CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 17-422/S-037

Name: BiCNU® (carmustine) for Injection, 100 mg/vial

Sponsor: Bristol-Myers Squibb Company

Approval Date: August 17, 2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-422/S-037

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-422/S-037

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-422/S-037

Bristol-Myers Squibb Company
Attention: Michael J. Theil
Group Manager, Global Regulatory Affairs, CMC
P.O. Box 191
New Brunswick, NJ 08903-0191

Dear Mr. Theil:

Please refer to your supplemental new drug application dated October 27, 2006, received October 31, 2006, and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BiCNU® (carmustine) for Injection, 100 mg/vial.

We acknowledge receipt of your submissions dated April 18, June 8, and August 14, 2007. Your submission dated April 18, 2007, constituted a complete response to our February 27, 2007, action letter.

This supplemental new drug application provides for the following:

- Adding Luitpold Pharmaceuticals, Shirley, NY, as an alternative manufacturing and quality control and stability testing site for the alcohol diluent,
- Modifications to the method of manufacture of the diluent,
- Addition of a glass ampule as a primary container for the diluent,
- Modifications to the release specifications for the diluent,
- Changes to the package insert, the BiCNU® and Dehydrated Alcohol Injection container labels, and the combination pack carton,
- Modification to the approved market-life stability protocol for BiCNU®, and
- Addition of an alternate secondary packaging site for the BiCNU® combination pack.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert submitted on June 8 and amended on August 14, 2007). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved supplemental NDA 17-422/S-037."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and/or submitted carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved supplemental NDA 17-422/S-037**." Approval of this submission by FDA is not required before the labeling is used.

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

LETTERS TO HEALTH CARE PROFESSIONALS

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

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

REPORTING REQUIREMENTS

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

If you have any questions, call Susan Jenney, Regulatory Health Project Manager, at (301) 796-0062.

Sincerely,

{See appended electronic signature page}

Hasmukh B. Patel, Ph.D.
Branch Chief
Branch VIII, Division of Post-Marketing Evaluation
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

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

/s/

Eric Duffy

8/17/2007 02:45:46 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-422/S-037

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-422/S-037

Bristol-Myers Squibb Company
Attention: Gerald DiDonato
Associate Director, Global Regulatory Sciences, CMC
P.O. Box 5400
Princeton, NJ 08540

Dear Mr. DiDonato:

Please refer to your supplemental new drug application dated October 27, 2006, received October 31, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BiCNU® (carmustine) for Injection, 100 mg/vial.

This supplemental new drug application provides for the following:

- Adding Luitpold Pharmaceuticals, Shirley, NY, as an alternative manufacturing and quality control and stability testing site for the alcohol diluent,
- Modifications to the method of manufacture,
- Addition of a glass ampule as a primary container,
- Modifications to the release specifications,
- Changes to the package insert, the BiCNU® and Dehydrated Alcohol Injection container labels, and the combination pack carton,
- Modification to the approved market-life stability protocol for BiCNU®, and
- Addition of an alternate secondary packaging site for the BiCNU® combination pack.

We have completed the review of this application and it is approvable. Before the application may be approved, however, you must address the following deficiencies:

1. (b) (4)
2.
3.
4.

5. (b) (4)

6.

7.

8.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Susan Jenney, Regulatory Health Project Manager, at (301) 796-0062.

Sincerely,

{See appended electronic signature page}

Hasmukh B. Patel, Ph.D.
Branch Chief
Branch VIII, Division of Post-Marketing Evaluation
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Hasmukh Patel

2/27/2007 04:12:36 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-422/S-037

LABELING

BiCNU

(carmustine for injection)

WARNINGS

BiCNU (carmustine for injection) should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

Bone marrow suppression, notably thrombocytopenia and leukopenia, which may contribute to bleeding and overwhelming infections in an already compromised patient, is the most common and severe of the toxic effects of BiCNU (see **WARNINGS** and **ADVERSE REACTIONS**).

Since the major toxicity is delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose (see **ADVERSE REACTIONS**). At the recommended dosage, courses of BiCNU should not be given more frequently than every 6 weeks.

The bone marrow toxicity of BiCNU is cumulative and therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see "Dosage Adjustment Table" under **DOSAGE AND ADMINISTRATION**).

Pulmonary toxicity from BiCNU appears to be dose related. Patients receiving greater than 1400 mg/m^2 cumulative dose are at significantly higher risk than those receiving less.

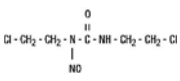
Delayed pulmonary toxicity can occur years after treatment, and can result in death, particularly in patients treated in childhood (see **ADVERSE REACTIONS** and **PRECAUTIONS: Pediatric Use**).

DESCRIPTION

BiCNU® (carmustine for injection) is one of the nitrosoureas used in the treatment of certain neoplastic diseases. It is 1,3-bis (2-chloroethyl)-1-nitrosourea. It is sterile lyophilized pale yellow flakes or congealed mass with a molecular weight of 214.06. It is highly soluble in alcohol and lipids, and poorly soluble in water. BiCNU is administered by intravenous infusion after reconstitution as recommended.

The structural formula is:

Image



BiCNU is available in 100 mg single dose vials of lyophilized material. Sterile diluent for constitution of BiCNU is co-packaged with the active drug product for use in constitution of the

lyophile. The diluent is supplied in an ampule containing 3 mL of Dehydrated Alcohol Injection, USP.

CLINICAL PHARMACOLOGY

Although it is generally agreed that carmustine alkylates DNA and RNA, it is not cross-resistant with other alkylators. As with other nitrosoureas, it may also inhibit several key enzymatic processes by carbamoylation of amino acids in proteins.

Intravenously administered carmustine is rapidly degraded, with no intact drug detectable after 15 minutes. However, in studies with ^{14}C-labeled drug, prolonged levels of the isotope were detected in the plasma and tissue, probably representing radioactive fragments of the parent compound.

It is thought that the antineoplastic and toxic activities of carmustine may be due to metabolites. Approximately 60% to 70% of a total dose is excreted in the urine in 96 hours and about 10% as respiratory CO_2. The fate of the remainder is undetermined.

Because of the high lipid solubility and the relative lack of ionization at physiological pH, carmustine crosses the blood-brain barrier quite effectively. Levels of radioactivity in the CSF are ≥50% of those measured concurrently in plasma.

INDICATIONS AND USAGE

BiCNU is indicated as palliative therapy as a single agent or in established combination therapy with other approved chemotherapeutic agents in the following:

1. Brain tumors—glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma, and metastatic brain tumors.

2. Multiple myeloma—in combination with prednisone.

3. Hodgkin's Disease—as secondary therapy in combination with other approved drugs in patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.

4. Non-Hodgkin's lymphomas—as secondary therapy in combination with other approved drugs for patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.

