

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***  
**ANDA 76-611**

***Name:*** Mitoxantrone Injection USP, (Concentrate), 2 mg/mL,  
packaged in 20 mg/10 mL, 25 mg/12.5 mL, and  
30 mg/15 mL Multiple-dose vials

***Sponsor:*** Bedford Laboratories

***Approval Date:*** April 11, 2006

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**ANDA 76-611**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 76-611**

**APPROVAL LETTER**

ANDA 76-611

APR 11 2006

Bedford Laboratories  
Attention: Molly Rapp  
Associate Director, Ben Venue Laboratories  
300 Northfield Road  
Bedford, OH 44146

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 26, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Mitoxantrone Injection USP, (Concentrate), 2 mg/mL, packaged in 20 mg/10 mL, 25 mg/12.5 mL, and 30 mg/15 mL Multiple-dose vials.

Reference is also made to the Tentative Approval letter issued by this office on February 19, 2004, and to your amendments dated August 27, 2004; and January 12, February 24, March 2, March 7, March 24, and March 28, 2006.

We have completed the review of this ANDA and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved. The Division of Bioequivalence has determined your Mitoxantrone Injection USP, (Concentrate), 2 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Novantrone Injection (Concentrate), 2 mg/mL, of Serono, Inc.).

The reference listed drug product (RLD) referenced in your application, Novantrone Injection (Concentrate), 2 mg/mL, of Serono, Inc. has been subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book" U.S. Patent No. 4,617,319 (the '319 patent) expired on June 13, 2005, and U.S. Patent No. 4,820,738 (the '738 patent) expired on April 11, 2006.

Your ANDA contains paragraph III certifications to each of the listed patents under section 505(j)(2)(A)(vii)(III) of the Act. These certifications state that Bedford Laboratories will not market Mitoxantrone Injection USP, (Concentrate), 2 mg/mL, under this ANDA prior to the expiration of both of the listed patents. Since each patent has expired, the agency is no longer precluded from approving your application.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA 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.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

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

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,



Gary Buehler 4/4/06  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

cc: ANDA 76-611  
Division File  
Field Copy  
HFD-610/R. West  
HFD-205  
HFD-610/Orange Book Staff

**Approved Electronic Labeling Located at:**

~~\\Cdse\subogd\76611\N000\2006-03-02\Labeling\MX0-P00.pdf~~

**Endorsements:**

HFD-620/K.Woodland/ *K.Woodland 3/31/06*  
HFD-620/R.Bykadi/ *R-Bykadi April 3, 2006*  
HFD-617/B.Danso/3-31-06 *BD 4/3/06*  
HFD-613/A.Payne/3-29-06 via email  
HFD-613/J.Grace/3-29-06 via email

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F/T by

**APPROVAL**

*Robert Bykadi*  
*4/4/2006*  
*TH → M*  
*PLANNED*  
*4/3/06*

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 76-611**

**TENTATIVE APPROVAL LETTER**

ANDA 76-611

FEB 19 2004

Bedford Laboratories  
Attention: Molly Rapp  
300 Northfield Road  
Bedford, OH 44146

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 26, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Mitoxantrone Injection USP, (Concentrate), 2 mg/mL, packaged in 20 mg/10 mL, 25 mg/12.5 mL and 30 mg/15 mL multiple-dose vials.

Reference is also made to your amendments dated July 3, August 5, September 3, October 9, October 28, November 20, December 1, and December 17, 2003; and January 13, 2004.

We have completed the review of this abbreviated application, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, final approval of your application is blocked at this time by patent protection as noted below. Therefore, your application is **tentatively approved**. This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, Novantrone Injection of Serono, Inc., is currently subject to periods of patent protection. As noted in the Agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", U.S. patent 4,617,319 (the '319 patent) is scheduled to expire on June 13, 2005, and U.S. patent 4,820,738 (the '738 patent) is

scheduled to expire on April 11, 2006. Your application contains a paragraph III certification to each patent under Section 505(j)(2)(A)(vii)(III) of the Act stating that you will not market this drug product prior to the expiration of each patent. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the '738 patent has expired, i.e., April 11, 2006.

In order to reactivate your application prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. An amendment should be submitted even if none of these changes were made. This submission should be designated clearly in your cover letter as a MINOR AMENDMENT-FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

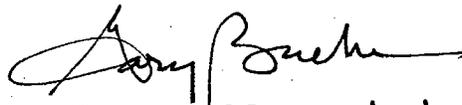
Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also delay the issuance of the final approval letter.

This drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Orange Book". Should you believe

that there are grounds for issuing the final approval letter prior to April 11, 2006, you should amend your application accordingly.

For further information on the status of your application, or prior to submitting your minor amendment to request final approval, please contact Wanda Pamphile, Pharm.D., Project Manager, at 301-827-5848, for further instructions.

Sincerely yours,



Gary Buehler 2/19/04  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

cc: ANDA 76-611  
Division File  
Field Copy  
HFD-610/R. West  
HFD-330  
HFD-205  
HFD-610/Orange Book Staff

Endorsements:

HFD-629/K.Woodland/ *K.Woodland 1/6/04 K.Woodland 1/21/04*  
HFD-625/S.Liu/ *S.H.Liu 1/6/04 S.H.Liu 1/11/04*  
HFD-617/W.Pamphile/ ~~WF~~ *1/6/04* ~~WF~~ *1/21/04*  
HFD-600/M.Stevens-Riley/ *Maia Stevens-Riley 1/6/04*  
HFD-600/N.Sweeney/ *N.Sweeney 1-6-04*  
HFD-613/A.Payne/ *A Payne 1/6/04*  
HFD-613/J.Grace/ *J Grace 1/2/2004*

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F/T by

TENTATIVE APPROVAL

*PS 1/21/04*

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 76-611**

**APPROVED LABELING**

**Rx ONLY**

**WARNING**

Mitoxantrone Injection USP should be administered under the supervision of a physician experienced in the use of cytotoxic chemotherapy agents.

Mitoxantrone should be given slowly into a freely flowing intravenous infusion. It must *never* be given subcutaneously, intramuscularly, or intra-arterially. Severe local tissue damage may occur if there is extravasation during administration. (See **ADVERSE REACTIONS, General, Cutaneous** and **DOSE AND ADMINISTRATION, Preparation and Administration Precautions**).

NOT FOR INTRATHECAL USE. Severe injury with permanent sequelae can result from intrathecal administration. (See **WARNINGS, General**).

Except for the treatment of acute nonlymphocytic leukemia, mitoxantrone therapy generally should not be given to patients with baseline neutrophil counts of less than 1,500 cells/mm<sup>3</sup>. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving mitoxantrone.

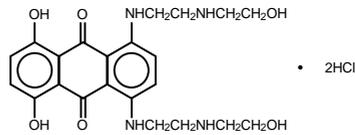
Use of mitoxantrone has been associated with cardiotoxicity. Cardiotoxicity can occur at any time during mitoxantrone therapy, and the risk increases with cumulative dose. Congestive heart failure (CHF), potentially fatal, may occur either during therapy with mitoxantrone or months to years after termination of therapy. All patients should be carefully assessed for cardiac signs and symptoms by history and physical examination prior to start of mitoxantrone therapy. Baseline evaluation of left ventricular ejection fraction (LVEF) by echocardiogram or multi-gated radionuclide angiography (MUGA) should be performed. In cancer patients, the risk of symptomatic congestive heart failure (CHF) was estimated to be 2.6% for patients receiving up to a cumulative dose of 140 mg/m<sup>2</sup>. Presence or history of cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, or concomitant use of other cardiotoxic drugs may increase the risk of cardiac toxicity. Cardiac toxicity with mitoxantrone may occur whether or not cardiac risk factors are present. For additional information, see **WARNINGS, Cardiac Effects**, and **DOSE AND ADMINISTRATION**.

Secondary acute myelogenous leukemia (AML) has been reported in cancer patients treated with mitoxantrone. In a cohort of mitoxantrone treated MS patients followed for varying periods of time, an elevated leukemia risk of 0.25% (2/802) has been observed. Postmarketing cases of secondary AML have also been reported. In 1774 patients with breast cancer who received mitoxantrone concomitantly with other cytotoxic agents and radiotherapy, the cumulative risk of developing treatment-related AML, was estimated as 1.1% and 1.6% at 5 and 10 years, respectively (see **WARNINGS**). Secondary acute myelogenous leukemia (AML) has been reported in cancer patients treated with anthracyclines. Mitoxantrone is an anthracenedione, a related drug.

The occurrence of refractory secondary leukemia is more common when anthracyclines are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated.

**DESCRIPTION**

Mitoxantrone hydrochloride is a synthetic antineoplastic anthracenedione for intravenous use. The molecular formula is C<sub>22</sub>H<sub>20</sub>N<sub>4</sub>O<sub>6</sub>·2HCl and the molecular weight is 517.40. It is supplied as a concentrate that MUST BE DILUTED PRIOR TO INJECTION. The concentrate is a sterile, nonpyrogenic, dark blue aqueous solution containing mitoxantrone hydrochloride equivalent to 2 mg/mL mitoxantrone free base, with sodium chloride (0.80% w/v), sodium acetate (0.005% w/v), glacial acetic acid (0.046% w/v), and water for injection as inactive ingredients. The solution has a pH of 3.0 to 4.5 and contains 0.14 mEq of sodium per mL. The product does not contain preservatives. The chemical name is 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]anthraquinone dihydrochloride and the structural formula is:



**CLINICAL PHARMACOLOGY**

**Mechanism of Action:** Mitoxantrone, a DNA-reactive agent that intercalates into deoxyribonucleic acid (DNA) through hydrogen bonding, causes crosslinks and strand breaks. Mitoxantrone also interferes with ribonucleic acid (RNA) and is a potent inhibitor of topoisomerase II, an enzyme responsible for uncoiling and repairing damaged DNA. It has a cytotoxic effect on both proliferating and nonproliferating cultured human cells, suggesting lack of cell cycle phase specificity.

Mitoxantrone has been shown *in vitro* to inhibit B cell, T cell, and macrophage proliferation and impair antigen presentation, as well as the secretion of interferon gamma, TNFα, and IL-2.

**Pharmacokinetics:** Pharmacokinetics of mitoxantrone in patients following a single intravenous administration of mitoxantrone can be characterized by a three-compartment model. The mean alpha half-life of mitoxantrone is 6 to 12 minutes, the mean beta half-life is 1.1 to 3.1 hours and the mean gamma (terminal or elimination) half-life is 23 to 215 hours (median approximately 75 hours). Pharmacokinetic studies have not been performed in humans receiving multiple daily dosing. Distribution to tissues is extensive: steady-state volume of distribution exceeds 1,000 L/m<sup>2</sup>. Tissue concentrations of mitoxantrone appear to exceed those in the blood during the terminal elimination phase. In the healthy monkey, distribution to brain, spinal cord, eye, and spinal fluid is low.

In patients administered 15 to 90 mg/m<sup>2</sup> of mitoxantrone intravenously, there is a linear relationship between dose and the area under the concentration-time curve (AUC).

Mitoxantrone is 78% bound to plasma proteins in the observed concentration range of 26 to 455 ng/mL. This binding is independent of concentration and is not affected by the presence of phenytoin, doxorubicin, methotrexate, prednisone, prednisolone, heparin, or aspirin.

**Metabolism and Elimination:** Mitoxantrone is excreted in urine and feces as either unchanged drug or as inactive metabolites. In human studies, 11% and 25% of the dose were recovered in urine and feces, respectively, as either parent drug or metabolite during the 5-day period following drug administration. Of the material recovered in urine, 65% was unchanged drug. The remaining 35% was composed of monocarboxylic and dicarboxylic acid derivatives and their glucuronide conjugates. The pathways leading to the metabolism of mitoxantrone have not been elucidated.

**Special Populations:**

*Gender* -The effect of gender on mitoxantrone pharmacokinetics is unknown.

*Geriatric* - In elderly patients with breast cancer, the systemic mitoxantrone clearance was 21.3 L/hr/m<sup>2</sup>, compared with 28.3 L/hr/m<sup>2</sup> and 16.2 L/hr/m<sup>2</sup> for non-elderly patients with nasopharyngeal carcinoma and malignant lymphoma, respectively.

*Pediatric* - Mitoxantrone pharmacokinetics in the pediatric population are unknown.

*Race* -The effect of race on mitoxantrone pharmacokinetics is unknown.

*Renal Impairment* - Mitoxantrone pharmacokinetics in patients with renal impairment are unknown.

*Hepatic Impairment* - Mitoxantrone clearance is reduced by hepatic impairment. Patients with severe hepatic dysfunction (bilirubin > 3.4 mg/dL) have an AUC more than three times greater than that of patients with normal hepatic function receiving the same dose. Patients with hepatic impairment should be treated with caution and dosage adjustment may be required.

**Drug Interactions:** *In vitro* drug interaction studies have demonstrated that mitoxantrone did not inhibit CYP450, 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 across a broad concentration range. The results of *in vitro* induction studies are inconclusive, but suggest that mitoxantrone may be a weak inducer of CYP450 2E1 activity.

