg/kg of fluorouracil was administered intravenously to male rats once a week for 52 weeks followed by observation for the remainder of their lifetimes with no evidence of carcinogenicity. Female mice were given 1 mg of fluorouracil intravenously once a week for 16 weeks with no effect on the incidence of lung adenomas. On the basis of the available data, no evaluation can be made of the carcinogenic risk of fluorouracil to humans.

Mutagenisis: Oncogenic transformation of fibroblasts from mouse embryo has been induced *in vitro* by fluorouracil, but the relationship between oncogenicity and mutagenicity is not clear. Fluorouracil has been shown to be mutagenic to several strains of *Salmonella typhimurium*, including TA 1535, TA 1537 and TA 1538, and to *Saccharomyces cerevisiae*, although no evidence of mutagenicity was found with *Salmonella typhimurium* strains TA 92, TA 98 and TA 100. In addition, a positive effect was observed in the micronucleus test on bone marrow cells of the mouse, and fluorouracil at very high concentrations produced chromosomal breaks in hamster fibroblasts *in vitro*.

Impairment of Fertility: Fluorouracil has not been adequately studied in animals to permit an evaluation of its effects on fertility and general reproductive performance. However, doses of 125 or 250 mg/kg, administered intraperitoneally, have been shown to induce chromosomal aberrations and changes in chromosomal organization of spermatogonia in rats. Spermatogonial differentiation was also inhibited by fluorouracil, resulting in transient infertility. However, in studies with a strain of mouse which is sensitive to the induction of sperm head abnormalities after exposure to a range of chemical mutagens and carcinogens, fluorouracil did not produce any abnormalities at oral doses of up to 80 mg/kg/day. In female rats, fluorouracil, administered intraperitoneally at weekly doses of 25 or 50 mg/kg for three weeks during the pre-ovulatory phase of oogenesis, significantly reduced the incidence of fertile matings, delayed the development of pre- and post-implantation embryos, increased the incidence of preimplantation lethality and induced chromosomal anomalies in these embryos. In a limited study in rabbits, a single 25 mg/kg dose of fluorouracil or 5 daily doses of 5 mg/kg had no effect on ovulation, appeared not to affect implantation and had only a limited effect in producing zygote destruction. Compounds such as fluorouracil, which interfere with DNA, RNA and protein synthesis, might be expected to have adverse effects on gametogenesis.

Pregnancy: Pregnancy Category D. See **WARNINGS** section.

Nonteratogenic Effects: Fluorouracil has not been studied in animals for its effects on peri- and postnatal development. However, fluorouracil has been shown to cross the placenta and enter into fetal circulation in the rat. Administration of fluorouracil has resulted in increased resorptions and embryolethality in rats. In monkeys, maternal doses higher than 40 mg/kg resulted in abortion of all embryos exposed to fluorouracil. Compounds which inhibit DNA, RNA and protein synthesis might be expected to have adverse effects on peri- and postnatal development.

Nursing Mothers: It is not known whether fluorouracil is excreted in human milk. Because fluorouracil inhibits DNA, RNA and protein synthesis, mothers should not nurse while receiving this drug.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS: Stomatitis, and esophagopharyngitis (which may lead to sloughing and ulceration), diarrhea, anorexia, nausea and emesis are commonly seen during therapy.

Leukopenia usually follows every course of adequate therapy with fluorouracil. The lowest white blood cell counts are commonly observed between the 9th and 14th days after the first course of treatment, although uncommonly the maximal depression may be delayed for as long as 20 days. By the 30th day the count has usually returned to the normal range.

Alopecia and dermatitis may be seen in a substantial number of cases. The dermatitis most often seen is a pruritic maculopapular rash usually appearing on the extremities and less frequently on the trunk. It is generally reversible and usually responsive to symptomatic treatment.

Other adverse reactions are:

Hematologic: pancytopenia, thrombocytopenia, agranulocytosis, anemia.

Cardiovascular: myocardial ischemia, angina.

Gastrointestinal: gastrointestinal ulceration and bleeding.

Allergic reactions: anaphylaxis and generalized allergic reactions.