CONTRAINDICATIONS

BiCNU should not be given to individuals who have demonstrated a previous hypersensitivity to it.

WARNINGS

Since the major toxicity is delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose (see **ADVERSE REACTIONS**). At the recommended dosage, courses of BiCNU should not be given more frequently than every 6 weeks.

The bone marrow toxicity of BiCNU is cumulative and therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see "Dosage Adjustment Table" under **DOSAGE AND ADMINISTRATION**).

Pulmonary toxicity from BiCNU appears to be dose related. Patients receiving greater than 1400 mg/m^2 cumulative dose are at significantly higher risk than those receiving less. Additionally delayed onset pulmonary fibrosis occurring up to 17 years after treatment has been reported in patients who receive BiCNU in childhood and early adolescence (see **ADVERSE REACTIONS**).

Long-term use of nitrosoureas has been reported to be associated with the development of secondary malignancies.

Liver and renal function tests should be monitored periodically (see **ADVERSE REACTIONS**).

BiCNU (carmustine for injection) may cause fetal harm when administered to a pregnant woman. BiCNU has been shown to be embryotoxic in rats and rabbits and teratogenic in rats when given in doses equivalent to the human dose. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

BiCNU has been administered through an intraarterial intracarotid route; this procedure is investigational and has been associated with ocular toxicity.

PRECAUTIONS

General

In all instances where the use of BiCNU is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risks of toxic effects or adverse reactions. Most such adverse reactions are reversible if detected early. When such effects or reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgment of the physician. Reinstitution of BiCNU therapy should be carried out with caution, and with adequate consideration of the further need for the drug and alertness as to possible recurrence of toxicity.

Laboratory Tests

Due to delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose.

Baseline pulmonary function studies should be conducted along with frequent pulmonary function tests during treatment. Patients with a baseline below 70% of the predicted Forced Vital Capacity (FVC) or Carbon Monoxide Diffusing Capacity (DL_{CO}) are particularly at risk.

Since BiCNU may cause liver dysfunction, it is recommended that liver function tests be monitored.

Renal function tests should also be monitored periodically.

Carcinogenesis, Mutagenesis, Impairment of Fertility

BiCNU is carcinogenic in rats and mice, producing a marked increase in tumor incidence in doses approximating those employed clinically. Nitrosourea therapy does have carcinogenic potential in humans (see **ADVERSE REACTIONS**). BiCNU also affects fertility in male rats at doses somewhat higher than the human dose.

Pregnancy

Pregnancy Category D

See **WARNINGS**.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because of the potential for serious adverse events in nursing infants, nursing should be discontinued while taking BiCNU.

Pediatric Use

Safety and effectiveness in children have not been established. Delayed onset pulmonary fibrosis occurring up to 17 years after treatment has been reported in a long-term study of patients who received BiCNU in childhood and early adolescence (1–16 years). Eight out of the 17 patients (47%) who survived childhood brain tumors, including all the five patients initially treated at less than five years of age, died of pulmonary fibrosis. Therefore, the risks and benefits of BiCNU therapy must be carefully considered, due to the extremely high risk of pulmonary toxicity. (See **ADVERSE REACTIONS: Pulmonary Toxicity**.)

Geriatric Use

No data from clinical studies of BiCNU are available for patients 65 years of age and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of

the dose range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

BiCNU and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored.

ADVERSE REACTIONS

Pulmonary Toxicity

Pulmonary toxicity characterized by pulmonary infiltrates and/or fibrosis has been reported to occur from 9 days to 43 months after treatment with BiCNU and related nitrosoureas. Most of these patients were receiving prolonged therapy with total doses of BiCNU greater than 1400 mg/m^2. However, there have been reports of pulmonary fibrosis in patients receiving lower total doses. Other risk factors include past history of lung disease and duration of treatment. Cases of fatal pulmonary toxicity with BiCNU have been reported.

Additionally, delayed onset pulmonary fibrosis occurring up to 17 years after treatment has been reported in a long-term study with 17 patients who received BiCNU in childhood and early adolescence (1–16 years) in cumulative doses ranging from 770 to 1800 mg/m^2 combined with cranial radiotherapy for intracranial tumors. Chest x-rays demonstrated pulmonary hypoplasia with upper zone contraction. Gallium scans were normal in all cases. Thoracic CT scans have demonstrated an unusual pattern of upper zone fibrosis. There was some late reduction of pulmonary function in all long-term survivors. This form of lung fibrosis may be slowly progressive and has resulted in death in some cases. In this long-term study, 8 of 17 died of delayed pulmonary lung fibrosis, including all those initially treated (5 of 17) at less than 5 years of age.

Hematologic Toxicity

A frequent and serious toxicity of BiCNU is delayed myelosuppression. It usually occurs 4 to 6 weeks after drug administration and is dose related. Thrombocytopenia occurs at about 4 weeks postadministration and persists for 1 to 2 weeks. Leukopenia occurs at 5 to 6 weeks after a dose of BiCNU and persists for 1 to 2 weeks. Thrombocytopenia is generally more severe than leukopenia. However, both may be dose-limiting toxicities.

BiCNU may produce cumulative myelosuppression, manifested by more depressed indices or longer duration of suppression after repeated doses.

The occurrence of acute leukemia and bone marrow dysplasias have been reported in patients following long-term nitrosourea therapy.

Anemia also occurs, but is less frequent and less severe than thrombocytopenia or leukopenia.

Gastrointestinal Toxicity

Nausea and vomiting after IV administration of BiCNU are noted frequently. This toxicity appears within 2 hours of dosing, usually lasting 4 to 6 hours, and is dose related. Prior administration of antiemetics is effective in diminishing and sometimes preventing this side effect.

Hepatotoxicity

A reversible type of hepatic toxicity, manifested by increased transaminase, alkaline phosphatase and bilirubin levels, has been reported in a small percentage of patients receiving BiCNU.

Nephrotoxicity

Renal abnormalities consisting of progressive azotemia, decrease in kidney size and renal failure have been reported in patients who received large cumulative doses after prolonged therapy with BiCNU and related nitrosoureas. Kidney damage has also been reported occasionally in patients receiving lower total doses.

Other Toxicities

Accidental contact of reconstituted BiCNU with skin has caused burning and hyperpigmentation of the affected areas.

Rapid IV infusion of BiCNU (carmustine for injection) may produce intensive flushing of the skin and suffusion of the conjunctiva within 2 hours, lasting about 4 hours. It is also associated with burning at the site of injection although true thrombosis is rare.

Neuroretinitis, chest pain, headache, allergic reaction, hypotension and tachycardia have been reported as part of ongoing surveillance.

OVERDOSAGE

No proven antidotes have been established for BiCNU overdosage.