Pharmacokinetic studies of the interaction of mitoxantrone with concomitantly administered medications in humans have not been performed. The pathways leading to the metabolism of mitoxantrone have not been elucidated. To date, post-marketing experience has not revealed any significant drug interactions in patients who have received mitoxantrone for treatment of cancer.

**CLINICAL TRIALS**

**Advanced Hormone-Refractory Prostate Cancer:** A multicenter Phase 2 trial of mitoxantrone and low-dose prednisone (M + P) was conducted in 27 symptomatic patients with hormone-refractory prostate cancer. Using NPCP (National Prostate Cancer Project) criteria for disease response, there was one partial responder and 12 patients with stable disease. However, nine patients or 33% achieved a palliative response defined on the basis of reduction in analgesic use or pain intensity.

These findings led to the initiation of a randomized multicenter trial (CCI-NOV22) comparing the effectiveness of (M + P) to low-dose prednisone alone (P). Eligible patients were required to have metastatic or locally advanced disease that had progressed on standard hormonal therapy, a castrate serum testosterone level, and at least mild pain at study entry. Mitoxantrone was administered at a dose of 12 mg/m<sup>2</sup> by short IV infusion every 3 weeks. Prednisone was administered orally at a dose of 5 mg twice a day. Patients randomized to the prednisone arm were crossed over to the M + P arm if they progressed or if they were not improved after a minimum of 6 weeks of therapy with prednisone alone.

A total of 161 patients were randomized, 80 to the M + P arm and 81 to the P arm. The median mitoxantrone dose administered was 12 mg/m<sup>2</sup> per cycle. The median cumulative mitoxantrone dose administered was 73 mg/m<sup>2</sup> (range of 12 to 212 mg/m<sup>2</sup>).

A primary palliative response (defined as a 2-point decrease in pain intensity in a 6-point pain scale, associated with stable analgesic use, and lasting a minimum of 6 weeks) was achieved in 29% of patients randomized to M + P compared to 12% of patients randomized to P alone (p = 0.011). Two responders left the study after meeting primary response criterion for two consecutive cycles. For the purposes of this analysis, these two patients were assigned a response duration of zero days. A secondary palliative response was defined as a 50% or greater decrease in analgesic use, associated with stable pain intensity, and lasting a minimum of 6 weeks. An overall palliative response (defined as primary plus secondary responses) was achieved in 38% of patients randomized to M + P compared to 21% of patients randomized to P (p = 0.025).

The median duration of primary palliative response for patients randomized to M + P was 7.6 months compared to 2.1 months for patients randomized to P alone (p = 0.0009). The median duration of overall palliative response for patients randomized to M + P was 5.6 months compared to 1.9 months for patients randomized to P alone (p = 0.0004).

Time to progression was defined as a 1-point increase in pain intensity, or a > 25% increase in analgesic use, or evidence of disease progression on radiographic studies, or requirement for radiotherapy. The median time to progression for all patients randomized to M + P was 4.4 months compared to 2.3 months for all patients randomized to P alone (p = 0.0001). Median time to death was 11.3 months for all patients on the M + P arm compared to 10.8 months for all patients on P alone (p = 0.2324).

Forty-eight patients on the P arm crossed over to receive M + P. Of these, thirty patients had progressed on P, while 18 had stable disease on P. The median cycle of crossover was 5 cycles (range of 2 to 16 cycles). Time trends for pain intensity prior to crossover were significantly worse for patients who crossed over than for those who remained on P alone (p = 0.012). Nine patients (19%) demonstrated a palliative response on M + P after crossover. The median time to death for patients who crossed over to M + P was 12.7 months.

The clinical significance of a fall in prostate-specific antigen (PSA) concentrations after chemotherapy is unclear. On the CCI-NOV22 trial, a PSA fall of 50% or greater for two consecutive follow-up assessments after baseline was reported in 33% of all patients randomized to the M + P arm and 9% of all patients randomized to the P arm. These findings should be interpreted with caution since PSA responses were not defined prospectively. A number of patients were inevaluable for response, and there was an imbalance between treatment arms in the numbers of evaluable patients. In addition, PSA reduction did not correlate precisely with palliative response, the primary efficacy endpoint of this study. For example, among the 26 evaluable patients randomized to the M + P arm who had a ≥ 50% reduction in PSA, only 13 had a primary palliative response. Also, among 42 evaluable patients on this arm who did not have this reduction in PSA, 8 nonetheless had a primary palliative response.

Investigators at Cancer and Leukemia Group B (CALGB) conducted a Phase 3 comparative trial of mitoxantrone plus hydrocortisone (M + H) versus hydrocortisone alone (H) in patients with hormone-refractory prostate cancer (CALGB 9182). Eligible patients were required to have metastatic disease that had progressed despite at least one hormonal therapy. Progression at study entry was defined on the basis of progressive symptoms, increases in measurable or osseous disease, or rising PSA levels. Mitoxantrone was administered intravenously at a dose of 14 mg/m<sup>2</sup> every 21 days and hydrocortisone was administered orally at a daily dose of 40 mg. A total of 242 subjects were randomized, 119 to the M + H arm and 123 to the H arm. There were no differences in survival between the two arms, with a median of 11.1 months in the M + H arm, and 12 months in the H arm (p = 0.3298).

Using NPCP criteria for response, partial responses were achieved in 10 patients (8.4%) randomized to the M + H arm compared with 2 patients (1.6%) randomized to the H arm (p = 0.018). The median time to progression, defined by NPCP criteria, for patients randomized to the M + H arm was 7.3 months compared to 4.1 months for patients randomized to H alone (p = 0.0654).

Approximately 60% of patients on each arm required analgesics at baseline. Analgesic use was measured in this study using a 5-point scale. The best percent change from baseline in mean analgesic use was -17% for 61 patients with available data on the M + H arm, compared with +17% for 61 patients on H alone (p = 0.014). A time trend analysis for analgesic use in individual patients also showed a trend favoring the M + H arm over H alone but was not statistically significant.

Pain intensity was measured using the Symptom Distress Scale (SDS) Pain Item 2 (a 5-point scale). The best percent change from baseline in mean pain intensity was -14% for 37 patients with available data on the M + H arm, compared with +8% for 38 patients on H alone (p = 0.057). A time trend analysis for pain intensity in individual patients showed no difference between treatment arms.

**Acute Nonlymphocytic Leukemia:** In two large randomized multicenter trials, remission induction therapy for acute nonlymphocytic leukemia (ANLL) with mitoxantrone 12 mg/m<sup>2</sup> daily for 3 days as a 10-minute intravenous infusion and cytarabine 100 mg/m<sup>2</sup> for 7 days given as a continuous 24-hour infusion was compared with daunorubicin 45 mg/m<sup>2</sup> daily by intravenous infusion for 3 days plus the same dose and schedule of cytarabine used with mitoxantrone. Patients who had an incomplete antileukemic response received a second induction course in which mitoxantrone or daunorubicin was administered for 2 days and cytarabine for 5 days using the same daily dosage schedule. Response rates and median survival information for both the U.S. and international multicenter trials are given in Table 1:

Trial	% Complete Response (CR)		Median Time to CR (days)		Survival (days)	
	MITO	DAUN	MITO	DAUN	MITO	DAUN
U.S.	63 (62/98)	53 (54/102)	35	42	312	237
International	50 (56/112)	51 (62/123)	36	42	192	230

MITO = mitoxantrone + cytarabine

DAUN = daunorubicin + cytarabine

In these studies, two consolidation courses were administered to complete responders on each arm. Consolidation therapy consisted of the same drug and daily dosage used for remission induction, but only 5 days of cytarabine and 2 days of mitoxantrone or daunorubicin were given. The first consolidation course was administered 6 weeks after the start of the final induction course if the patient achieved a complete remission. The second consolidation course was generally administered 4 weeks later. Full hematologic recovery was necessary for patients to receive consolidation therapy. For the U.S. trial, median granulocyte nadirs for patients receiving mitoxantrone + cytarabine for consolidation courses 1 and 2 were 10/mm<sup>3</sup> for both courses, and for those patients receiving daunorubicin + cytarabine nadirs were 170/mm<sup>3</sup> and 200/mm<sup>3</sup>, respectively. Median platelet nadirs for patients who received mitoxantrone + cytarabine for consolidation courses 1 and 2 were 17,000/mm<sup>3</sup> and 14,000/mm<sup>3</sup>, respectively, and were 33,000/mm<sup>3</sup> and 22,000/mm<sup>3</sup> in courses 1 and 2 for those patients who received daunorubicin + cytarabine. The benefit of consolidation therapy in ANLL patients who achieve a complete remission remains controversial. However, in the only well-controlled prospective, randomized multicenter trials with mitoxantrone in ANLL, consolidation therapy was given to all patients who achieved a complete remission. During consolidation in the U.S. study, two myelosuppression-related deaths occurred on the mitoxantrone arm and one on the daunorubicin arm. However, in the international study there were eight deaths on the mitoxantrone arm during consolidation which were related to the myelosuppression and none on the daunorubicin arm where less myelosuppression occurred.

**INDICATIONS AND USAGE**  
Mitoxantrone in combination with corticosteroids is indicated as initial chemotherapy for the treatment of patients with pain related to advanced hormone-refractory prostate cancer.

Mitoxantrone in combination with other approved drug(s) is indicated in the initial therapy of acute nonlymphocytic leukemia (ANLL) in adults. This category includes myelogenous, promyelocytic, monocytic, and erythroid acute leukemias.

**CONTRAINDICATIONS**

Mitoxantrone is contraindicated in patients who have demonstrated prior hypersensitivity to it.

**WARNINGS**

WHEN MITOXANTRONE IS USED IN HIGH DOSES (> 14 mg/m<sup>2</sup>d x 3 days) SUCH AS INDICATED FOR THE TREATMENT OF LEUKEMIA, SEVERE MYELOSUPPRESSION WILL OCCUR. THEREFORE, IT IS RECOMMENDED THAT MITOXANTRONE BE ADMINISTERED ONLY BY PHYSICIANS EXPERIENCED IN THE CHEMOTHERAPY OF THIS DISEASE. LABORATORY AND SUPPORTIVE SERVICES MUST BE AVAILABLE FOR HEMATOLOGIC AND CHEMISTRY MONITORING AND ADJUNCTIVE THERAPIES, INCLUDING ANTIBIOTICS. BLOOD AND BLOOD PRODUCTS MUST BE AVAILABLE TO SUPPORT PATIENTS DURING THE EXPECTED PERIOD OF MEDULLARY HYPOPLASIA AND SEVERE MYELOSUPPRESSION. PARTICULAR CARE SHOULD BE GIVEN TO ASSURING FULL HEMATOLOGIC RECOVERY BEFORE UNDERTAKING CONSOLIDATION THERAPY (IF THIS TREATMENT IS USED) AND PATIENTS SHOULD BE MONITORED CLOSELY DURING THIS PHASE. MITOXANTRONE ADMINISTERED AT ANY DOSE CAN CAUSE MYELOSUPPRESSION.

**General:** Patients with preexisting myelosuppression as the result of prior drug therapy should not receive mitoxantrone unless it is felt that the possible benefit from such treatment warrants the risk of further medullary suppression.

The safety of mitoxantrone injection in patients with hepatic insufficiency is not established (see **CLINICAL PHARMACOLOGY**). Safety for use by routes other than intravenous administration has not been established.

Mitoxantrone is not indicated for subcutaneous, intramuscular, or intra-arterial injection. There have been reports of local/regional neuropathy, some irreversible, following intra-arterial injection.

Mitoxantrone must not be given by intrathecal injection. There have been reports of neuropathy and neurotoxicity, both central and peripheral, following intrathecal injection. These reports have included seizures leading to coma and severe neurologic sequelae, and paralysis with bowel and bladder dysfunction.

Topoisomerase II inhibitors, including mitoxantrone, have been associated with the development of acute leukemia and myelodysplasia.

**Cardiac Effects:** Because of the possible danger of cardiac effects in patients previously treated with daunorubicin or doxorubicin, the benefit-to-risk ratio of mitoxantrone therapy in such patients should be determined before starting therapy.

Functional cardiac changes including decreases in left ventricular ejection fraction (LVEF) and irreversible congestive heart failure can occur with mitoxantrone. Cardiac toxicity may be more common in patients with prior treatment with anthracyclines, prior mediastinal radiotherapy, or with preexisting cardiovascular disease. Such patients should have regular cardiac monitoring of LVEF from the initiation of therapy. Cancer patients who received cumulative doses of 140 mg/m<sup>2</sup> either alone or in combination with other chemotherapeutic agents had a cumulative 2.6% probability of clinical congestive heart failure. In comparative oncology trials, the overall cumulative probability rate of moderate or severe decreases in LVEF at this dose was 13%.

*Leukemia* - Acute congestive heart failure may occasionally occur in patients treated with mitoxantrone for ANLL. In first-line comparative trials of mitoxantrone + cytarabine vs daunorubicin + cytarabine in adult patients with previously untreated ANLL, therapy was associated with congestive heart failure in 6.5% of patients on each arm. A causal relationship between drug therapy and cardiac effects is difficult to establish in this setting since myocardial function is frequently depressed by the anemia, fever and infection, and hemorrhage that often accompany the underlying disease.