Neurologic: acute cerebellar syndrome (which may persist following discontinuance of treatment), nystagmus, headache.

Dermatologic: dry skin; fissuring; photosensitivity, as manifested by erythema or increased pigmentation of the skin; vein pigmentation; palmar-plantar erythrodysesthesia syndrome, as manifested by tingling of the hands and feet followed by pain, erythema and swelling.

Ophthalmic: lacrimal duct stenosis, visual changes, lacrimation, photophobia.

Psychiatric: disorientation, confusion, euphoria.

Miscellaneous: thrombophlebitis, epistaxis, nail changes (including loss of nails).

OVERDOSAGE: The possibility of overdosage with fluorouracil is unlikely in view of the mode of administration. Nevertheless, the anticipated manifestations would be nausea, vomiting, diarrhea, gastrointestinal ulceration and bleeding, bone marrow depression (including thrombocytopenia, leukopenia and agranulocytosis). No specific antidotal therapy exists. Patients who have been exposed to an overdose of fluorouracil should be monitored hematologically for at least four weeks. Should abnormalities appear, appropriate therapy should be utilized.

The acute intravenous toxicity of fluorouracil is as follows:

Species	LD_{50} (mg/kg ± S.E.)
Mouse	340 ± 17
Rat	165 ± 26
Rabbit	27 ± 5.1
Dog	31.5 ± 3.8

DOSAGE AND ADMINISTRATION: *General Instructions:* Fluorouracil Injection should be administered only intravenously, using care to avoid extravasation. No dilution is required.

All dosages are based on the patient's actual weight. However, the estimated lean body mass (dry weight) is used if the patient is obese or if there has been a spurious weight gain due to edema, ascites or other forms of abnormal fluid retention.

It is recommended that prior to treatment each patient be carefully evaluated in order to estimate as accurately as possible the optimum initial dosage of Fluorouracil Injection.

Dosage: Twelve mg/kg are given intravenously once daily for four successive days. The daily dose should not exceed 800 mg. *If no toxicity is observed,* 6 mg/kg are given on the 6th, 8th, 10th and 12th days *unless toxicity occurs.* No therapy is given on the 5th, 7th, 9th or 11th days. *Therapy is to be discontinued at the end of the 12th day, even if no toxicity has become apparent.* (See **WARNINGS** and **PRECAUTIONS** sections.)

Poor risk patients or those who are not in an adequate nutrional state (see **CONTRAINDICATIONS** and **WARNINGS** sections) should receive 6 mg/kg/day for

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-379

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 40-379

3. NAME AND ADDRESS OF APPLICANT
Bigmar Pharmaceuticals (BP)
9711 Sportsman Club Road
Johnstown, OH 43031

4. BASIS OF SUBMISSION
Listed drug product: ADRUCIL Injection (Fluorouracil Injection USP) Pharmacy Bulk Package manufactured by Pharmacia & Upjohn approved in ANDA 81-225.

Patent certification: No patents that claim the listed drug and no exclusivity exist for the drug product.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Fluorouracil Injection USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 7-19-99
Fax Amendment: 2-11-00 (Response to NA letter dated 1-13-00)
FPL: 2-22-00
Telephone Amendment: 3-2-00
Minor (Micro) Amendment: 5-17-00 (Response to 3-28-00)
- Minor Amendment: 10-19-00 (Response to 6-23-00 Micro deficiencies letter)

FDA:
Acknowledgment letters issued on: 8-12-99
NA letter: 1-13-00
NA letter (Micro deficiencies): 3-28-00
NA letter (Micro deficiencies): 6-23-00

10. PHARMACOLOGICAL CATEGORY
Antineoplastic

11. Rx or OTC
Rx

Treatment of carcinoma of colon, rectum, breast, stomach and pancreas

12. RELATED IND/NDA/DMF(s)
ANDA 40-291 (5 ml and 10 ml vial) Approved ANDA for Bigmar
DMF Manufacturer

Fluorouracil drug substance.