DOSAGE AND ADMINISTRATION

The recommended dose of BiCNU as a single agent in previously untreated patients is 150 to 200 mg/m^2 intravenously every 6 weeks. This may be given as a single dose or divided into daily injections such as 75 to 100 mg/m^2 on 2 successive days. When BiCNU is used in combination with other myelosuppressive drugs or in patients in whom bone marrow reserve is depleted, the doses should be adjusted accordingly.

Doses subsequent to the initial dose should be adjusted according to the hematologic response of the patient to the preceding dose. The following schedule is suggested as a guide to dosage adjustment:

Nadir After Prior Dose		Percentage of Prior Dose tobe Given
Leukocytes/mm3	Platelets/mm3	
>4000	>100,000	100%
3000–3999	75,000–99,999	100%
2000–2999	25,000–74,999	70%
<2000	<25,000	50%

A repeat course of BiCNU should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/mm3, leukocytes above 4,000/mm3), and this is usually in 6 weeks. Adequate number of neutrophils should be present on a peripheral blood smear. Blood counts should be monitored weekly and repeat courses should not be given before 6 weeks because the hematologic toxicity is delayed and cumulative.

Administration Precautions

As with other potentially toxic compounds, caution should be exercised in handling BiCNU and preparing the solution of BiCNU. Accidental contact of reconstituted BiCNU with the skin has caused transient hyperpigmentation of the affected areas. The use of gloves is recommended. If BiCNU lyophilized material or solution contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

The reconstituted solution should be used intravenously only and should be administered by IV drip. Injection of BiCNU over shorter periods of time than 1 to 2 hours may produce intense pain and burning at the site of injection.

Preparation of Intravenous Solutions

First, dissolve BiCNU with 3 mL of the supplied sterile diluent (Dehydrated Alcohol Injection, USP). Second, aseptically add 27 mL Sterile Water for Injection, USP. Each mL of resulting solution contains 3.3 mg of BiCNU in 10% ethanol. Such solutions should be protected from light.

Reconstitution as recommended results in a clear, colorless to yellowish solution which may be further diluted with 5% Dextrose Injection, USP. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Important Note

The lyophilized dosage formulation contains no preservatives and is not intended for use as a multiple dose vial.

Stability

The unopened vial of the dry drug must be stored in a refrigerator (2°-8°C, 36°-46°F). The diluent ampules may be stored at controlled room temperature (59°-86°F, 15°-30°C) or in a refrigerator (2°-8°C, 36°-46°F). The recommended storage of unopened BiCNU vials provides a stable product for up to 3 years. After reconstitution as recommended, BiCNU is stable for 24 hours under refrigeration (2°-8°C, 36°-46°F). Reconstituted vials should be examined for crystal formation prior to use. If crystals are observed, they may be redissolved by warming the vial to room temperature with agitation.

Vials reconstituted as directed and further diluted to a concentration of 0.2 mg/mL in 5% Dextrose Injection, USP, should be stored at room temperature, protected from light and utilized within 8 hours.

Glass containers were used for the stability data provided in this section. Only use glass containers for BiCNU administration.

Important Note

BiCNU has a low melting point (30.5°-32.0°C or 86.9°-89.6°F). Exposure of the drug to this temperature or above will cause the drug to liquefy and appear as an oil film on the vials. This is a sign of decomposition and vials should be discarded. If there is a question of adequate refrigeration upon receipt of this product, immediately inspect the vial in each individual carton. Hold the vial to a bright light for inspection. The BiCNU will appear as a very small amount of dry flakes or dry congealed mass. If this is evident, the BiCNU is suitable for use and should be refrigerated immediately.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing BiCNU. This includes all handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration.

HOW SUPPLIED

BiCNU® (carmustine for injection). Each package includes a vial containing 100 mg carmustine and an ampule containing 3 mL sterile diluent.

NDC 0015-3012-60

STORAGE

Store in a refrigerator (2°-8°C, 36°-46°F).

Store diluent at controlled room temperature (59°-86°F, 15°-30°C) or in a refrigerator (2°-8°C, 36°-46°F).

REFERENCES

5. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice. Pittsburgh, PA: Oncology Nursing Society; 1999:32-41.

6. Recommendations for the safe handling of parenteral antineoplastic drugs. Washington, DC: Division of Safety, Clinical Center Pharmacy Department and Cancer Nursing Services, National Institutes of Health; 1992. US Dept of Health and Human Services, Public Health Service Publication NIH 92-2621.

7. AMA Council on Scientific Affairs. Guidelines for handling parenteral antineoplastics. *JAMA*. 1985;253:1590-1592.

8. National Study Commission on Cytotoxic Exposure. Recommendations for handling cytotoxic agents. 1987. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.

9. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Aust*. 1983;1:426-428.

10. Jones RB, Frank R, Mass T. Safe handling of chemotherapeutic agents: a report from The Mount Sinai Medical Center. *CA Cancer J Clin*. 1983;33:258-263.

11. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm*. 1990;47:1033-1049.

12. Controlling occupational exposure to hazardous drugs. (OSHA Work-Practice Guidelines.) *Am J Health-Syst Pharm*. 1996;53:1669-1685.

BiCNU manufactured by:Ben Venue Laboratories, Inc.Bedford, OH 44146Diluent manufactured by:Luitpold Pharmaceuticals, Inc.Shirley, NY 11967Distributed by:Bristol-Myers Squibb CompanyPrinceton, NJ 08543 USA

[Print Code TBD]Rev TBD

Fred J. Frullo
Director Oncology
Global Regulatory Sciences
PRI

P. O. Box 4000 Princeton, NJ 08543-4000
Tel 609-252-5741 Fax 609-252-6000
fred.frullo@bms.com

Bristol-Myers Squibb Company

FINAL PRINTED CARTON AND LABELS
FOR APPROVED SUPPLEMENTAL NDA 17-422/S-037

NDA 17-422 BICNU®
(carmustine for injection)

October 2, 2007

Robert Justice, M.D., Director
Division of Drug Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-150)
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

Dear Dr. Justice:

Reference is made to our approved New Drug Application 17-422 for BicNU® (Carmustine for Injection) and to the FDA approval letter for supplement S-037 received on August 17, 2007. We are now submitting Final Printed Carton and Container in accordance with the approval letter.

This submission is being submitted in eNDA format via the FDA Electronic Gateway, therefore paper copies will not be supplied at this time, but are available upon your request.