*Hormone-Refractory Prostate Cancer* - Functional cardiac changes such as decreases in LVEF and congestive heart failure may occur in patients with hormone-refractory prostate cancer treated with mitoxantrone. In a randomized comparative trial of mitoxantrone plus low-dose prednisone vs low-dose prednisone, 7 of 128 patients (5.5%) treated with mitoxantrone had a cardiac event defined as any decrease in LVEF below the normal range, congestive heart failure (n = 3), or myocardial ischemia. Two patients had a prior history of cardiac disease. The total mitoxantrone dose administered to patients with cardiac effects ranged from > 48 to 212 mg/m<sup>2</sup>. Among 112 patients evaluable for safety on the mitoxantrone + hydrocortisone arm of the CALGB trial, 18 patients (19%) had a reduction in cardiac function, 5 patients (5%) had cardiac ischemia, and 2 patients (2%) experienced pulmonary edema. The range of total mitoxantrone doses administered to these patients is not available.

**Pregnancy:** Mitoxantrone may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant. Mitoxantrone is considered a potential human teratogen because of its mechanism of action and the developmental effects demonstrated by related agents. Treatment of pregnant rats during the organogenesis period of gestation was associated with fetal growth retardation at doses ≥0.1 mg/kg/day (0.01 times the recommended human dose on a mg/m<sup>2</sup> basis). When pregnant rabbits were treated during organogenesis, an increased incidence of premature delivery was observed at doses ≥0.1 mg/kg/day (0.01 times the recommended human dose on a mg/m<sup>2</sup> basis). No teratogenic effects were observed in these studies, but the maximum doses tested were well below the recommended human dose (0.02 and 0.05 times in rats and rabbits, respectively, on a mg/m<sup>2</sup> basis). 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 this drug, the patient should be apprised of the potential risk to the fetus.

**Secondary Leukemia:** Secondary leukemia has been reported in cancer patients treated with mitoxantrone. The largest published report involved 1774 patients with breast cancer treated with mitoxantrone in combination with methotrexate with or without mitomycin. In this study, the cumulative probability of developing secondary leukemia was estimated to be 1.1% and 1.6% at 5 and 10 years, respectively. The second largest report involved 449 patients with breast cancer treated with mitoxantrone, usually in combination with radiotherapy and/or other cytotoxic agents. In this study, the cumulative probability of developing secondary leukemia was estimated to be 2.2% at 4 years.

Secondary AML has also been reported in cancer patients treated with anthracyclines. Mitoxantrone is an anthracenedione, a related drug. The occurrence of refractory secondary leukemia is more common when anthracyclines are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated.

**PRECAUTIONS**

**General:** Therapy with mitoxantrone should be accompanied by close and frequent monitoring of hematologic and chemical laboratory parameters, as well as frequent patient observation.

Systemic infections should be treated concomitantly with or just prior to commencing therapy with mitoxantrone.

**Information for Patients:** Mitoxantrone may impart a blue-green color to the urine for 24 hours after administration, and patients should be advised to expect this during therapy. Bluish discoloration of the sclera may also occur. Patients should be advised of the signs and symptoms of myelosuppression.

**Laboratory Tests:** A complete blood count, including platelets, should be obtained prior to each course of mitoxantrone and in the event that signs and symptoms of infection develop. Liver function tests should also be performed prior to each course of therapy. In leukemia treatment, hyperuricemia may occur as a result of rapid lysis of tumor cells by mitoxantrone. Serum uric acid levels should be monitored and hypouricemic therapy instituted prior to the initiation of antileukemic therapy.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:**

*Carcinogenesis* - Intravenous treatment of rats and mice, once every 21 days for 24 months, with mitoxantrone resulted in an increased incidence of fibroma and external auditory canal tumors in rats at a dose of 0.03 mg/kg (0.02 fold the recommended human dose, on a mg/m<sup>2</sup> basis), and hepatocellular adenoma in male mice at a dose of 0.1 mg/kg (0.03 fold the recommended human dose, on a mg/m<sup>2</sup> basis). Intravenous treatment of rats, once every 21 days for 12 months with mitoxantrone resulted in an increased incidence of external auditory canal tumors in rats at a dose of 0.3 mg/kg (0.15 fold the recommended human dose, on a mg/m<sup>2</sup> basis).

*Mutagenesis* - Mitoxantrone was clastogenic in the *in vivo* rat bone marrow assay. Mitoxantrone was also clastogenic in two *in vitro* assays, it induced DNA damage in primary rat hepatocytes and sister chromatid exchanges in Chinese hamster ovary cells. Mitoxantrone was mutagenic in bacterial and mammalian test systems (Ames/Salmonella and *E. coli* and L5176Y TK+/-mouse lymphoma).



**Drug Interactions:** Mitoxantrone and its metabolites are excreted in bile and urine, but it is not known whether the metabolic or excretory pathways are saturable, may be inhibited or induced, or if mitoxantrone and its metabolites undergo enterohepatic circulation. To date, post-marketing experience has not revealed any significant drug interactions in patients who have received mitoxantrone for treatment of cancer.

Following concurrent administration of mitoxantrone with corticosteroids, no evidence of drug interactions has been observed.

**Special Populations:**

**Hepatic Impairment** - Mitoxantrone should be administered with caution to patients with hepatic impairment. In patients with severe hepatic impairment, the AUC is more than three times greater than the value observed in patients with normal hepatic function.

**Pregnancy: Teratogenic Effects; Pregnancy Category D** (see **WARNINGS**).

**Nursing Mothers:** Mitoxantrone is excreted in human milk and significant concentrations (18 ng/mL) have been reported for 28 days after the last administration. Because of the potential for serious adverse reactions in infants from mitoxantrone, breast feeding should be discontinued before starting treatment.

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

**Geriatric Use:**

**Hormone-Refractory Prostate Cancer** – One hundred forty-six patients aged 65 and over and 52 younger patients (<65 years) have been treated with mitoxantrone in controlled clinical studies. These studies did not include sufficient numbers of younger patients to determine whether they respond differently from older patients. However, greater sensitivity of some older individuals cannot be ruled out.

**Acute Nonlymphocytic Leukemia** – Although definitive studies with mitoxantrone have not been performed in geriatric patients with ANLL, toxicity may be more frequent in the elderly. Elderly patients are more likely to have age-related comorbidities due to disease or disease therapy.

**ADVERSE REACTIONS**

**Leukemia:** Mitoxantrone has been studied in approximately 600 patients with ANLL. Table 2 represents the adverse reaction experience in the large U.S. comparative study of mitoxantrone + cytarabine vs daunorubicin + cytarabine. Experience in the large international study was similar. A much wider experience in a variety of other tumor types revealed no additional important reactions other than cardiomyopathy (see **WARNINGS**). It should be appreciated that the listed adverse reaction categories include overlapping clinical symptoms related to the same condition, e.g., dyspnea, cough and pneumonia. In addition, the listed adverse reactions cannot all necessarily be attributed to chemotherapy as it is often impossible to distinguish effects of the drug and effects of the underlying disease. It is clear, however, that the combination of mitoxantrone + cytarabine was responsible for nausea and vomiting, alopecia, mucositis/stomatitis, and myelosuppression.

Table 2 summarizes adverse reactions occurring in patients treated with mitoxantrone + cytarabine in comparison with those who received daunorubicin + cytarabine for therapy of ANLL in a large multicenter randomized prospective U.S. trial. Adverse reactions are presented as major categories and selected examples of clinically significant subcategories.

**Table 2**

Event	Adverse Events Occurring in ANLL Patients Receiving Mitoxantrone or Daunorubicin			
	Induction		Consolidation	
	[%pts entering induction]		[%pts entering induction]	
	MITO N=102	DAUN N=102	MITO N=55	DAUN N=49
Cardiovascular	26	28	11	24
CHF	5	6	0	0
Arrhythmias	3	3	0	4
Bleeding	37	41	20	6
GI	16	12	2	2
Petechiae/ecchymoses	7	9	11	2
Gastrointestinal	88	85	58	51
Nausea/vomiting	72	67	31	31
Diarrhea	47	47	18	8
Abdominal pain	15	9	9	4
Mucositis/stomatitis	29	33	18	8
Hepatic	10	11	14	2
Jaundice	3	8	7	0
Infections	66	73	60	43
UTI	7	2	7	2
Pneumonia	9	7	9	0
Sepsis	34	36	31	18
Fungal infections	15	13	9	6
Renal failure	8	6	0	2
Fever	78	71	24	18
Alopecia	47	40	22	16
Pulmonary	43	43	24	14
Cough	13	9	9	2
Dyspnea	18	20	6	0
CNS	30	30	34	35
Seizures	4	4	2	8
Headache	10	9	13	8
Eye	7	6	2	4
Conjunctivitis	5	1	0	0

MITO = mitoxantrone, DAUN = daunorubicin

**Hormone-Refractory Prostate Cancer:** Detailed safety information is available for a total of 353 patients with hormone-refractory prostate cancer treated with mitoxantrone, including 274 patients who received mitoxantrone in combination with corticosteroids.

Table 3 summarizes adverse reactions of all grades occurring in ≥ 5% of patients in Trial CCI-NOV22.

**Table 3**

Event	Adverse Events of Any Intensity Occurring in ≥ 5% of Patients Trial CCI-NOV22				
	M + P (n=80) %	P (n=81) %	Event	M + P (n=80) %	P (n=81) %
Nausea	61	35	Emesis	9	5
Fatigue	39	14	Pain	8	9
Alopecia	29	0	Fever	6	3
Anorexia	25	6	Hemorrhage/bruise	6	1
Constipation	16	14	Anemia	5	3
Dyspnea	11	5	Cough	5	0
Nail bed changes	11	0	Decreased LVEF	5	0
Edema	10	4	Anxiety/depression	5	3
Systemic infection	10	7	Dyspepsia	5	6
Mucositis	10	0	Skin infection	5	3
UTI	9	4	Blurred vision	3	5

M = mitoxantrone, P = prednisolone

No nonhematologic adverse events of Grade 3/4 were seen in ≥ 5% of patients.

Table 4 summarizes adverse events of all grades occurring in ≥ 5% of patients in Trial CALGB 9182.

**Table 4**  
**Adverse Events of Any Intensity Occurring in ≥5% of Patients Trial CALGB 9182**

Event	M + H (n =112)		H (n = 113)	
	n	%	n	%
Decreased WBC	96	87	4	4
Granulocytes/bands	88	79	3	3
Decreased hemoglobin	83	75	42	39
Lymphocytes	78	72	27	25
Pain	45	41	44	39
Platelets	43	39	8	7
Alkaline Phosphatase	41	37	42	38
Malaise/fatigue	37	34	16	14
Hyperglycemia	33	31	32	30
Edema	31	30	15	14
Nausea	28	26	9	8
Anorexia	24	22	16	14
BUN	24	22	22	20
Transaminase	22	20	16	14
Alopecia	20	20	1	1
Cardiac function	19	18	0	0
Infection	18	17	4	4
Weight loss	18	17	13	12
Dyspnea	16	15	9	8
Diarrhea	16	14	4	4
Fever in absence of infection	15	14	7	6
Weight gain	15	14	16	15
Creatinine	14	13	11	10
Other gastrointestinal	13	14	11	11
Vomiting	12	11	6	5
Other neurologic	11	11	5	5
Hypocalcemia	10	10	5	5
Hematuria	9	11	5	6
Hyponatremia	9	9	3	3
Sweats	9	9	2	2
Other liver	8	8	8	8
Stomatitis	8	8	1	1
Cardiac dysrhythmia	7	7	3	3
Hypokalemia	7	7	4	4
Neuro/constipation	7	7	2	2
Neuro/motor	7	7	3	3
Neuro/mood	6	6	2	2
Skin	6	6	4	4
Cardiac ischemia	5	5	1	1
Chills	5	5	0	0
Hemorrhage	5	5	3	3
Myalgias/arthralgias	5	5	3	3
Other kidney/bladder	5	5	3	3
Other endocrine	5	6	3	4
Other pulmonary	5	5	3	3
Hypertension	4	4	5	5
Impotence/libido	4	7	2	3
Proteinuria	4	6	2	3
Sterility	3	5	2	3

M = mitoxantrone, H= hydrocortisone

**General:**

**Allergic Reaction** - Hypotension, urticaria, dyspnea, and rashes have been reported occasionally.

Anaphylaxis/anaphylactoid reactions have been reported rarely.

**Cutaneous** - Extravasation at the infusion site has been reported, which may result in erythema, swelling, pain, burning, and/or blue discoloration of the skin. Extravasation can result in tissue necrosis with resultant need for debridement and skin grafting. Phlebitis has also been reported at the site of the infusion.

**Hematologic** - Topoisomerase II inhibitors, including mitoxantrone, in combination with other antineoplastic agents, have been associated with the development of acute leukemia (see **WARNINGS**).

**Leukemia** - Myelosuppression is rapid in onset and is consistent with the requirement to produce significant marrow hypoplasia in order to achieve a response in acute leukemia. The incidences of infection and bleeding seen in the U.S. trial are consistent with those reported for other standard induction regimens.