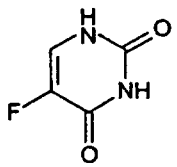
r stopper.
ng facility

13. DOSAGE FORM
Liquid

14. POTENCY
50 mg/mL (100 mL Pharmacy Bulk Package Vial)

15. CHEMICAL NAME AND STRUCTURE
Name:
Fluorouracil. 2,4(1*H*,3*H*)-Pyrimidinedione, 5-fluoro-.

MF: $C_4H_3FN_2O_2$



16. RECORDS AND REPORTS
N/A

17. COMMENTS
1. ANDA 40-291 for the same drug product with different strength has been approved for Bigmar.
2. Referenced DMF # 3062 of PCR, Inc adequate per review conducted by this reviewer on 3-1-00. No information regarding manufacturing or control testing is submitted since the last review. Name change is reported.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved.

19. REVIEWER: Mujahid L. Shaikh
DATE COMPLETED: 11-7-00

Page(s) 10

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

Chem Rev 4
11/7/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-379

MICROBIOLOGY REVIEW

Office of Generic Drugs, HFD-620
Microbiology Review #3
October 26, 2000

A. 1. ANDA: 40-379

APPLICANT: Bigmar, Inc.
9711 Sportsman Club Road
Johnstown, OH 43031

2. PRODUCT NAME: Fluorouracil Injection USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 5 g/100 mL Pharmacy Bulk Pack; Intravenous injection

4. METHOD OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Antineoplastic

B. 1. DATE OF INITIAL SUBMISSION: July 19, 1999 (Received July 20, 1999)

2. DATE OF AMENDMENT: May 17, 2000 (Received May 19, 2000)

October 19, 2000 (Received October 23, 2000)
Subject of this Review

3. RELATED DOCUMENTS:

:es

4. ASSIGNED FOR REVIEW: October 26, 2000

C. REMARKS: The subject drug product is aseptically filled at the Bigmar Pharmaceuticals SA facility in Barbengo, Switzerland.

D. CONCLUSIONS: The submission is **recommended** for approval on the basis of sterility assurance. Specific comments regarding the aseptic filling process are provided in "E. REVIEW NOTES".

Paul C DeLeo 10/31/2000
Paul C. DeLeo, Ph.D.

c:

OBW 10/31/00

Page(s) 2

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

micro Rev. 3

10/26/2000

Office of Generic Drugs, HFD-620
Microbiology Review #2
June 5, 2000

A. 1. ANDA: 40-379

APPLICANT: Bigmar, Inc.
9711 Sportsman Club Road
Johnstown, OH 43031

2. PRODUCT NAME: Fluorouracil Injection USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 5 g/100 mL Pharmacy Bulk Pack; Intravenous injection

4. METHOD OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Antineoplastic

B. 1. DATE OF INITIAL SUBMISSION: July 19, 1999 (Received July 20, 1999)

2. DATE OF AMENDMENT: May 17, 2000 (Received May 19, 2000).

Subject of this Review

3. RELATED DOCUMENTS:

ANDA 40-291 – Fluorouracil Injection USP (50 mg/mL); 5-mL and 10-mL fills

4. ASSIGNED FOR REVIEW: June 5, 2000

C. REMARKS: The subject drug product is aseptically filled at the Bigmar Pharmaceuticals SA facility in Barbengo, Switzerland.

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments regarding the process are provided in "E. REVIEW NOTES" and "MICROBIOLOGY COMMENTS TO BE PROVIDED TO THE APPLICANT" found at the end of this review. The deficiencies noted represent a **Minor Amendment**.

Paul C. DeLeo, Ph.D.

c:

40379MR2.DOC

Page(s) 4

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

MICRO REV 2

6/5/00

Office of Generic Drugs, HFD-620
Microbiology Review #1
March 15, 2000

A. 1. ANDA: **40-379**

APPLICANT: Bigmar, Inc.
9711 Sportsman Club Road
Johnstown, OH 43031

2. PRODUCT NAME: Fluorouracil Injection USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 5 g/100 mL Pharmacy Bulk Pack; Intravenous injection