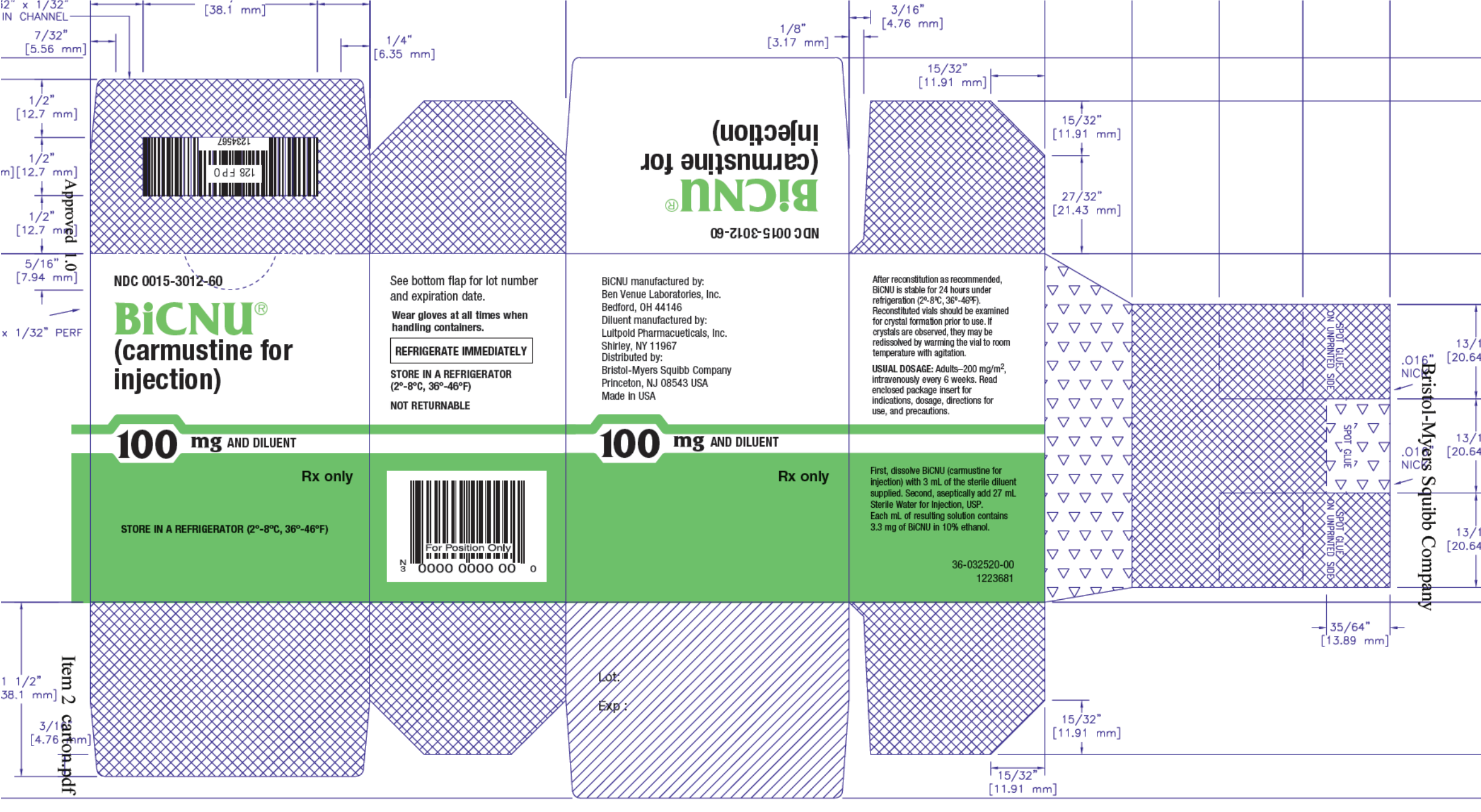
If you require additional information regarding this submission, please contact me by telephone at (609) 252-5741, or via fax at (609) 252-6000. I can also be reached via secure electronic mail at: *fred.frullo@bms.com*.

Sincerely,

Fred J. Frullo

Fred J. Frullo
Director Oncology
Global Regulatory Sciences

FJF/MF/tmc


NDC 0015-3012-60
BiCNU®
(carmustine for injection)
100 mg AND DILUENT
Rx only
STORE IN A REFRIGERATOR (2°-8°C, 36°-46°F)
See bottom flap for lot number and expiration date.
Wear gloves at all times when handling containers.
REFRIGERATE IMMEDIATELY
STORE IN A REFRIGERATOR (2°-8°C, 36°-46°F)
NOT RETURNABLE
For Position Only
BiCNU manufactured by:
Ben Venue Laboratories, Inc.
Bedford, OH 44146
Diluent manufactured by:
Luitpold Pharmaceuticals, Inc.
Shirley, NY 11967
Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
Made in USA
After reconstitution as recommended, BiCNU is stable for 24 hours under refrigeration (2°-8°C, 36°-46°F). Reconstituted vials should be examined for crystal formation prior to use. If crystals are observed, they may be redissolved by warming the vial to room temperature with agitation.
USUAL DOSAGE: Adults–200 mg/m², intravenously every 6 weeks. Read enclosed package insert for indications, dosage, directions for use, and precautions.
First, dissolve BiCNU (carmustine for injection) with 3 mL of the sterile diluent supplied. Second, aseptically add 27 mL Sterile Water for Injection, USP.
Each mL of resulting solution contains 3.3 mg of BiCNU in 10% ethanol.
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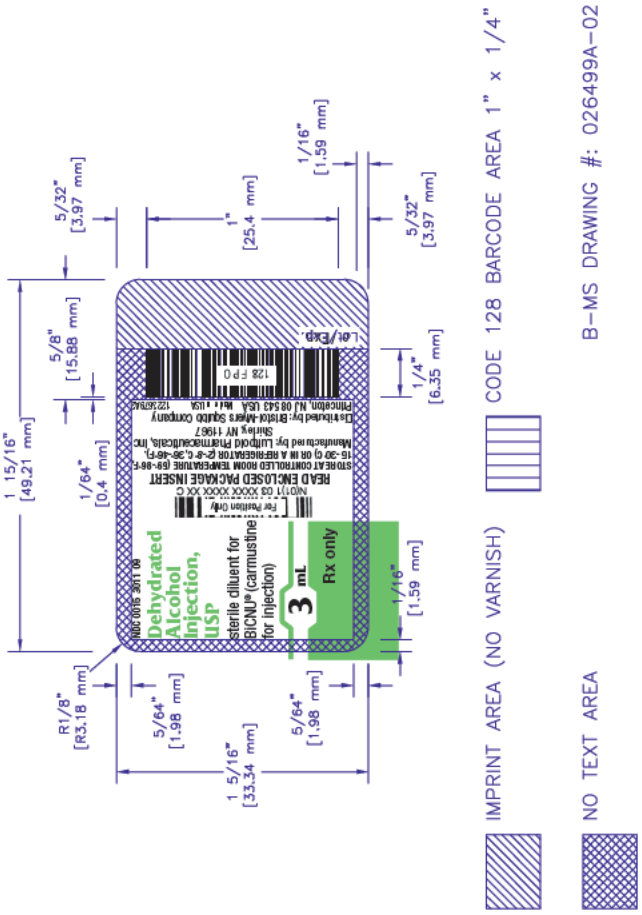
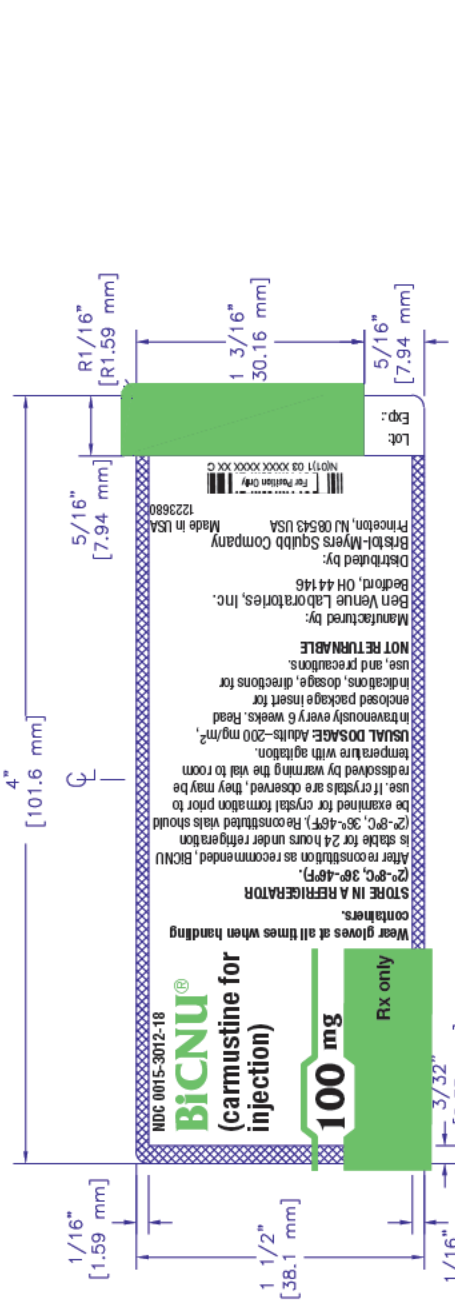
Exp :
Bristol-Myers Squibb Company
Approved 1.0
Item 2 carton.pdf