**Hormone-Refractory Prostate Cancer** - In a randomized study where dose escalation was required for neutrophil counts greater than 1000/mm<sup>3</sup>, Grade 4 neutropenia (ANC < 500 /mm<sup>3</sup>) was observed in 54% of patients treated with mitoxantrone + low-dose prednisone. In a separate randomized trial where patients were treated with 14 mg/m<sup>2</sup>, Grade 4 neutropenia in 23% of patients treated with mitoxantrone + hydrocortisone was observed. Neutropenic fever/infection occurred in 11% and 10% of patients receiving mitoxantrone + corticosteroids, respectively, on the two trials. Platelets <50,000/mm<sup>3</sup> were noted in 4% and 3% of patients receiving mitoxantrone + corticosteroids on these trials, and there was one patient death on mitoxantrone + hydrocortisone due to intracranial hemorrhage after a fall.

**Gastrointestinal** - Nausea and vomiting occurred acutely in most patients and may have contributed to reports of dehydration, but were generally mild to moderate and could be controlled through the use of antiemetics. Stomatitis/mucositis occurred within 1 week of therapy.

**Cardiovascular** - Congestive heart failure, tachycardia, EKG changes including arrhythmias, chest pain, and asymptomatic decreases in left ventricular ejection fraction have occurred. (See **WARNINGS**.)

**Pulmonary** - Interstitial pneumonitis has been reported in cancer patients receiving combination chemotherapy that included mitoxantrone.

**OVERDOSAGE**

There is no known specific antidote for mitoxantrone. Accidental overdoses have been reported. Four patients receiving 140 to 180 mg/m<sup>2</sup> as a single bolus injection died as a result of severe leukopenia with infection. Hematologic support and antimicrobial therapy may be required during prolonged periods of severe myelosuppression.

Although patients with severe renal failure have not been studied, mitoxantrone is extensively tissue bound and it is unlikely that the therapeutic effect or toxicity would be mitigated by peritoneal or hemodialysis.

**DOSAGE AND ADMINISTRATION**

(See also **WARNINGS**.)

**Hormone-Refractory Prostate Cancer:** Based on data from two Phase 3 comparative trials of mitoxantrone plus corticosteroids versus corticosteroids alone, the recommended dosage of mitoxantrone is 12 to 14 mg/m<sup>2</sup> given as a short intravenous infusion every 21 days.

**Combination Initial Therapy for ANLL in Adults:** For induction, the recommended dosage is 12 mg/m<sup>2</sup> of mitoxantrone daily on Days 1 to 3 given as an intravenous infusion, and 100 mg/m<sup>2</sup> of cytarabine for 7 days given as a continuous 24-hour infusion on Days 1 to 7. Most complete remissions will occur following the initial course of induction therapy. In the event of an incomplete antileukemic response, a second induction course may be given. Mitoxantrone should be given for 2 days and cytarabine for 5 days using the same daily dosage levels.

If severe or life-threatening nonhematologic toxicity is observed during the first induction course, the second induction course should be withheld until toxicity resolves.

Consolidation therapy which was used in two large randomized multicenter trials consisted of mitoxantrone, 12 mg/m<sup>2</sup> given by intravenous infusion daily on Days 1 and 2 and cytarabine, 100 mg/m<sup>2</sup> for 5 days given as a continuous 24-hour infusion on Days 1 to 5. The first course was given approximately 6 weeks after the final induction course, the second was generally administered 4 weeks after the first. Severe myelosuppression occurred. (See **CLINICAL PHARMACOLOGY**.)

**Hepatic Impairment:** For patients with hepatic impairment, there is at present no laboratory measurement that allows for dose adjustment recommendations. (See **CLINICAL PHARMACOLOGY, Special Populations, Hepatic Impairment**.)

**Preparation and Administration Precautions:**

**MITOXANTRONE INJECTION MUST BE DILUTED PRIOR TO USE.**

The dose of mitoxantrone should be diluted to at least 50 mL with either 0.9% Sodium Chloride Injection or 5% Dextrose Injection. Mitoxantrone may be further diluted into Dextrose 5% in Water, Normal Saline or Dextrose 5% with Normal Saline and used immediately. DO NOT FREEZE.

Mitoxantrone should not be mixed in the same infusion as heparin since a precipitate may form. Because specific compatibility data are not available, it is recommended that mitoxantrone not be mixed in the same infusion with other drugs. The diluted solution should be introduced slowly into the tubing as a freely running intravenous infusion of 0.9% Sodium Chloride Injection or 5% Dextrose Injection over a period of not less than 3 minutes. Unused infusion solutions should be discarded immediately in an appropriate fashion. In the case of multidose use, after penetration of the stopper, the remaining portion of the undiluted mitoxantrone injection should be stored not longer than 7 days between 15° to 25°C (59° to 77°F) or 14 days under refrigeration. DO NOT FREEZE. CONTAINS NO PRESERVATIVE.

Care in the administration of mitoxantrone will reduce the chance of extravasation. Mitoxantrone should be administered into the tubing of a freely running intravenous infusion of sodium chloride injection (0.9%) or 5% dextrose injection. The tubing should be attached to a Butterfly needle or other suitable device and inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. Care should be taken to avoid extravasation at the infusion site and to avoid contact of mitoxantrone with the skin, mucous membranes or eyes. MITOXANTRONE SHOULD NOT BE ADMINISTERED SUBCUTANEOUSLY. If any signs or symptoms of extravasation have occurred, including burning, pain, pruritis, erythema, swelling, blue discoloration, or ulceration, the injection or infusion should be immediately terminated and restarted in another vein. During intravenous administration of mitoxantrone extravasation may occur with or without an accompanying stinging or burning sensation even if blood returns well on aspiration of the infusion needle. If it is known or suspected that subcutaneous extravasation has occurred, it is recommended that intermittent ice packs be placed over the area of extravasation and that the affected extremity be elevated. Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and surgery consultation obtained early if there is any sign of a local reaction.

Skin accidentally exposed to mitoxantrone should be rinsed copiously with warm water and if the eyes are involved, standard irrigation techniques should be used immediately. The use of goggles, gloves, and protective gowns is recommended during preparation and administration of the drug.

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

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

**HOW SUPPLIED**

Mitoxantrone Injection USP is a sterile aqueous solution containing mitoxantrone hydrochloride at a concentration equivalent to 2 mg mitoxantrone free base per mL supplied in vials for multidose use as follows:

- NDC 55390-083-01**; 10 mL/multidose vial (20 mg); individually-boxed
- NDC 55390-084-01**; 12.5 mL/multidose vial (25 mg); individually-boxed
- NDC 55390-085-01**; 15 mL/multidose vial (30 mg); individually-boxed

Store between 15° to 25°C (59° to 77°F). DO NOT FREEZE.

**REFERENCES**

- Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
- AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. JAMA 1985;253:1590.
- 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.
- Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. Med J Australia 1983; 1:426.
- Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. CA Cancer J Clin 1983; 33:258.
- American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic and hazardous drugs. Am J Hosp Pharm 1990; 47:1033.
- Controlling occupational exposure to hazardous drugs. Am J Health-System Pharm 1996; 53:1669.

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Ben Venue Laboratories, Inc.  
Bedford, OH 44146  
January 2006

Manufactured for:  
Bedford Laboratories™  
Bedford, OH 44146

MXO-P00

Note: Keyline does not print

<p><b>MitoXANTRONE</b> <b>Injection USP</b> <b>(Concentrate)</b></p> <p><b>FOR IV INFUSION</b> <b>AFTER DILUTION</b></p> <p><b>20 mg/10 mL</b></p> <p>2 mg/mL in 10 mL Rx ONLY</p>	<p>NDC 55390-083-01 10 mL Sterile <b>MULTIDOSE</b> Vial Usual Dosage: See package insert. Each mL contains mitoxantrone HCl equivalent to 2 mg mitoxantrone free base.</p> <p>Store between 15° to 25°C (59° to 77°F). <b>DO NOT FREEZE.</b> CONTAINS NO PRESERVATIVE.</p> <p>Manufactured for: Bedford Laboratories™ Bedford, OH 44146</p> <p><b>MXO-V01</b></p>	<p>Non-Varnish Window / TTC Coating</p>
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<b>WTP Proofread:</b>	/	<input checked="" type="checkbox"/> PMS 1805 Red	<input type="checkbox"/> TTC Coating	

Note: Keyline does not print

<b>MitoXANTRONE Injection USP (Concentrate)</b>	NDC 55390-084-01 12.5 mL Sterile <b>MULTIDOSE</b> Vial Usual Dosage: See package insert. Each mL contains mitoxantrone HCl equivalent to 2 mg mitoxantrone free base. Store between 15° to 25°C (59° to 77°F). <b>DO NOT FREEZE.</b> CONTAINS NO PRESERVATIVE. Manufactured for: Bedford Laboratories™ Bedford, OH 44146 <b>MXO-VA01</b>	Non-Varnish Window / TTC Coating
FOR IV INFUSION AFTER DILUTION <div style="background-color: #800040; color: white; padding: 2px; display: inline-block; margin: 5px 0;"> <b>25 mg/12.5 mL</b> </div> Cytotoxic Agent 2 mg/mL in 12.5 mL <b>Rx ONLY</b>		

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Note: Keyline does not print.

**MitoXANTRONE  
Injection USP  
(Concentrate)**

FOR IV INFUSION  
AFTER DILUTION

**30 mg/15 mL**

Cytotoxic Agent  
2 mg/mL in 15 mL  
Rx ONLY

NDC 55390-085-01

15 mL Sterile **MULTIDOSE** Vial

Usual Dosage: See package insert.

Each mL contains mitoxantrone HCl  
equivalent to 2 mg mitoxantrone  
free base.

Store between 15° to 25°C (59° to  
77°F). **DO NOT FREEZE.**

CONTAINS NO PRESERVATIVE.

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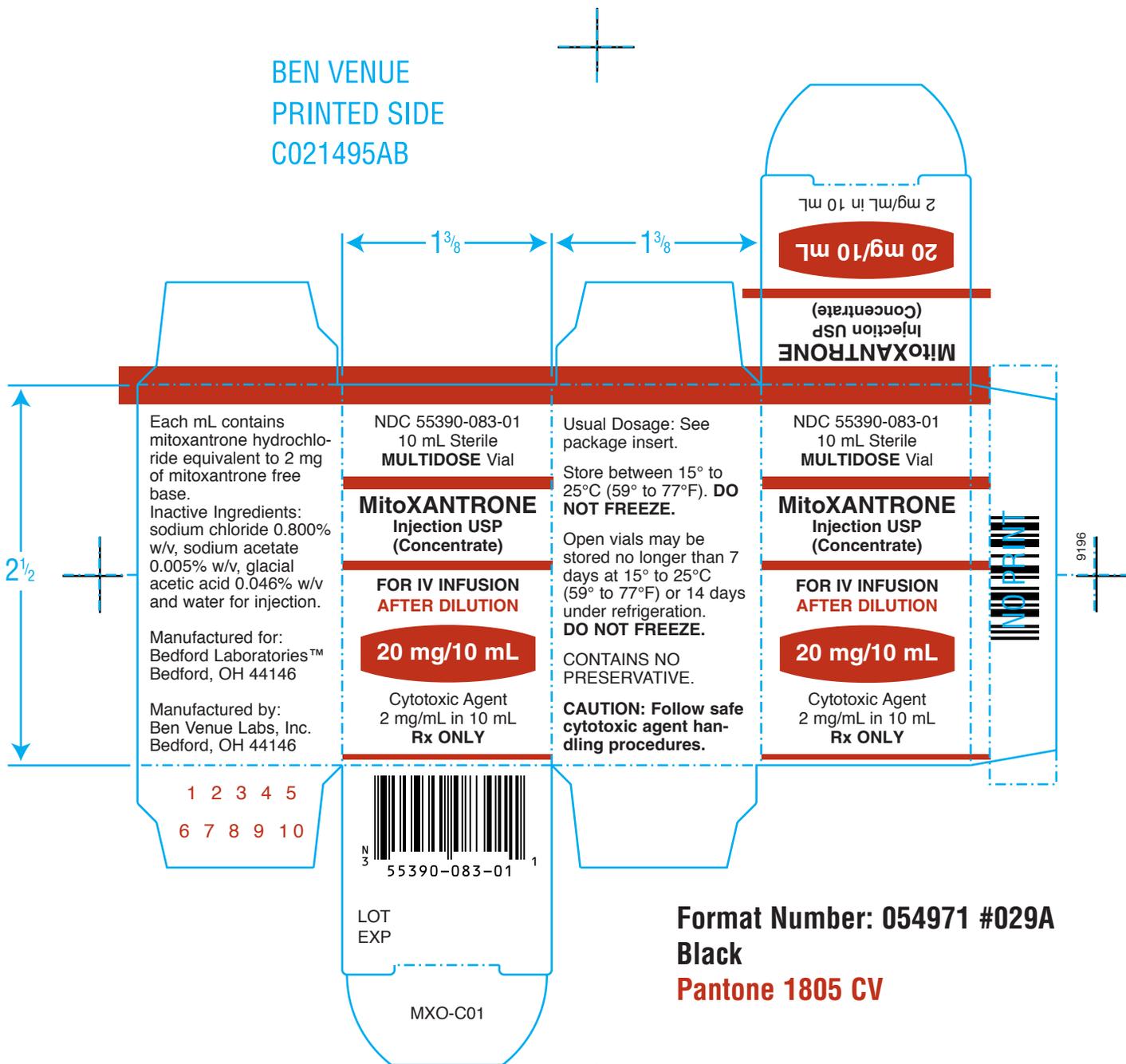
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**MXO-VB01**