4. METHOD OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Antineoplastic

B. 1. DATE OF INITIAL SUBMISSION: July 19, 1999 (Received July 20, 1999)
Subject of this Review

2. DATE OF AMENDMENT: No amendments relevant to sterility assurance

3. RELATED DOCUMENTS:

ervices

ANDA 40-291 – Fluorouracil Injection USP (50 mg/mL); 5-mL and 10-mL fills

4. ASSIGNED FOR REVIEW: March 6, 2000

C. REMARKS: The subject drug product is at the Bigmar Pharmaceuticals SA facility in Barbengo, Switzerland.

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments regarding the aseptic filling process are provided in "E. REVIEW NOTES" and "MICROBIOLOGY COMMENTS TO BE PROVIDED TO THE APPLICANT" found at the end of this review. The deficiencies noted represent a **Minor Amendment**.

Paul C DeLeo 3/15/2000
Paul C. DeLeo, Ph.D.

CDW 3/15/00

c:

DOC

Page(s) 7

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

Micro Rev 1
3/18/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-379

BIOEQUIVALENCE

Fluorouracil Injection, USP
50 mg/mL, in 100 mL
Pharmacy Bulk Package Vials
ANDA # 40-379
Reviewer: Pradeep M. Sathe

Bigmar Inc
Johnstown, OH-43031
Submission Date:
July 19, 1999

Review of a Waiver Request

BACKGROUND

1. The firm has approved 50 mg/ml, 5 mL and 10 mL Vials (ANDA 40-291) Fluorouracil injection products on the market. In this application, the firm is requesting a waiver of *in vivo* bioequivalence study requirements for its drug product, Fluorouracil Injection, USP, 50 mg/mL in 100 mL *Pharmacy Bulk Package* Vials. The reference listed drug (RLD) is Adrucil® (Fluorouracil Injection, USP) 50 mg/mL in 100 mL Pharmacy Bulk Package Vials, manufactured by Pharmacia and Upjohn's (NDA #81-225, approved August 28, 1991).

2. The drug is indicated for the palliative management of carcinoma of the colon, rectum, breast, stomach and pancreas.

3. It is noted that in this ANDA the firm is not requesting a waiver for 50 mL pharmacy bulk vial.

FORMULATION COMPARISON

Components and composition of the test and the reference products are as follows:

Comparison of Formulations		
Ingredient	Test Product (mg/mL)	RLD (mg/mL)
-Fluorouracil, USP	50	50
Sodium hydroxide,	To adjust pH*	To adjust pH*
Hydrochloric acid,	To adjust pH	To adjust pH
Water for Injection	Qs to 1 mL	Qs to 1 mL
Nitrogen	Inert Atmosphere	----
pH	9.0	9.2

COMMENTS

1. The drug is classified "AP" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluation".

2. The test drug product contains the same active and inactive ingredients in the same concentrations as the currently approved listed reference product and is intended solely for administration by injection.

3. The waiver of *in vivo* bioequivalence study requirements may be granted based on 21 CFR § 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations.

RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Bigmar Inc. demonstrates that its Fluorouracil Injection, USP, 50 mg/mL in 100 mL Pharmacy Bulk Package Vials falls under 21 CFR § 320.22(b)(1) of Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study for Fluorouracil Injection, USP 50 mg/mL in 100 mL Pharmacy Bulk Package Vials of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems Bigmar's Fluorouracil Injection, USP 50 mg/mL in 100 mL Pharmacy Bulk Package Vials bioequivalent to the reference listed product, Pharmacia and Upjohn's Adrucil® 50 mg/mL, 100 mL Pharmacy Bulk Package Vials.

8/18/99
Pradeep M. Sathe
Division of Bioequivalence
Review Branch II

RD INITIALLED SGNerurkar
FT INITIALLED SGNerurkar Date: 8/18/1999

Concur Date: 8/31/99

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-379

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 40-379

FIRM: Bigmar Pharmaceuticals
9711 Sportsman Club Road
Johnstown, OH 43031

DOSAGE FORM: Injection

STRENGTH: 50 mg/mL [100 mL Pharmacy Bulk Package Vial]

DRUG: Fluorouracil Injection USP

CGMP STATEMENT/EIR UPDATED STATUS:
EER for all facilities listed in section # 33 of this ANDA (CR # 4) is acceptable as of 2-7-00.