1 15/16" [49.21 mm]
5/8" [15.88 mm]
1/64" [0.4 mm]
5/32" [3.97 mm]
1" [25.4 mm]
1/16" [1.59 mm]
5/32" [3.97 mm]
1/4" [6.35 mm]
1/16" [1.59 mm]
R1/8" [R3.18 mm]
5/64" [1.98 mm]
1 5/16" [33.34 mm]
5/64" [1.98 mm]
Dehydrated Alcohol Injection, USP
sterile diluent for BiCNU® (carmustine) for injection
3 mL
Rx only
Lot/Exp.
128 FPO
IMPRINT AREA (NO VARNISH)
CODE 128 BARCODE AREA 1" x 1/4"
NO TEXT AREA
B-MS DRAWING #: 026499A-02



B–MS DRAWING #: 002826A–02

NO TEXT AREA

LASER BATCH CODE AREA

NOTE TO DESIGNER: ADD COLORED BOX TO LASER BATCH CODE AREA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-422/S-037

LABELING REVIEWS

REGULATORY PROJECT MANAGER REVIEW OF LABELING

NDA 17-422/S037

Drug: BiCNU (carmustine for injection) **Tradename (generic name) dosage form**

Applicant: BMS

Submission Date(s): October 27, 2006 (SCS)

Receipt Date(s): October 31, 2006

BACKGROUND:

This supplement was submitted as a prior approval supplement and provides for a new manufacturer of the alcohol diluent, a change in the container of the diluent from a Type 1 glass vial to a Type 1 glass, flame-sealed ampule, and the related changes in the carton/container labels and package insert.

DOCUMENTS REVIEWED:

The latest submitted approved labeling was that submitted on June 6, 2005 for supplement S036, which was approved on October 20, 2005. The approval letter mistakenly refers to September 15, 2005 as the date of amended labeling for this supplement, but the September 15 submission did not contain any labeling and was simply a narrative response to some FDA questions. Additionally, the labeling submitted with S037 indicates that the version they were making revisions to was the June 05 version. No FPL was ever submitted for S036.

I compared the "clean" version of the S037 labeling (submitted electronically) to the June 6, 2005 draft labeling. Below are the only differences noted.

REVIEW:

Under **DOSAGE and ADMINISTRATION, Stability**, a "The" has been added to the first sentence and "s" deleted from "vial" in the first sentence. The following sentence has then been inserted:

> The diluent ampules may be stored at controlled room temperature (59^{o}-86^{o}F, 15^{o}-(b)(4)C) or in a refrigerator (2^{o}-8^{o}C, 36^{o}-46^{o}F).

"BiCNU" has been added before "vials" in the third sentence.

In the **HOW SUPPLIED** section, first sentence, "a vial" has been changed to "an ampule" and the NDC number changed.

In the **STORAGE** section, first sentence, “dry powder” has been deleted, the temperatures in the parens separated by a “-“ instead of “to”, and the following sentence added:

> Store diluent at controlled room temperature (59°-86°F, 15°-(b)(4)°C) or in a refrigerator (2°-8°C, 36°-46°F).

The above changes and the carton/container label revisions are all acceptable, according to the February 26, 2007 chemist’s review.

CONCLUSION - RECOMMENDED REGULATORY ACTION:

The labeling revisions for the supplement have been found to be acceptable, and the supplement may be approved pending findings of the chemist and microbiologist.

NOTE: the chemist and microbiologist have recommended an approvable action, so an approvable letter will issue.

_____
Dotti Pease
Chief, Project Management Staff

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/s/

Dotti Pease
2/27/2007 03:17:38 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-422/S-037

CHEMISTRY REVIEWS

CHEMIST REVIEW
OF **SUPPLEMENT**
Prior Approval

1. **ORGANIZATION**: ONDQA-DPE
2. **NDA NUMBER:** 17-422 / SCM 037

3. **SUPPLEMENT DATES:**
   Letter Date: 27-Oct-2006
   Stamp Date: 31-Oct-2006
   Due Date: **28-Feb-2007**
4. **AMENDMENT:** **None**
5. **RECEIVED BY CHEMIST:** Nov 2006

6. **SPONSOR NAME AND ADDRESS**
   Bristol-Myers Squibb Co.
   Princeton, NJ

7. **SUPPLEMENT PROVIDES FOR:** addition of Luitpold Pharmaceuticals, Shirley, NY, as an alternative manufacturing and quality control and stability testing site for the alcohol diluent

8.	**DRUG PRODUCT NAME:**	BiCNU
9.	**NONPROPRIETARY NAME:**	Carmustine for Injection
10.	**DRUG SUBSTANCE:**	1,3-bis(2-chloroethyl)-1-nitrosourea
11.	**DOSAGE FORM/STRENGTH**	lyophilized powder for injection; 100 mg/vial
12.	**ROUTE OF ADMINSTRATION:**	IV
13.	**INDICATION:**	chemotherapy agent
14.	**HOW DISPENSED:**	Rx
15.	**RELATED IND/NDA/DMF:**	None

16. **COMMENTS:**
The supplement proposes a new manufacturer of the alcohol diluent, and a change in the container of the diluent from a Type 1 glass vial to a Type 1 glass, flame-sealed, ampule. Additional changes are the following: change in diluent manufacturing process; change in expiry of diluent from 36 months to 42 months; change in storage temperature of diluent from refrigerator conditions to either refrigerator or room temperature conditions; and a change in the diluent product specification to add a test for particulate matter. Comparative batch release data from three commercial scale batches of diluent manufactured by the approved manufacturer and the proposed manufacturer are provided.