Non-Varnish Window /  
TTC Coating

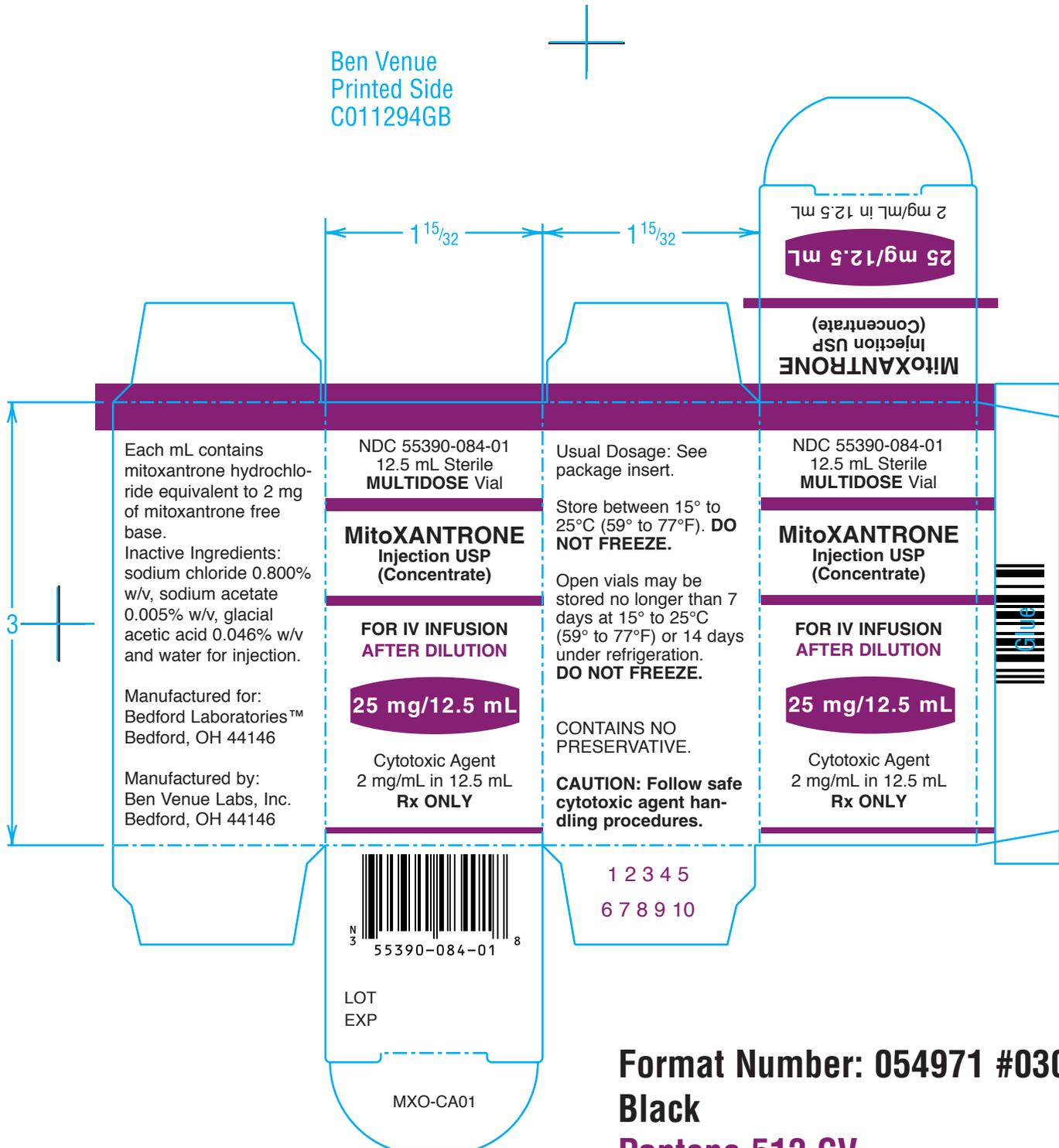
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<b>WTP Proofread:</b>	/	<input checked="" type="checkbox"/> PMS 145 Orange	<input type="checkbox"/> TTC Coating	

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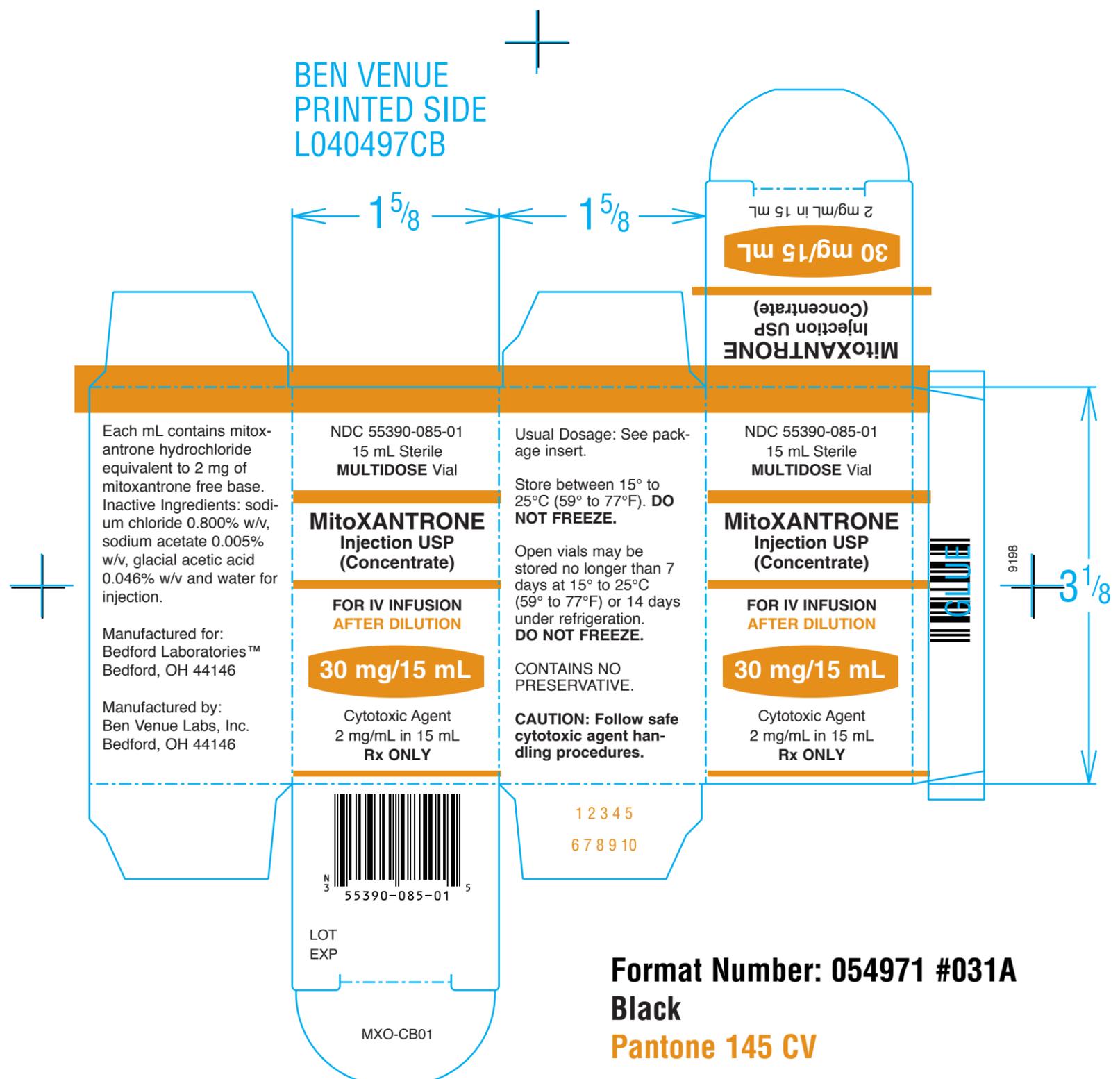
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**Format Number: 054971 #030A**  
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**Pantone 512 CV**

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Each mL contains mitoxantrone hydrochloride equivalent to 2 mg of mitoxantrone free base. Inactive Ingredients: sodium chloride 0.800% w/v, sodium acetate 0.005% w/v, glacial acetic acid 0.046% w/v and water for injection.

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NDC 55390-085-01  
15 mL Sterile  
**MULTIDOSE Vial**

**MitoXANTRONE**  
Injection USP  
(Concentrate)

**FOR IV INFUSION**  
**AFTER DILUTION**

**30 mg/15 mL**

Cytotoxic Agent  
2 mg/mL in 15 mL  
**Rx ONLY**

Usual Dosage: See package insert.

Store between 15° to 25°C (59° to 77°F). **DO NOT FREEZE.**

Open vials may be stored no longer than 7 days at 15° to 25°C (59° to 77°F) or 14 days under refrigeration. **DO NOT FREEZE.**

CONTAINS NO PRESERVATIVE.

**CAUTION: Follow safe cytotoxic agent handling procedures.**

NDC 55390-085-01  
15 mL Sterile  
**MULTIDOSE Vial**

**MitoXANTRONE**  
Injection USP  
(Concentrate)

**FOR IV INFUSION**  
**AFTER DILUTION**

**30 mg/15 mL**

Cytotoxic Agent  
2 mg/mL in 15 mL  
**Rx ONLY**

LOT  
EXP

55390-085-01

MXO-CB01

1 2 3 4 5  
6 7 8 9 10

**Format Number: 054971 #031A**  
**Black**  
**Pantone 145 CV**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 76-611**

**LABELING REVIEW(S)**

**REVIEW OF PROFESSIONAL LABELING #1  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

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ANDA Number: **76-611**

Dates of Submission: December 26, 2002 (original)

Applicant's Name: Bedford Laboratories

Established Name: Mitoxantrone Injection USP, 2 mg/mL; 10 mL, 12.5 mL and 15 mL MDV vials

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Labeling Deficiencies:

**1. CONTAINER** (2 mg/mL: 10 mL, 12.5 mL and 15 mL):

- a. Add an "Each mL contains Mitoxantrone HCl equivalent to 2 mg Mitoxantrone free base.
- b. If space permits add "cytotoxic agent".
- c. Add, "(concentrate)" to the main panel. This word is seen on the reference listed drug labels and would give added emphasis that this product **must** be diluted before injection.

**2. CARTON** (1s: 20 mg/10mL; 25 mg/12.5 mL or 30 mg/15 mL): - See comments under Container.

**3. INSERT:**

a. GENERAL COMMENT

Please be advise that your proposed labeling will need to be revised according to the most recently approved labeling for Novantrone Injection (Mitoxantrone HCl; NDA 19-297/S-027; Approved 1/13/03; Serono, Inc). The current label for this drug product is not available in electronic format from FDA. To obtain a current label, please contact the Company, We note the revised RLD labeling is not available to our office at this time. Review of your proposed labeling is pending.

b. DESCRIPTION

"Acetic acid" should be replace by the proper USP name which is Glacial Acetic Acid' and sterile water, USP should be added as an inactive ingredient to be consistent with your component/composition statement.

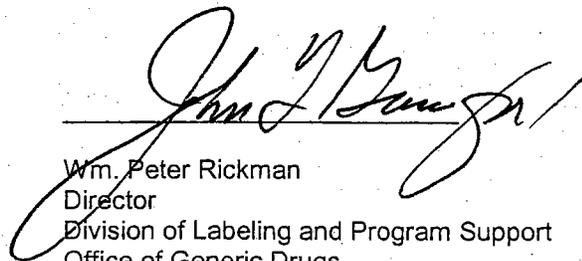
**4. PATIENT INFORMATION SHEET** - See comments under INSERT.

Please revise your labels and labeling, as instructed above, and submit in final print container labels and draft patient and insert labeling.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

<http://www.fda.gov/cder/cdernew/listserv.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 the most recent Novantrone labeling with all differences annotated and explained.

A handwritten signature in black ink, appearing to read "Wm. Peter Rickman", is written over a horizontal line. The signature is cursive and somewhat stylized.