BIO STUDY:
Bio status: Acceptable (See section # 34 of CR # 4).

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
MV: Not required

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
Containers used in the stability studies are identical to those listed in container section.

LABELING:
Acceptable for approval per T. Watkins's review completed on 2-23-00.

STERILIZATION VALIDATION (IF APPLICABLE):
Micro review: Acceptable as of 10-31-00.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Bio waiver is requested.

Source of NDS:
: Adequate per review completed on 3-1-00 by this reviewer.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)
Exhibit batches:

Lot 980045-1: Batch size is liters.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

Maximum intended production batch size: liters

Manufacturing process for the intended production size is identical to that used for the exhibit/bio/stability batch.

Mujahid L. Shaikh/11/7/00 Mujahid Shaikh 11/14/00
Review Chemist
Division of Chemistry I
OGD/CDER

M Smela 11/14/00

RECORD OF TELEPHONE CONVERSATION

DATE: 7-14-00

PRODUCT NAME: Fluorouracil Injection USP, 50 mg/mL

ANDA NUMBER: 40-379

FIRM NAME: Bigmar Pharmaceuticals

NAME AND TITLE OF PERSON WITH
WHOM CONVERSATION WAS HELD: P. Diane Woods, Agent for Bigmar

PARTICIPANT(S) TELEPHONE: 1-908-281-6161

OGD PARTICIPANT(S): Paul DeLeo, Reviewing Microbiologist
Joe Buccine, Project Manager 7-14-00

Reference is made to the firm's fax dated June 26, 2000 (attached). The fax requests clarification of two micro deficiencies transmitted on 6/23/00. OGD's responses are listed below.

- Data from the preceding period is now being requested because the original request listed the wrong dates. We want to see media fill failures for Jan-Feb 97, not Apr-Nov 97, and learn how they are being handled. It was agreed that the firm may submit a summary of failures from Jan-Feb 97 including descriptions. A copy of the current SOP would satisfy our need to know the process in which failures are handled.

- Regarding our request to clarify the consequences of exceeding the temperature limit, the firm will identify their acceptance criteria. Again, a copy of the current SOP will be provided to explain of what happens if autoclave temperatures are exceeded.

The firm plans to submit a MINOR amendment in about 2 weeks.

Cc:

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-379 **Date of Submission: July 19, 1999**
Applicant's Name: Bigmar, Inc.
Established Name: Fluorouracil Injection USP, 50 mg/mL (Pharmacy Bulk Package)

Labeling Deficiencies:

1. CONTAINER (100 mL)

   a. Relocate "(5 g/100 mL)" to appear above "(50 mg/mL)" rather than beside it as does the reference listed drug, ADRUCIL® in it's most recently approved container/carton labeling (approved July 30, 1999). We also encourage you to utilize color to highlight this total concentration.

2. CARTON (5 x 100 mL)

   a. See comment (a) under CONTAINER.

3. INSERT

   a. TITLE

      We encourage the inclusion of "Rx only" in this section.

   b. REFERENCES

      Delete reference #1, then renumber the remaining references 1-7 and correct in the text.

Please revise your container labels, carton and insert labeling, as instructed above, and submit 12 copies of final printed container labels, along with 12 copies of final printed carton and insert labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance

with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-379

CORRESPONDENCE

Pharmaceuticals
Bigmar

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

19 October 2000

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

ORIG AMENDMENT
N/AM

Re: ANDA 40-379

Fluorouracil Injection USP, 50 mg/mL (Pharmacy Bulk Package)

MINOR AMENDMENT: RESPONSE TO MICROBIOLOGY DEFICIENCIES

Dear Sir or Madam:

The purpose of this correspondence is to amend the above referenced application. Specifically, we wish to respond to a deficiency letter dated June 23, 2000. Additionally, reference is made to a follow-up phone conversation with Mr. Joseph Buccine and Dr. Paul DeLeo, July 14, regarding clarification of the Microbiology comments.

To facilitate your review, each FDA Comment and corresponding response is provided as an attachment to this amendment. Supportive documentation is provided as necessary.