Revisions to the carton, container label, and the stability, how supplied, and storage sections of the label have been made. The proposed changes are acceptable. See this review for an evaluation.

(b) (4)

The Office of Compliance has recommended the site for approval.

The Microbiologist reviewer finds the supplement to be APPROVABLE from a microbiological quality assurance perspective. See review by Dr. S. Langille, dated 26-Feb-2007.

17. CONCLUSIONS AND RECOMMENDATIONS

Based on deficiencies from a microbiological quality perspective, this supplement is APPROVABLE.

Issue an Approvable (AE) Letter, with the following:

For this supplement to be approved, responses to the following deficiencies must be adequate:

(1) (b) (4) [redacted].

(2) [add Deficiencies from the Microbiologist Review]

18. REVIEWER NAME — **DATE COMPLETED**

J. Salemme, Ph.D., Chemistry reviewer, ONDQA-DPE — 26-Feb-2007

PM: S. Jenney, Project Manager, ONDQA-DPE, and PM in HFD-580
Reviewed: Dr. Hasmukh Patel, Branch Chief, ONDQA-DPE

Background
The drug product, BiCNU, carmustine for injection, is a lyophilized powder. It is marketed in a combination package consisting of the lyophilized drug product in a vial packaged with a vial of dehydrated alcohol injection, USP, the diluent for reconstitution. The drug product is reconstituted with alcohol diluent before use, and administered by IV for chemotherapy treatment. The combination pack is labeled for refrigerated storage, based on the stability requirements of the drug product. The diluent vial is a 5 mL Type 1 flint glass vial containing (b) (4) alcohol and labeled to contain 3 mL.

Supplement
The supplement provides for an alternate manufacturer of the alcohol diluent, and a change in the diluent container, from the approved 5 mL Type 1 glass vial/cap to a 5-mL Type 1 glass, flame-sealed, ampule. As a result of the change in diluent manufacturer, some changes have been made to the diluent manufacturing process and controls. A validation report is provided to support the changes in manufacturing, and three commercial batches of diluent in the proposed ampule have been manufactured to support this supplement. Additionally, based on commercial, historical stability data provided for the diluent in the ampule, a change in expiration period of the diluent from 36 months to 42 months, and a change in storage temperature from refrigerator to refrigerator or room temperature, is requested.

The carton, container label, and the stability, how supplied, and storage sections of the label have been amended to reflect changes proposed in this supplement.

For the drug product, some minor changes in the approved CMC have been made and are reported in this supplement. These are: (b) (4) timepoint has been added to the stability protocol for the combination pack of drug product and diluent, and a secondary packaging site has been added.

Review

Proposed Manufacturer, Quality Control, and Stability Testing of Dehydrated Alcohol Diluent

Luitpold Pharmaceuticals, Inc.
Shirley, NY

Evaluation: The Office of Compliance recommends this site for approval. See the EER in Appendix 1 of this review.

Change in Diluent Manufacturing Controls **DEFICIENT**
Some changes have been made in the (b) (4) process as a result of manufacturing controls used by the proposed manufacturer. A validation report has been provided [section 3.2.p.3.5]. This section has been reviewed by the Microbiology Reviewer and found to be Deficient. See review by Dr. S. Langille, dated 25-Feb-2007.

Evaluation: The microbiologist reviewer has evaluated the manufacturing and found deficiencies. The sponsor will be provided the deficiencies in the Approvable Letter.

Following this page, 6 pages withheld in full - (b)(4)

APPENDIX

22-FEB-2007 FDA CDER EES Page 1 of 1

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 17422/037
Org Code : 150
Priority : 1S

Sponsor: BRISTOL
BOX 4755
SYRACUSE, NY 132214755

Stamp Date : 31-OCT-2006
PDUFA Date : 28-FEB-2007
Action Goal :
District Goal: 24-JAN-2007

Brand Name : BICNU
Estab. Name:
Generic Name: CARMUSTINE
Dosage Form: (INJECTION)
Strength : 100 MG/VIAL

FDA Contacts:	V. JIMENEZ	Project Manager	301-796-1345
	J. SALEMME	Review Chemist	301-796-1746
	D. LEWIS	Team Leader	301-796-1694

Overall Recommendation: ACCEPTABLE on 28-NOV-2006by J. D AMBROGIO(HFD-322) 301-827-9073

Establishment : CFN : 2410375 FEI : 2410375
LUITPOLD PHARMACEUTICALS INC
1 LUITPOLD DR
SHIRLEY, NY 11967

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : SVS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-NOV-06
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

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/s/

Jean Salemme
2/26/2007 02:30:09 PM
CHEMIST

Hasmukh Patel
2/26/2007 04:34:36 PM
CHEMIST

CHEMIST REVIEW #2
OF **SUPPLEMENT**
Prior Approval RESPONSE TO AE

1. **ORGANIZATION**: ONDQA-DPE
2. **NDA NUMBER:** 17-422 / SCM 037
3. **SUPPLEMENT DATES:**
   Letter Date: 27-Oct-2006
   Stamp Date: 31-Oct-2006
   Due Date: 28-Feb-2007
4. **AMENDMENT: AC**
   Stamp Date: 19-Apr-2007
   Due Date: 19-Aug-2007
5. **RECEIVED BY CHEMIST:** Apr 2007

6. **SPONSOR NAME AND ADDRESS**
   Bristol-Myers Squibb Co.
   Princeton, NJ

7. **SUPPLEMENT PROVIDES FOR:** addition of Luitpold Pharmaceuticals, Shirley, NY, as an alternate manufacturing and quality control and stability testing site for the alcohol diluent

8.	**DRUG PRODUCT NAME:**	BiCNU
9.	**NONPROPRIETARY NAME:**	Carmustine for Injection
10.	**DRUG SUBSTANCE:**	1,3-bis(2-chloroethyl)-1-nitrosourea
11.	**DOSAGE FORM/STRENGTH**	lyophilized powder for injection; 100 mg/vial
12.	**ROUTE OF ADMINSTRATION:**	IV
13.	**INDICATION:**	chemotherapy agent
14.	**HOW DISPENSED:**	Rx
15.	**RELATED IND/NDA/DMF:**	None

16. **COMMENTS:**
The supplement proposes a new manufacturer of the alcohol diluent, and a change in the container of the diluent from a Type 1 glass vial to a Type 1 glass, flame-sealed, ampule. Additional changes are the following: change in diluent manufacturing process; change in expiry of diluent from 36 months to 42 months; change in storage temperature of diluent from refrigerator conditions to either refrigerator or room temperature conditions; and a change in the diluent product specification to add a test for particulate matter. See Chemistry Review No. 1 by Dr. J. Salemme.