Wm. Peter Rickman  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**APPEARS THIS WAY  
ON ORIGINAL**

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

ANDA Number	76-611
Date of Submission	
Applicant	Bed ford
Drug Name	Mitoxantrone Injection USP
Strength(s)	2 mg/mL/ 10 mL, 12.5 mL and 15 mL vials

FPL Approval Summary

Container Labels	XXXXXXXX	Submitted vol XX
Package Insert Labeling Patient leaflet	#XXXXRev.	vol XX

BASIS OF APPROVAL:

Patent Data For NDA 19-297

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019297	001	4617319	JUN 13,2005	U-390
019297	001	4820738	APR 11,2006	U-98

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
019297	001	ODE	NOV 13,2003
019297	001	I-324	OCT 13,2003
019297	001	ODE	OCT 13,2007

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4617319	JUN 13,2005	u-390	METHOD OF USING THE DRUG TO TREAT NEUROIMMUNOLOGIC DISEASES (INCLUDING MULTIPLE SCLEROSIS)	PIII	Same as
4820738	APR 11,2006	u-98	A METHOD OF INDUCING REGRESSION OF LEUKEMIA CELL GROWTH IN A MAMMAL	PIII	Same as



REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. <b>USP 24</b>	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
<i>PACKAGING</i> -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
<i>LABELING</i>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	

Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
<b>Scoring:</b> Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
<b>Inactive Ingredients:</b> (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?			X
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
<b>USP Issues:</b> (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
<b>Bioequivalence Issues:</b> (Compare bioequivalency values; insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
<b>Patent/Exclusivity Issues:</b> FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. <b>NONE</b>			

**NOTE TO CHEMIST:**

**FOR THE RECORD:**

1. MODEL LABELING

This review was based on the labeling

2. PATENTS/EXCLUSIVITIES: See above

[Vol. A1.1 pg. 5]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Bedford laboratories, 270 Irthfield Rd. Bedford, Ohio, 44146

[Vol. A1.1 page 163]

4. CONTAINER/CLOSURE

RLD:

ANDA: Type I Glass Container, stopper and flip off Seal

[Vol. A1.2 pg. 817-820]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.1 pg. 114]

6. PACKAGING CONFIGURATIONS

RLD: 2 mg/mL/ 10 mL, 12.5 mL and 15 mL vials

ANDA: 2 mg/mL/ 10 mL, 12.5 mL and 15 mL vials

[Vol. ]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP:

RLD: store between CRT 15° - 30°C(59° - 86°F). Do Not Freeze

ANDA: 15° - 30°C(59° - 86°F). \_\_\_\_\_

8. DISPENSING STATEMENTS COMPARISON

USP: None

RLD: None

ANDA (*Insert*): None

9. BIOAVAILABILITY/BIOEQUIVALENCE:

10. OTHER: Both The RLD and ANDA are sterile Dark Blue aqueous solutions.

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Date of Review: 3/19/03

Date of Submission: 12/26/02

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cc:

ANDA: 76-611

DUP/DIVISION FILE

HFD-613/Apayne/JGrace (no cc)

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Review

*John J. Grace* 4/14/03  
*John J. Grace* 4/24/2003

Tentative APPROVAL SUMMARY (NDA)  
 REVIEW OF PROFESSIONAL LABELING  
 DIVISION OF LABELING AND PROGRAM SUPPORT  
 LABELING REVIEW BRANCH

ANDA Number	76-611
Date of Submission	Dec. 1, 2003
Applicant	Bed ford
Drug Name	Mitoxantrone Injection USP
Strength(s)	2 mg/mL, 10 mL, 12.5 mL and 15 mL vials

**FPL Approval Summary**

Container Labels	Submitted
2 mg/mL 10 mL, 12.5 mL and 15 mL vials	Dec 1, 2003, vol. 3.1
Carton labeling 1 x 10 mL, 12.5 mL and 15 mL	Dec. 1, 2003, vol. 3.1
Package Insert Labeling MXT-P00B Rev. 12/03	Dec. 1, 2003, vol 3.1 Draft
Patient leaflet	Does not need

**BASIS OF APPROVAL:**

**Patent Data For NDA 19-297**

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4617319	JUN 13,2005	u-390	METHOD OF USING THE DRUG TO TREAT NEUROIMMUNOLOGIC DISEASES (INCLUDING MULTIPLE SCLEROSIS)	PIII	Same as
4820738	APR 11,2006	u-98	A METHOD OF INDUCING REGRESSION OF LEUKEMIA CELL GROWTH IN A MAMMAL	PIII	Same as

**Exclusivity Data For NDA 19-297**

Code/sup	Expiration	Description	Labeling impact
ode	Oct 13, 2007	Treatment of secondary-progressive multiple sclerosis Treatment of progressive-relapsing multiple sclerosis	Carved out

ode	Nov 13, 2003	Treatment of acute myelogenous leukemia,	Same as
I-324	Oct 13, 2003	REDUCING NEUROLOGIC DISABILITY AND/OR FREQUENCY OF CLINICAL RELAPSES IN PATIENTS WITH SECONDARY (CHRONIC) PROGRESSIVE, PROGRESSIVE RELAPSING, OR WORSENING RELAPSING-REMITTING MULTIPLE SCLEROSIS	Carved out based on ODE expiration dated

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**Reference Listed Drug**

RLD on the 356(h) form Novatrone  
 NDA Number 19-297  
 RLD established name Mitoxantrone for injection concentrate  
 Firm Immunex/Sereno/Lederel  
 Currently approved PI S-027  
 AP Date 1/13/03

Note. First generic. Firm has excluded the text regarding multiple sclerosis that provided a patient leaflet. Firm must also provide a revised insert prior to approval to include changes found in RLD S-026 and the Division cover letter. The RLD had only draft labeling available for S-027 and S-026.

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**APPEARS THIS WAY  
ON ORIGINAL**

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. <b>USP 24</b>	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
<b>PACKAGING</b> -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
<b>LABELING</b>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert		X	

labeling? Note: Chemist should confirm the data has been adequately supported.			
<b>Scoring:</b> Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
<b>Inactive Ingredients:</b> (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?			X
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
<b>USP Issues:</b> (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
<b>Bioequivalence Issues:</b> (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
.Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
<b>Patent/Exclusivity Issues:</b> FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. NONE			

**NOTE TO CHEMIST:**

**FOR THE RECORD:**

**1. MODEL LABELING**

This review was based on the labeling for Novantrone Injection (Mitoxantrone HCl; NDA 19-297/S-025, s-026, s-027; Approved 1/13/03; Serono, Inc).

**INSERT:**

a. Please be advise that your proposed labeling will need to be revised according to the most recently approved labeling for Novantrone Injection (Mitoxantrone HCl; NDA 19-297/S-026; Approved 1/13/03; Serono, Inc). The current label for this drug product is not available in FPL or electronic format from FDA. To obtain a current label, please contact the Company, We note the revised RLD labeling is not available to our office at this time, but only in draft for both S-026 and S-027. S-027 does not incorporate S-026

changes in draft

We provided the firm with the RLD draft for both S-026 and S-027. Firm must revise labeling to include missed text from S-026. We hope that by that time the RLD has FPL available that reflects changes to both S-026 and S-027.

Note: under Warnings, General, last paragraph "myelodysplasia" should read "myelodysplasia".

b. The RLD provide a patient leaflet for the MULTIPLE SCLEROSIS use only. Since our applicant will not market for the MS indication the patient leaflet is not need for approval at this time.

2. PATENTS/EXCLUSIVITIES: See above. [Vol. A1.1 pg. 5]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM  
Bedford laboratories, 270 Irthfield Rd. Bedford, Ohio, 44146, [Vol. A1.1 page 163]

4. CONTAINER/CLOSURE

RLD:

ANDA: Type I Glass Container, stopper and flip off Seal, [Vol. A1.2 pg. 817-820]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.1 pg. 114]

6. PACKAGING CONFIGURATIONS

RLD: 2 mg/mL/ 10 mL, 12.5 mL and 15 mL vials

ANDA: Same

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP:

RLD: store between CRT 15° - 30°C(59° - 86°F). Do Not Freeze

ANDA: 15° - 30°C(59° - 86°F). ~~Do Not Freeze~~ Asked to use our standard statement

8. DISPENSING STATEMENTS COMPARISON

USP: None

RLD: dispense patient leaflet for MS indication

ANDA (Insert): None

9. BIOAVAILABILITY/BIOEQUIVALENCE:

10. OTHER: Both The RLD and ANDA are sterile Dark Blue aqueous solutions.

11. USP has mitoxantrone injection former title was mitoxantrone for injection concentrate

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Date of Review: 12/16/03

Date of Submission: 12/01/03

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cc:

ANDA: 76-611  
DUP/DIVISION FILE  
HFD-613/Apayne/JJGrace (no cc)  
V:\FIRMSAM\BEDFORD\LTRS&REV\76611tap.lab  
Review

*Apayne* 12/16/03  
*JJGrace* 12/17/03

**APPROVAL SUMMARY #1  
 REVIEW OF PROFESSIONAL LABELING  
 DIVISION OF LABELING AND PROGRAM SUPPORT  
 LABELING REVIEW BRANCH**

<b>ANDA Number</b>	76-611
<b>Date of Submission</b>	12 Jan 2006
<b>Applicant</b>	Bed ford
<b>Drug Name</b>	Mitoxantrone Injection USP (concentrate)
<b>Strength(s)</b>	2 mg/mL, 10 mL, 12.5 mL and 15 mL vials

**FPL Approval Summary**

<b>Container Labels</b>	<b>Submitted e-FPL</b>
2 mg/mL	
10 mL,	<a href="#">\\cdsesub1\N76611\N_000\2006-01-12\MXO-V00.pdf</a>
12.5 mL	<a href="#">\\cdsesub1\N76611\N_000\2006-01-12\MXO-VA00.pdf</a>
15 mL vials	<a href="#">\\cdsesub1\N76611\N_000\2006-01-12\MXO-VB00.pdf</a>
<b>Carton labeling</b>	
1 x 10 mL,	<a href="#">\\cdsesub1\N76611\N_000\2006-01-12\MXT-C00A.pdf</a>
12.5 mL	<a href="#">\\cdsesub1\N76611\N_000\2006-01-12\MXT-CA00A.pdf</a>
15 mL	<a href="#">\\cdsesub1\N76611\N_000\2006-01-12\MXT-CB00A.pdf</a>
<b>Package Insert Labeling</b>	<a href="#">\\cdsesub1\N76611\N_000\2006-01-12\MXO-P00.pdf</a>
<b>Patient leaflet</b>	<b>Not needed-</b>

**BASIS OF APPROVAL:**

**Patent Data For NDA 19-297**

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4617319	JUN 13,2005	u-390	METHOD OF USING THE DRUG TO TREAT NEUROIMMUNOLOGIC DISEASES (INCLUDING MULTIPLE SCLEROSIS)	PIII	Same as
4820738	APR 11,2006	u-98	A METHOD OF INDUCING REGRESSION OF LEUKEMIA CELL GROWTH IN A MAMMAL	PIII	Same as

**Exclusivity Data For NDA 19-297**

Code/sup	Expiration	Description	Labeling impact

ode	Oct 13, 2007	Treatment of secondary-progressive multiple sclerosis Treatment of progressive-relapsing multiple sclerosis	Carved out
ode	Nov 13, 2003	Treatment of acute myelogenous leukemia,	Same as
I-324	Oct 13, 2003	REDUCING NEUROLOGIC DISABILITY AND/OR FREQUENCY OF CLINICAL RELAPSES IN PATIENTS WITH SECONDARY (CHRONIC) PROGRESSIVE, PROGRESSIVE RELAPSING, OR WORSENING RELAPSING-REMITTING MULTIPLE SCLEROSIS	Carved out based on ODE expiration dated

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**Reference Listed Drug**

RLD on the 356(h) form    Novatrone  
NDA Number                19-297  
RLD established name    Mitoxantrone for injection concentrate  
Firm                            Imunex/Sereno/Lederle  
Currently approved PI    S-028  
AP Date                      4/27/05

Note. First generic. Firm has excluded the text regarding multiple sclerosis that provided a patient leaflet.

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**APPEARS THIS WAY  
ON ORIGINAL**

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. <b>USP 24</b>	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
<b>PACKAGING -See applicant's packaging configuration in FTR</b>			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
<b>LABELING</b>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert		X	

labeling? Note: Chemist should confirm the data has been adequately supported.			
<b>Scoring:</b> Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
<b>Inactive Ingredients:</b> (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?			X
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
<b>USP Issues:</b> (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
<b>Bioequivalence Issues:</b> (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
<b>Patent/Exclusivity Issues:</b> FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. <b>NONE</b>			

**NOTE TO CHEMIST:**

**FOR THE RECORD:**

1. MODEL LABELING

This review was based on the labeling for Novantrone Injection (Mitoxantrone HCl; NDA 19-297/S-025, s-026, s-027; Approved 1/13/03; Serono, Inc).

**INSERT:**

a. Please be advise that your proposed labeling will need to be revised according to the most recently approved labeling for Novantrone Injection (Mitoxantrone HCl; NDA 19-297/S-026; Approved 1/13/03; Serono, Inc). The current label for this drug product is not available in FPL or electronic format from FDA. To obtain a current label, please contact the Company, We note the revised RLD labeling is not available to our office at this time, but only in draft for both S-026 and S-027. S-027 does not incorporate S-026

changes in draft

Note: under Warnings, General, last paragraph "myelodysplasia" should read "myelodysplasia".

b. The RLD provide a patient leaflet for the MULTIPLE SCLEROSIS use only. Since our applicant will not market for the MS indication the patient leaflet is not need for approval at this time.