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 amendment provides a thorough response to the Agency's letter dated June 23, 2000. Please contact me via phone or fax at 908-281-6161 if you have any questions regarding this correspondence or at the Agent address listed on the Form FDA 356(h).

Sincerely,

P. Diane Wood
(Agent for Bigmar Inc.)
enclosure

JUN 23 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-379 APPLICANT: Bigmar Pharmaceuticals, Inc

DRUG PRODUCT: Fluorouracil Injection USP, 50 mg/mL (100 mL Pharmacy Bulk Package Vial)

The deficiencies presented below represent Minor deficiencies.

Sterility assurance for this product has not been demonstrated. Please respond to the attached deficiencies.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Microbiology Comments to be Provided to the Applicant

ANDA: **40-379** APPLICANT: **Bigmar, Inc.**

DRUG PRODUCT: **Fluorouracil Injection USP**

A. Microbiology Deficiencies:

1. Your response to Deficiency 4 of the correspondence dated March 28, 2000 was unacceptable; Microbiological Control of Glove Surfaces "Contact-Test" gives provisions for monitoring the gloves within the only. In addition, you should monitor the gloves (hands) of personnel working in the manufacturing area who are involved in the filling operation.

2. The revised bulk drug solution (in-process solution) bioburden limit is too high and should be reduced.

3. Your response to Deficiency 6.a of the correspondence dated March 28, 2000 was unacceptable; you did not clarify the consequences of exceeding the temperature limit of the cycle during the validation of the autoclave. Please provide a summary of the procedures to be followed if the temperature exceeds the limit during a validation cycle, and provide the protocol that the summary is derived from.

4. Please provide a summary of the investigations of the media fill failures for January/February 1997 (Batch #s 970002-1, 970003-1 and 970004-1).

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter. The deficiencies noted represent a Minor Amendment.

Sincerely yours,

Mary Fanning, M.D., Ph.D.
Associate Director of Medical Affairs
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

May 17, 2000

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/Am

Re: ANDA 40-379

Fluorouracil Injection USP, 50 mg/mL (Pharmacy Bulk Package)

MINOR AMENDMENT RESPONSE

Dear Sir or Madam:

The purpose of this correspondence is to amend the above referenced application. Specifically, we wish to respond to a deficiency letter dated March 28, 2000. As discussed with Michelle Dillahunt, Project Manager, on April 20, 2000, because this response is submitted more than 30 calendar days from the date of FDA's correspondence, this response is being submitted as a minor amendment

To facilitate your review, each FDA Comment and corresponding response is provided as an attachment to this amendment. Supportive documentation is provided as necessary.

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 amendment provides a thorough response to the Agency's letter dated March 28, 2000. Please contact me via phone or fax at 908-281-6161 if you have any questions regarding this correspondence or at the Agent address listed on the Form FDA 356(h).

Sincerely,

P. Diane Wood
(Agent for Bigmar Inc.)
enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 19 2000
OGD

mw 5-22-00

MAR 28

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-379 APPLICANT: Bigmar Pharmaceuticals, Inc

DRUG PRODUCT: Fluorouracil Injection USP, 50 mg/mL (100 mL Pharmacy Bulk Package Vial)

The deficiencies presented below represent FAX deficiencies.

Sterility assurance for this product has not been demonstrated. Please respond to the attached deficiencies.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Microbiology Comments to be Provided to the Applicant

ANDA: **40-379** APPLICANT: **Bigmar, Inc.**

DRUG PRODUCT: **Fluorouracil Injection USP**

A. Microbiology Deficiencies:

1. With regard to the facility:

   a. You should provide material and personnel flow diagrams for the manufacture of the drug product.

   b. You should identify the rooms in the manufacturing facility by number.

2. For environmental monitoring within the . if an alert or action limit is exceeded, an Environmental Action Report (EAR) is prepared. The SOP for the EAR does not indicate the disposition of the batch in the event an alert or action limit is exceeded. Please explain the disposition of the manufactured batch in the event an alert or action limit is exceeded and the factors that decide the ultimate fate of a batch.