This review evaluates the responses to the Approvable Letter. The response to the CMC deficiency has been evaluated in this review and is acceptable. Other deficiencies, which pertain to Microbiology, have been evaluated by the Microbiologist reviewer, Dr. S. Langille, and found to be acceptable. See Microbiology Review No. 2 dated 4-May-2007.

17. **CONCLUSIONS AND RECOMMENDATIONS**
Adequate information has been provided to support the proposed changes. This supplement, therefore, is recommended for approval. ISSUE AN APPROVAL LETTER

18. REVIEWER NAME	**DATE COMPLETED**
J. Salemme, Ph.D., Chemistry reviewer, ONDQA-DPE	21-May-2007

PM: S. Jenney, Project Manager, ONDQA-DPE
Reviewed: Dr. David Lewis, for Dr. Hasmukh Patel, Branch Chief, ONDQA-DPE

Background

The drug product, BiCNU, carmustine for injection, is a lyophilized powder. It is marketed in a combination package consisting of the lyophilized drug product in a vial packaged with a vial of dehydrated alcohol injection, USP, the diluent for reconstitution. The drug product is reconstituted with alcohol diluent before use, and administered by IV for chemotherapy treatment. The combination pack is labeled for refrigerated storage, based on the stability requirements of the drug product. The diluent vial is a 5 mL Type 1 flint glass vial containing (b) (4) alcohol and labeled to contain 3 mL.

Review

This review evaluates the response to the following deficiency:

(b) (4)

Response:

(b) (4)

Evaluation: Satisfactory. Adequate information has been provided to justify the use of room temperature storage conditions for the alcohol diluent.

Change in Diluent Manufacturing Controls

Some changes have been made in the (b) (4) process as a result of manufacturing controls used by the proposed manufacturer. The deficiencies provided in the Approvable Letter have been reviewed by the Microbiology Reviewer and found to be Acceptable. See review by Dr. S. Langille, dated 4-May-2007.

Evaluation: Satisfactory. The microbiologist reviewer has evaluated responses and finds them to be acceptable. The supplement is recommended for approval from a Microbiology Quality perspective. deficiencies.

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/s/

Jean Salemme
5/21/2007 01:52:59 PM
CHEMIST

David Lewis
5/21/2007 01:59:22 PM
CHEMIST
Concur; adeqaute responses were provided to the deficiencies from CR1. The application is recommended for APPROVAL from the standpoint of CMC. Signing for H. Patel.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-422/S-037

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review

26-FEB-2007

NDA: 17-422/SCM037

Drug Product Name
Proprietary: BiCNU®
Non-proprietary: carmustine for injection
Drug Product Priority Classification: Standard

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
10/27/06	10/31/06	11/20/06	11/30/06

Submission History (for amendments only): Not applicable

Applicant/Sponsor
Name: Bristol Myers Squibb Co.
Address: P.O. Box 5400
Princeton, NJ 08540
Representative: Gerald DiDonato
Telephone: (609) 818-6043

Name of Reviewer: Stephen E. Langille, Ph.D.

Conclusion: Approvable pending revision

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Prior approval supplement

2. SUBMISSION PROVIDES FOR: Alternate manufacturing facility, modifications to the manufacturing protocol, alternate container system for Dehydrated Alcohol Injection, USP, the diluent for carmustine for injection.

3. MANUFACTURING SITE: Luitpold Pharmaceuticals Inc.
1 Luitpold Drive
Shirley, NY 11967

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Liquid injectable
- intravenous
- 100 mg/vial

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: diluent for cancer therapy product

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: This document provides information supporting a site change for the alcohol diluent for Carmustine for injection. The application was submitted electronically in CTD format. There was no initial quality assessment for this supplement in DFS.

filename: N017422S037R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

NDA 17-422/SCM037 is approvable pending the resolution of microbiology deficiencies.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -

Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

Dehydrated Alcohol Injection, USP will be (b) (4) processed at an alternate manufacturing site and packaged in an alternate container.

B. Brief Description of Microbiology Deficiencies -

The applicant failed to provide adequate information regarding

- (b) (4)
-
-
-

C. Assessment of Risk Due to Microbiology Deficiencies -

Failure to address the microbiological deficiencies could result in endotoxin and/or microbial contamination of the drug product.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Bryan Riley, Ph.D.

C. CC Block

N/A

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/s/

Stephen Langille
2/26/2007 09:41:27 AM
MICROBIOLOGIST

Bryan Riley
2/26/2007 09:53:14 AM
MICROBIOLOGIST

Product Quality Microbiology Review

4-May-2007

NDA: 17-422/SCM037-AC

Drug Product Name
Proprietary: BiCNU®
Non-proprietary: carmustine for injection
Drug Product Priority Classification: Standard

Review Number: 2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
4/18/07	4/19/07	4/25/07	4/30/07

Submission History (for amendments only):

Submission Date(s)	Microbiology Review #	Review Date(s)
10/27/06	1	2/26/07

Applicant/Sponsor
Name: Bristol Myers Squibb Co.
Address: P.O. Box 5400
Princeton, NJ 08540
Representative: Gerald DiDonato
Telephone: (609) 818-6043

Name of Reviewer: Stephen E. Langille, Ph.D.

Conclusion: Recommended for approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Prior approval supplement

2. SUBMISSION PROVIDES FOR: Alternate manufacturing facility, modifications to the manufacturing protocol, alternate container system for Dehydrated Alcohol Injection, USP, diluent for carmustine for injection.

3. MANUFACTURING SITE: Luitpold Pharmaceuticals Inc.
1 Luitpold Drive
Shirley, NY 11967

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Liquid injectable
- intravenous
- 100 mg/vial

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: diluent for cancer therapy product

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: This document provides information supporting a site change for the alcohol diluent for Carmustine for injection. The application was submitted electronically in CTD format. There was no initial quality assessment for this supplement in DFS. The first review was completed on 2/26/07.

filename: N017422S037R2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

NDA 17-422/SCM037 is recommended for approval on the basis of microbiological product quality.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -

Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

Dehydrated Alcohol Injection, USP will be (b) (4) processed at an alternate manufacturing site and packaged in an alternate container.