2. PATENTS/EXCLUSIVITIES: See above. [Vol. A1.1 pg. 5]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM  
Bedford laboratories, 270 Irthfield Rd. Bedford, Ohio, 44146, [Vol. A1.1 page 163]

4. CONTAINER/CLOSURE

RLD:

ANDA: Type I Glass Container, stopper and flip off Seal, [Vol. A1.2 pg. 817-820]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.1 pg. 114]

6. PACKAGING CONFIGURATIONS

RLD: 2 mg/mL/ 10 mL, 12.5 mL and 15 mL vials

ANDA: Same

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP:

RLD: store between CRT 15° - 30°C(59° - 86°F). Do Not Freeze

ANDA: 15° - 30°C(59° - 86°F).                      Asked to use our standard statement

8. DISPENSING STATEMENTS COMPARISON

USP: None

RLD: dispense patient leaflet for MS indication

ANDA (*Insert*): None

9. BIOAVAILABILITY/BIOEQUIVALENCE:

10. OTHER: Both The RLD and ANDA are sterile Dark Blue aqueous solutions.

11. USP has mitoxantrone injection former title was mitoxantrone for injection concentrate

---

Date of Review: 2/23/06

Date of Submission: 1/12/06

---

cc:

ANDA: 76-611  
DUP/DIVISION FILE  
HFD-613/APayne/JGrace (no cc)  
V:\FIRMSAM\BEDFORD\LTRS&REV\76611ap1.lab  
Review; digital signature: APayne 2/23/06  
EDR-FPL carton, container and insert

*Payne 2/23/06*  
*John A. Payne 2.28.06*

**APPROVAL SUMMARY #2  
REVIEW OF PROFESSIONAL LABELING  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

<b>ANDA Number</b>	76-611
<b>Date of Submission</b>	2 MAR 2006
<b>Applicant</b>	Bed ford
<b>Drug Name</b>	MitoXANTrone Injection USP (concentrate)
<b>Strength(s)</b>	2 mg/mL, 10 mL, 12.5 mL and 15 mL vials

**FPL Approval Summary**

<b>Container Labels</b>	<b>Submitted e-FPL</b>
2 mg/mL	
10 mL,	\\cdsesub1\N76611\N_000\2006-03-02\MXO-V01.pdf
12.5 mL	\\cdsesub1\N76611\N_000\2006-03-02\MXO-VA01.pdf
15 mL vials	\\cdsesub1\N76611\N_000\2006-03-02\MXO-VB01.pdf
<b>Carton labeling</b>	
1 x 10 mL,	\\cdsesub1\N76611\N_000\2006-03-02\MXO-C01.pdf
12.5 mL	\\cdsesub1\N76611\N_000\2006-03-02\MXO-CA01.pdf
15 mL	\\cdsesub1\N76611\N_000\2006-03-02\MXO-CB01.pdf
<b>Package Insert Labeling</b>	\\cdsesub1\N76611\N_000\2006-03-02\MXO-P00.pdf
<b>Patient leaflet</b>	<b>Not needed- ODE for Multiple Sclerosis</b>

**BASIS OF APPROVAL:**

**Patent Data For NDA 19-297**

<b>Patent No</b>	<b>Patent Expiration</b>	<b>Use Code</b>	<b>Description</b>	<b>How Filed</b>	<b>Labeling Impact</b>
4617319	JUN 13,2005	u-390	METHOD OF USING THE DRUG TO TREAT NEUROIMMUNOLOGIC DISEASES (INCLUDING MULTIPLE SCLEROSIS)	PIII	Same as
4820738	APR 11,2006	u-98	A METHOD OF INDUCING REGRESSION OF LEUKEMIA CELL GROWTH IN A MAMMAL	PIII	Same as

**Exclusivity Data For NDA 19-297**

<b>Code/sup</b>	<b>Expiration</b>	<b>Description</b>	<b>Labeling impact</b>

ode	Oct 13, 2007	Treatment of secondary-progressive multiple sclerosis Treatment of progressive-relapsing multiple sclerosis	Carved out
ode	Nov 13, 2003	Treatment of acute myelogenous leukemia,	Same as
I-324	Oct 13, 2003	REDUCING NEUROLOGIC DISABILITY AND/OR FREQUENCY OF CLINICAL RELAPSES IN PATIENTS WITH SECONDARY (CHRONIC) PROGRESSIVE, PROGRESSIVE RELAPSING, OR WORSENING RELAPSING-REMITTING MULTIPLE SCLEROSIS	Carved out based on ODE expiration dated

---

**Reference Listed Drug**

RLD on the 356(h) form Novatrone  
NDA Number 19-297  
RLD established name Mitoxantrone for injection concentrate  
Firm Immunex/Sereno/Lederle  
Currently approved PI S-028  
AP Date 4/27/05

Note. First generic. Firm has excluded the text regarding multiple sclerosis that provided a patient leaflet.

---

APPEARS THIS WAY  
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. <b>USP 24.</b>	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
<b>PACKAGING -See applicant's packaging configuration in FTR</b>			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
<b>LABELING</b>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert		X	

labeling? Note: Chemist should confirm the data has been adequately supported.			
<b>Scoring:</b> Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
<b>Inactive Ingredients:</b> (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?			X
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
<b>USP Issues:</b> (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
<b>Bioequivalence Issues:</b> (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
<b>Patent/Exclusivity Issues:</b> FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. <b>NONE</b>			

**NOTE TO CHEMIST:**

**FOR THE RECORD:**

1. MODEL LABELING

This review was based on the labeling for Novantrone Injection (Mitoxantrone HCl; NDA 19-297/S-025, s-026, s-027; Approved 1/13/03; Serono, Inc).

**INSERT:**

a. Please be advise that your proposed labeling will need to be revised according to the most recently approved labeling for Novantrone Injection (Mitoxantrone HCl; NDA 19-297/S-026; Approved 1/13/03; Serono, Inc). The current label for this drug product is not available in FPL or electronic format from FDA. To obtain a current label, please contact the Company, We note the revised RLD labeling is not available to our office at this time, but only in draft for both S-026 and S-027. S-027 does not incorporate S-026

changes in draft

Note: under Warnings, General, last paragraph "myclodysplasia" should read "myeclodysplasia".

b. The RLD provide a patient leaflet for the MULTIPLE SCLEROSIS use only. Since our applicant will not market for the MS indication the patient leaflet is not need for approval at this time.

2. PATENTS/EXCLUSIVITIES: See above. [Vol. A1.1 pg. 5]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM  
Bedford laboratories, 270 Irthfield Rd. Bedford, Ohio, 44146, [Vol. A1.1 page 163]

4. CONTAINER/CLOSURE

RLD:

ANDA: Type I Glass Container, stopper and flip off Seal, [Vol. A1.2 pg. 817-820]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.1 pg. 114]

6. PACKAGING CONFIGURATIONS

RLD: 2 mg/mL/ 10 mL, 12.5 mL and 15 mL vials

ANDA: Same

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP:

RLD: store between CRT 15° - 30°C(59° - 86°F). Do Not Freeze

ANDA: 15° - 30°C(59° - 86°F). ~~Asked to use our standard statement~~

8. DISPENSING STATEMENTS COMPARISON

USP: None

RLD: dispense patient leaflet for MS indication

ANDA (*Insert*): None

9. BIOAVAILABILITY/BIOEQUIVALENCE:

10. OTHER: Both The RLD and ANDA are sterile Dark Blue aqueous solutions.

11. USP has mitoxantrone injection former title was mitoxantrone for injection concentrate

Date of Review: 3/13/06

Date of Submission: 3/2/06

Primary Reviewer: Angela Payne

Date: *apayne 3/13/06*

Team Leader: John Grace

Date: *John J. Grace 3-16-2006*

cc:

ANDA: 76-611

DUP/DIVISION FILE

HFD-613/Apayne/JGrace (no cc)

V:\FIRMSAM\BEDFORD\LTRS&REV\76611ap2lab

EDR-FPL carton, container and insert

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 76-611**

**CHEMISTRY REVIEW(S)**



**ANDA 76-611**

**Mitoxantrone Injection**  
**2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial**

**Bedford Laboratories**

**Kathy P. Woodland**  
**Division of Chemistry I**  
**Team 5**



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# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### Chemistry Review Data Sheet

1. ANDA 76-611
2. REVIEW #: 1
3. REVIEW DATE: May 10, 2003
4. REVIEWER: Kathy P. Woodland

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original Submission  
Acceptable for filing  
Telephone Amendment  
New Correspondence

December 26, 2002  
December 30, 2002  
February 5, 2003  
March 18, 2003

7. NAME & ADDRESS OF APPLICANT:

Name: Bedford Laboratories  
Address: 300 Northfield Road  
Bedford, OH 44146  
Representative: Molly L. Rapp  
Telephone: 440-201-3576



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Mitoxantrone Injection, USP

9. LEGAL BASIS FOR SUBMISSION: The RLD is Novantrone, NDA 19-297, Immunex Corporation. The applicant certifies that in their opinion and to the best of their knowledge, Patent 4,617,319 and Patent 4822738, held by Immunex Corp., will expire on June 13, 2005 and April 11, 2006, respectively. Orphan Drug Exclusivities are in effect for this product until November 13, 2003 and October 13, 2007. In addition, a marketing exclusivity for I-324 is in effect until October 13, 2003. Bedford Laboratories will not market this product before the expiration of 2003 ODE or the 2003 I-324 exclusivity. Bedford will not market this drug product as an Orphan drug with respect to the 2007 exclusivity and will pursue approval of the application prior to the expiration of the 2007 Orphan Drug Exclusivity.

10. PHARMACOL. CATEGORY: Indicated as initial chemotherapy for prostate cancer and acute nonlymphocytic leukemia.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 2 mg/mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

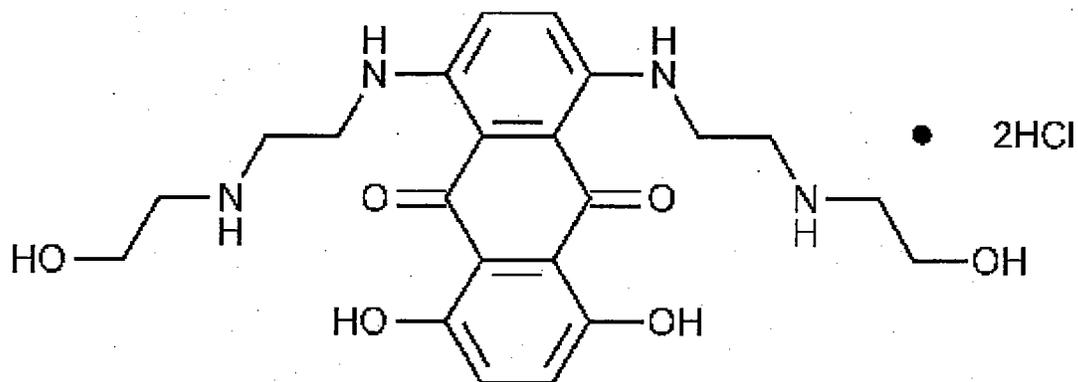
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

## Chemistry Review Data Sheet

1,4-dihydroxy-5,8-bis((2-((2-hydroxyethyl)amino)ethyl)amino)-9,10-anthracenedione  
dihydrochloride

MW:  $C_{22}H_{29}ClN_4O_6$

CAS number: 70476-82-3



17. RELATED/SUPPORTING DOCUMENTS: None



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [note2] 1	STATUS [note25]2	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	1	Inadequate	5/9/03	Reviewed by K. Woodland
/	III	/	/	4	N/A		
/	III	/	/	4	N/A		

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents: N/A

#### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Acceptable	5/28/03	J. D'Ambrogio (HFD-322)
Methods Validation	N/A		
Labeling	Deficient	4/29/03	A. Payne
Bioequivalence	(Waiver requested) Pending		
EA	N/A		
Radiopharmaceutical	N/A		



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:

**APPEARS THIS WAY  
ON ORIGINAL**

## Executive Summary Section

**The Chemistry Review for ANDA 76-611****The Executive Summary****I. Recommendations**

- A. Recommendation and Conclusion on Approvability:** The ANDA is not approvable pending clarification of MINOR Chemistry issues and Labeling deficiencies. Bioequivalence and Microbiology are pending.
- B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**  
N/A

**II. Summary of Chemistry Assessments****A. Description of the Drug Product(s) and Drug Substance(s)**

- The drug substance Mitoxantrone Hydrochloride USP as well as the drug product Mitoxantrone Injection USP, 2 mg/mL are both listed in USP. The product will be packaged in 10 mL, 12.5 mL, and 15 mL fill size.
- The DMF associated with this application (DMF — ) was reviewed this cycle by K. Woodland and was found inadequate on 5/9/03.
- Bedford Laboratories is the applicant. The manufacturer of the drug product is Ben Venue Laboratories.
- Ben Venue has developed their own in-house methods for the drug substance assay and the drug product assay, residual oxygen content, and related substances. The method validations were submitted and found to be satisfactory.

**B. Description of How the Drug Product is Intended to be Used**

Mitoxantrone in combination with corticosteroids is indicated as initial chemotherapy for the treatment of patients with pain related to advance hormone refractory prostate cancer.