3. You reported individual limits for environmental monitoring of surfaces. However, it was not clear whether these were alert or action limits; please clarify these limits.

4. You did not describe any personnel monitoring; even though the product is filled within an you should test the gloves of personnel involved in the filling operation.

5. The bulk drug solution (in-process solution) bioburden limit is too high and should be reduced. The bioburden limit should be adjusted based on trends in the historical data.

6. With regard to the revalidation studies for the .

   a. The protocol for the heat distribution studies states: "Verify that the thermal data for all thermocouples are within for the set-point during steady state exposure, and maintain a minimum temperature of during the entire exposure period." However, based on the T_{max} and T_{min} data reported by you, it appears that the limit was exceeded for all five runs. Please clarify the limits and the consequences of exceeding them. In addition, for run #3, one

thermocouple was below the , but you stated that "This deviation will have no impact on the validation results or the conclusions drawn from them." You should establish meaningful acceptance criteria/limits for validation runs.

b. Please report the revalidation frequency of the .

7. With regard to the Tunnel:

a. Please report the production parameters (temperature and belt speed) for sterilization of the 100-mL vials in the

b. What is the revalidation frequency of the

8. With regard to media fills:

a. Please clarify how conditions for 100-mL vial media fill runs (1997 or more recent unreported data) compare to potential worst-case production conditions with respect to line speed, production (Pharmacy Bulk Pack vial) vs. media fill vial, or other factors that are specific to each vial size used for media fill runs.

b. What was the line speed used for 100-mL vial media fill runs?

c. You should provide a summary of the investigations of the media fill failures for April-November 1997.

9. You should report validation data for sterility testing of the drug product including bacteriostasis/fungistasis testing.

10. You should report validation data for endotoxin testing including determination of the maximum valid dilution and inhibition/enhancement testing.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter. The deficiencies noted represent a Minor Amendment.

Sincerely yours,

Mary Fanning, M.D., Ph.D.
Associate Director of Medical Affairs
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

ORIG AMENDMENT

March 2, 2000

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 40-379
Fluorouracil Injection USP, 50 mg/mL (Pharmacy Bulk Package)
TELEPHONE AMENDMENT RESPONSE

Dear Mr. Sporn:

The purpose of this correspondence is to amend the above referenced application. Specifically, we wish to respond to the telephone comments of 1 March 2000 from M. Smela and M. Shaikh. Mr. Smela indicated that Bigmar's response should be submitted as a Telephone Amendment.

To facilitate your review, the response is provided as an attachment to this amendment.

We believe this amendment provides a thorough response to the telephone contact of 1 March 2000. Please contact me at the above address or at 908-281-6161 if you have any questions regarding this correspondence.

Sincerely,

P. Diane Wood
Agent for Bigmar, Inc.

Pharmaceuticals
Bigmar

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

February 22, 2000

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
FA

Re: ANDA 40-379
Fluorouracil Injection USP, 50 mg/mL (Pharmacy Bulk Package)
FINAL PRINTED LABELING

Dear Sir or Madam:

Reference is made to the above referenced application and additionally to a deficiency letter dated January 13th, 2000. As indicated by the Agency, Bigmar's response was submitted as a facsimile amendment on February 11, 2000. In the facsimile response we indicated that the requested FINAL PRINTED LABELING (FPL) would be transmitted under separate cover.

At this time we are submitting 12 copies of FINAL PRINTED LABELING as requested in the deficiency letter of January 13, 2000. This labeling - container, carton, and package insert - contain the revisions delineated on our response of February 11, 2000

We believe this submission of FPL completes our response to the Agency's letter dated January 13th, 2000. Please contact me at the above address or at 908-281-6161 if you have any questions regarding this correspondence.

Sincerely,

P. Diane Wood
(Agent for Bigmar, Inc.)

enclosure: labeling

Pharmaceuticals
Bigmar

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

February 11, 2000

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

NEW CORRESP

Re: ANDA 40-379
Fluorouracil Injection USP, 50 mg/mL (Pharmacy Bulk Package)
FACSIMILE AMENDMENT RESPONSE

Dear Sir or Madam:

The purpose of this correspondence is to amend the above referenced application. Specifically, we wish to respond to a deficiency letter dated January 13th, 2000. The Agency indicated that Bigmar's response should be submitted as a facsimile amendment.