B. Brief Description of Microbiology Deficiencies -

No deficiencies were identified based upon the information provided.

C. Assessment of Risk Due to Microbiology Deficiencies -

Not applicable.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Bryan Riley, Ph.D.

C. CC Block

N/A

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/s/

Stephen Langille
5/7/2007 02:17:43 PM
MICROBIOLOGIST

Bryan Riley
5/7/2007 02:30:45 PM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-422/S-037

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Bristol-Myers Squibb Company P. O. Box 5400 Princeton, NJ 08543-5400 609-818-3000

Chemistry, Manufacturing and Controls Supplement
Prior Approval Supplement

NDA 17-422
BiCNU® (carmustine for injection), 100 mg/vial

October 27, 2006

Richard Pazdur, M.D., Director
Division of Oncologic Drug Products, (HFD 150)
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448

Dear Dr. Pazdur:

This supplemental New Drug Application for BiCNU® (carmustine for injection), 100 mg/Vial is being submitted to propose the addition of Luitpold Pharmaceuticals, Inc, of Shirley, NY, USA, as an alternate manufacturing and quality control site for the alcohol diluent, Dehydrated Alcohol Injection, USP. Dehydrated Alcohol Injection, USP is co-packaged with the BiCNU® lyophile.

In addition to the alternate manufacturing and quality control site, this supplement also proposes modifications to the method of manufacture, the addition of a glass ampule as a primary container, and modifications to the release specifications. Minor changes to the package insert, the BiCNU® and Dehydrated Alcohol Injection container labels, and the combination pack carton, are also proposed.

This supplement also proposes a modification to the approved market-life stability protocol for BiCNU®, and the addition of an alternate secondary packaging site for the BiCNU® combination pack.

A copy of the cover letter will be provided to Nancy Rolli, FDA North Brunswick Office, 120 North Center Drive, North Brunswick, NJ 08902. Bristol-Myers Squibb certifies that the copy is a true copy of the filing.

If any question arises, please contact the undersigned at (609) 818-6043, or Cathy Ku, Director, Global Regulatory Sciences-CMC, at (609) 818-6427.

Sincerely,

Gerald DiDonato

Gerald DiDonato, Associate Director
Global Regulatory Sciences - CMC

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Director, New Drug Microbiology Staff (NDMS),
HFD-805
WO21 RM3657

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Susan Jenney, ONDQA
(301) 796-0062

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 20, 2006		17-422	SCM-037	October 27, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Bicnu	standard		January 26, 2007

NAME OF FIRM: Bristol

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This supplement provides for an alternate manufacturing and quality control site for the alcohol diluent. Please review, if additional information is needed contact Susan Jenney at x6-0062.

This submission is located in the EDR.

Goal Date is February 28, 2007.

SIGNATURE OF REQUESTOR
Valerie Jimenez

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Valerie Jimenez

11/20/2006 01:54:29 PM

Bristol-Myers Squibb Company P. O. Box 5400 Princeton, NJ 08543-5400 609-818-3000

Other: Chemistry, Manufacturing and Controls
Amendment to Prior Approval Supplement

NDA 17-422/S-037
BiCNU® (carmustine for injection), 100 mg/vial

June 8, 2007

Richard Pazdur, M.D., Director
Division of Oncologic Drug Products, (HFD 150)
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Pazdur:

Please reference our supplemental New Drug Application NDA 17-422/S-037 for BiCNU (carmustine for injection), 100 mg/Vial, dated October 27, 2006 to seek approval of an alternate manufacturing, quality control and stability site. Furthermore, reference is made to a telephone conversation with Ms. Susan Jenney, Regulatory Project Manager, of your office on May 31, 2007, requesting Structured Product Labeling (SPL) for the above referenced supplement.

As requested, enclosed please find SPL for the labeling changes proposed in S-037 to this NDA.

If you have any questions, please do not hesitate to contact me at (609) 818-6043, or Cathy Ku, Director, at (609) 818-6427.

Sincerely,

Gerald DiDonato

Gerald DiDonato, Ph. D.
Associate Director
Global Regulatory Sciences - CMC
Tel: 609 818 6043
FAX: 609 818 5831

Cc: Ms. Susan Jenney (Desk Copy)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-422/S-037

Bristol-Myers Squibb Company
Attention: Gerald DiDonato
Associate Director, Global Regulatory Affairs, CMC
P.O. Box 5400
Princeton, NJ 08540

Dear Mr. DiDonato:

Please refer to your supplemental new drug application dated October 27, 2006, received October 31, 2006, and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BiCNU® (carmustine) for Injection.

We also refer to your submissions dated April 18 and June 8, 2007.

We are reviewing the SPL section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application.

1. The Final Printed Labeling should reflect "BiCNU® (carmustine for injection)" and not (b) (4) (b) (4)" to in the heading of the package insert to be consistent with the rest of the labeling.
2. Please indicate that the product is co-packaged with a vial containing 10% ethyl alcohol in the DESCRIPTION section.
3. Please indicate that the product is sterile in the DESCRIPTION section, such as, "It is a sterile lyophilized pale yellow…"
4. Please change the dehydrated alcohol to list this formulation component from an "Active Moiety" to an inactive ingredient in the SPL labeling.

Specific questions concerning entering the SPL elements should be directed to SPL@FDA.HHS.GOV . If you have any other questions, call Susan Jenney, Regulatory Health Project Manager, at (301) 796-0062.

Sincerely,

{See appended electronic signature page}

Hasmukh B. Patel, Ph.D.
Branch Chief
Branch VIII, Division of Post-Marketing Evaluation
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Hasmukh Patel
8/7/2007 01:04:50 PM

Bristol-Myers Squibb
Pharmaceutical Research institute
P.O. Box 5400 Princeton, NJ 08543-5400

Chemistry, Manufacturing and Controls
Amendment to Prior Approval Supplement

NDA 17-422/S-037
BiCNU® (carmustine for injection), 100 mg/vial

August 14, 2007

Robert Justice, M.D., Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Justice:

Please reference our supplemental New Drug Application NDA 17-422/S-037 for BiCNU (carmustine for injection), 100 mg/Vial, dated October 27, 2006 to seek approval of an alternate manufacturing, quality control and stability test site for the alcohol diluent.

In response to a letter dated 8/7/07 from Hasmukh B. Patel, Ph.D., BMS is amending NDA 17-422/S-037 to provide clarifications and propose modifications to the SPL.

If you have any questions, please do not hesitate to contact me at (732) 227-5944.

Sincerely,

Michael J. Theil

Michael J. Theil
Group Manager
Global Regulatory Sciences - CMC
Tel: (732) 227-5944
FAX: (732) 227-3712

cc: Ms. Susan Jenney (Desk Copy)