To facilitate your review, each observation and corresponding response is provided as an attachment to this amendment. Supportive documentation is also provided for each response.

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 amendment provides a thorough response to the Agency's letter dated January 13th, 2000. Please contact me at the above address or at 908-281-6161 if you have any questions regarding this correspondence.

Sincerely,

P. Diane Wood
(Agent for Bigmar Pharmaceuticals)
enclosure

1 copy

JAN 13 20

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-379

APPLICANT: Bigmar Pharmaceuticals, Inc

DRUG PRODUCT: Fluorouracil Injection USP, 50 mg/mL (100 mL Pharmacy Bulk Package Vial).

The deficiencies presented below represent FAX deficiencies.

A. Chemistry Deficiencies:

1.

2. as

3.

4. ed

e

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The cGMP compliance of the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

2. Sterility validation data for the manufacturing process is pending review.

3. Labeling deficiencies will also need to be addressed in your reply.

Sincerely yours,

for Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS

ANDA: #40-379 APPLICANT: Bigmar Inc

DRUG PRODUCT: Fluorouracil Injection, USP 50 mg/mL; 100 mL Pharmacy Bulk Package Vials

The Division of Bioequivalence has completed its review of your application 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,

for Barbara McDaniel, Ph.D.

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

ANDA 40-379

AUG 12 1999

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

Dear Sir:

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

NAME OF DRUG: Fluorouracil Injection USP, 50 mg/mL, (Pharmacy Bulk Package)

DATE OF APPLICATION: July 19, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 20, 1999

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:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

Harvey A. Healey
for

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Pharmaceuticals

Bigmar

ack for filing
S. Middleton
505 (j)(2)(A)

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

July 19, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Metro Park North II
HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

Re: Fluorouracil Injection, USP 50 mg/mL
100 mL - Pharmacy Bulk Package
ANDA Submission - 5 Volumes

Dear Sir or Madam,

In accordance with the provisions set forth in 21 CFR 314.94, we are submitting this abbreviated new drug application (ANDA), in duplicate, for Fluorouracil Injection, USP 50 mg/mL - 100 mL Pharmacy Bulk Package. Fluorouracil Injection is effective in the palliative management of carcinoma of the colon, rectum, breast, stomach and pancreas.

This ANDA is being filed by Bigmar, Inc., a pharmaceutical company with headquarters in the Columbus, Ohio area. The subject drug product is produced by Bigmar Pharmaceuticals SA, a Swiss division of Bigmar, Inc. Bigmar recently received FDA approval for one other Fluorouracil based product, ANDA # 40-291. Information included within that application provides the basis for this ANDA.

Fluorouracil Injection, USP 50 mg/mL is a sterile drug product. Sterility assurance data is provided for your review under section XXII of this submission.

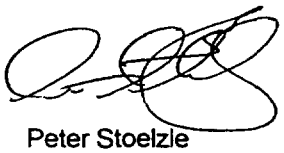
An analytical methods validation package, which includes three (3) additional copies of non-compendial assay procedures and their corresponding validation studies, is provided under separate cover. Bigmar, Inc. hereby commits to resolve and report any issues identified in the methods validation process after approval of this ANDA submission.

Standard operating procedures (SOPs) are provided throughout this application as an aid in the review process. Revisions may be made to these SOPs after appropriate in-house review and approval. Changes which influence the manufacture of Fluorouracil Injection, 50 mg/mL will be reported to the agency per the criteria established under CFR 314.70. A number of the SOPs provided in this application are written in Italian, the language spoken at Bigmar's Swiss manufacturing facility. English translations of those procedures immediately follow the corresponding Italian version.

In accordance with 21 CFR 314.94(d)(5), we certify that a true field copy has been sent to our FDA district office in Cincinnati, Ohio. The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

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

Sincerely,



Peter Stoelzle
Executive Vice President
Bigmar Incorporated
9711 Sportsman Club Road
Johnstown, OH 43031

Enclosures