Dosage: 12 to 14 mg/m<sup>2</sup> given as a short intravenous infusion every 21 days. Mitoxantrone in combination with other approved drug(s) is indicated in the initial therapy of acute nonlymphocytic leukemia in adults.

Dosage: For induction: 12 mg/m<sup>2</sup> daily on Days 1 to 3 given as an intravenous infusion, and 100 mg/m<sup>2</sup> of cytarabine for 7 days given as a continuous 24-hour infusion on days 1 to 7.

The product is to be stored between 15°-25°C (59° to 77°F). DO NOT FREEZE.



Executive Summary Section

**C. Basis for Approvability or Not-Approval Recommendation**

The ANDA is not approvable at this time for the following reasons:

MINOR Chemistry issues (DMF deficiencies, controls of drug substance, components/composition)

Deficient labeling

Pending Bio

Pending Microbiology

**III. Administrative**

**A. Reviewer's Signature**

*Kathy P. Woodland*

**B. Endorsement Block**

Chemist/K. Woodland/ *K Woodland 5/30/03*  
ChemistryTeamLeader/S. Liu Ph.D./ *S. H. Liu 6/5/03*  
ProjectManager/W. Pamphile, Pharm. D./ *WP 6/6/03*  
V:\FIRMSAM\BEDFORD\LTRS&REV\76611.rv1.doc

**C. CC Block**

Redacted 10 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

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## CHEMISTRY REVIEW



### Chemistry Assessment Section

The Applicant has certified that no environmental assessment is required for this application and it meets the exclusion criteria. Ben Venue Laboratories, Inc. is in compliance with federal, state, and local environmental laws.

**APPEARS THIS WAY  
ON ORIGINAL**



## CHEMISTRY REVIEW



Chemistry Assessment Section

### 36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

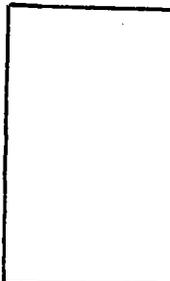
ANDA: 76-611

APPLICANT: Bedford Laboratories

DRUG PRODUCT: Mitoxantrone Injection, 2 mg/mL; 10 mL, 12.5 mL and 15 mL vials

The deficiencies presented below represent MINOR deficiencies.

#### A. Deficiencies:

1. The Drug Master File # \_\_\_\_\_ is currently inadequate. The DMF holder has been notified. Please do not respond to this letter until the DMF holder has informed you that a complete response to the DMF deficiencies has been submitted to the agency.
2. Please test the drug substance for residual solvents and submit a revised drug substance COA. You should not use the vendor's test results before you have qualified your vendor based on your vendor qualification program.
3. 
4. 

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

1. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.
2. Your Sterility Assurance information is pending review. Deficiencies, if any, will be communicated separately.



## CHEMISTRY REVIEW



### Chemistry Assessment Section

3. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.
4. Please submit any updated stability data.

Sincerely yours,

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



# CHEMISTRY REVIEW



## Chemistry Assessment Section

cc: ANDA 76-611  
ANDA DUP 76-611  
DIV FILE  
Field Copy

### Endorsements (Draft and Final with Dates):

HFD-627/K. Woodland/ *K. Woodland 6/30/03*  
HFD-627/S. Liu, Ph.D./ *S.H. Liu 06/05/03*  
HFD-617/W. Pamphile, Pharm.D./ ~~W~~ *6/6/03*  
F/T by /

V:\FIRMS\AMBEDFORD\LTRS&REV\76611.rv1.doc

**TYPE OF LETTER: NOT APPROVABLE - MINOR**

#2



**ANDA 76-611**

**Mitoxantrone Injection USP  
2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial**

**Bedford Laboratories**

**Kathy P. Woodland  
Division of Chemistry I  
Team 5**



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III. Administrative.....9

    A. Reviewer’s Signature ..... 9

    B. Endorsement Block ..... 9

    C. CC Block..... 9

**Chemistry Assessment**..... 8



Chemistry Review Data Sheet

1. ANDA 76-611
2. REVIEW #: 2
3. REVIEW DATE: August 26, 2003  
January 8, 2004  
January 16, 2004 (revised)

4. REVIEWER: Kathy P. Woodland

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

Original Submission  
Acceptable for filing  
Telephone Amendment  
New Correspondence

December 26, 2002  
December 30, 2002  
February 5, 2003  
March 18, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Amendment (Labeling)  
Amendment (Labeling)  
Amendment (Micro)  
Amendment  
Amendment  
Telephone Amendment  
Telephone Amendment  
Amendment  
Telephone Amendment  
Clarification fax

December 17, 2003  
December 1, 2003  
November 20, 2003  
October 28, 2003  
October 9, 2003  
September 3, 2003  
August 5, 2003  
July 3, 2003  
January 13, 2004  
January 14, 2004



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Bedford Laboratories  
Address: 300 Northfield Road  
Bedford, OH 44146  
Representative: Molly L. Rapp  
Telephone: 440-201-3576

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Mitoxantrone Injection, USP

9. LEGAL BASIS FOR SUBMISSION: See review #1

10. PHARMACOL. CATEGORY: Indicated as initial chemotherapy for prostate cancer and acute nonlymphocytic leukemia.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 2 mg/mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

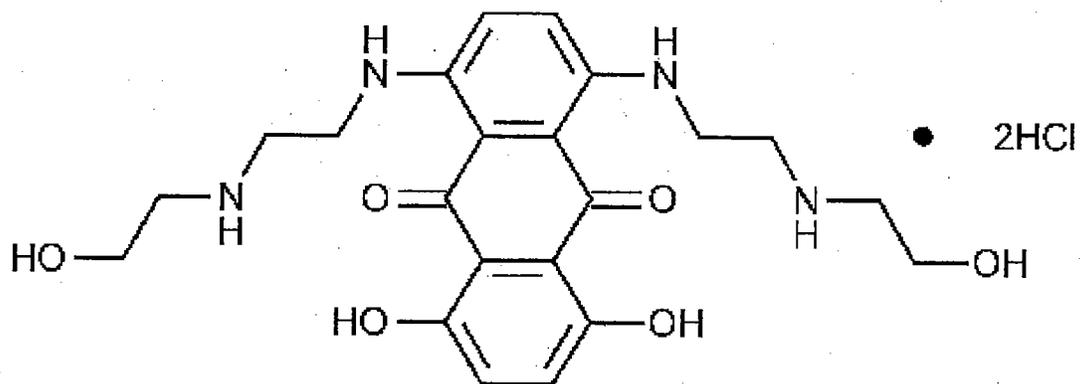
## Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1,4-dihydroxy-5,8-bis((2-((2-hydroxyethyl)amino)ethyl)amino)-9,10-anthracenedione dihydrochloride

MW:  $C_{22}H_{29}ClN_4O_6$

CAS number: 70476-82-3



17. RELATED/SUPPORTING DOCUMENTS: None



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE1	STATUS2	DATE REVIEW COMPLETE D	COMMENTS
/	II	/	/	1	Adequate	8/26/03	Reviewed by K. Woodland
/	III	/	/	4	N/A		
/	III	/	/	4	N/A		

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents: N/A

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	12/10/03	M. Stevens-Riley
EES	Acceptable	5/28/03	J. D'Ambrogio (HFD-322)
Methods Validation	N/A		
Labeling	Acceptable	12/17/03	A. Payne
Bioequivalence	Acceptable	8/22/03	S. Shrivastava
EA	N/A		
Radiopharmaceutical	N/A		



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

#### 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:

**APPEARS THIS WAY  
ON ORIGINAL**



## Executive Summary Section

**The Chemistry Review for ANDA 76-611****The Executive Summary****I. Recommendations**

- A. Recommendation and Conclusion on Approvability:** The ANDA is approvable.
- B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**  
N/A

**II. Summary of Chemistry Assessments****A. Description of the Drug Product(s) and Drug Substance(s)**

- The drug substance Mitoxantrone Hydrochloride USP as well as the drug product Mitoxantrone Injection USP, 2 mg/mL are both listed in USP. The product will be packaged in 10 mL, 12.5 mL, and 15 mL fill size.
- The DMF associated with this application (DMF — ) was reviewed in this cycle by K. Woodland and was found adequate on 8/26/03.
- Bedford Laboratories is the applicant. The manufacturer of the drug product is Ben Venue Laboratories.
- Ben Venue has developed their own in-house methods for the drug substance assay and the drug product assay, residual oxygen content, and related substances. The method validations were submitted and found to be satisfactory.

**B. Description of How the Drug Product is Intended to be Used**

Mitoxantrone in combination with corticosteroids is indicated as initial chemotherapy for the treatment of patients with pain related to advance hormone refractory prostate cancer.

Dosage: 12 to 14 mg/m<sup>2</sup> given as a short intravenous infusion every 21 days. Mitoxantrone in combination with other approved drug(s) is indicated in the initial therapy of acute nonlymphocytic leukemia in adults.

Dosage: For induction: 12 mg/m<sup>2</sup> daily on Days 1 to 3 given as an intravenous infusion, and 100 mg/m<sup>2</sup> of cytarabine for 7 days given as a continuous 24-hour infusion on days 1 to 7.

The product is to be stored between 15°-25°C (59° to 77°F). DO NOT FREEZE.



Executive Summary Section

**C. Basis for Approvability or Not-Approval Recommendation**

CMC, labeling, bioequivalence, micro, and EER are all acceptable.

**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

Chemist/K. Woodland/9/5/03 *K Woodland 1/16/04*  
ChemistryTeamLeader/S.Liu Ph.D./9/11/03 *S.H. Liu 1/21/04*  
ProjectManager/W.Pamphile, Pharm. D./ ~~WP~~ *1/21/04*  
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**C. CC Block**

APPEARS THIS WAY  
ON ORIGINAL

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information from

CHEMISTRY REVIEW #2

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# CHEMISTRY REVIEW



## Chemistry Assessment Section

inverted			15 mL per vial
2210-116-455586 upright	0,1,2,3 months	0,3,6,12 months	2mg/mL, 12.5 mL per vial
2210-116-455586 inverted	0,1,2,3 months	0,3,6,12 months	2mg/mL, 12.5 mL per vial

All stability data submitted was within the proposed specifications.

**30. MICROBIOLOGY** Acceptable on 12/10/03 by M. Stevens-Riley

**31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS**

The drug substance and drug product are both USP. Therefore no method validation was required.

**32. LABELING** Acceptable on 12/17/03 by A. Payne

**33. ESTABLISHMENT INSPECTION** Acceptable 5/28/03, J.D' Ambrigio

**34. BIOEQUIVALENCE** Acceptable on 8/22/03 by S. Shrivastava

**35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:**

Satisfactory Rv#1

**APPEARS THIS WAY  
ON ORIGINAL**



# CHEMISTRY REVIEW



## Chemistry Assessment Section

cc: ANDA 76-611  
ANDA DUP 76-611  
DIV FILE  
Field Copy

### Endorsements (Draft and Final with Dates):

HFD-627/K.Woodland/ *K.Woodland 1/16/04*  
HFD-627/S.Liu,Ph.D./ *S.H.Liu 1/21/04*  
HFD-617/W.Pamphile,Pharm.D./ *WP 1/21/04*  
F/T by /

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**TYPE OF LETTER: APPROVABLE**

**APPEARS THIS WAY  
ON ORIGINAL**

#3



**ANDA 76-611**

**Mitoxantrone Injection USP  
2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial**

**Bedford Laboratories**

**Kathy P. Woodland  
Division of Chemistry I  
Team 5**



**Table of Contents**

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    A. Recommendation and Conclusion on Approvability ..... 7

    B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... 7

II. Summary of Chemistry Assessments.....7

    A. Description of the Drug Product(s) and Drug Substance(s) ..... 7

    B. Description of How the Drug Product is Intended to be Used..... 7

    C. Basis for Approvability or Not-Approval Recommendation ..... 8

**Chemistry Assessment**..... 9

**APPEARS THIS WAY  
ON ORIGINAL**



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### Chemistry Review Data Sheet

1. ANDA 76-611
2. REVIEW #: 3
2. REVIEW DATE: March 28, 2006
4. REVIEWER: Kathy P. Woodland
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Amendment (Labeling)	December 17, 2003
Amendment (Labeling)	December 1, 2003
Amendment (Micro)	November 20, 2003
Amendment	October 28, 2003
Amendment	October 9, 2003
Telephone Amendment	September 3, 2003
Telephone Amendment	August 5, 2003
Amendment	July 3, 2003
Telephone Amendment	January 13, 2004
Clarification fax	January 14, 2004

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Minor Amendment	January 12, 2006
Telephone Amendment Micro	February 24, 2006
Telephone Amendment Labeling	March 2, 2006
Telephone Amendment Micro	March 7, 2006
Telephone Amendment CMC	March 24, 2006
Telephone Amendment CMC	March 28, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Bedford Laboratories
Address:	300 Northfield Road Bedford, OH 44146



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

Representative:	Molly L. Rapp
Telephone:	440-201-3576

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Mitoxantrone Injection, USP

9. LEGAL BASIS FOR SUBMISSION: See review #1

10. PHARMACOL. CATEGORY: Indicated as initial chemotherapy for prostate cancer and acute nonlymphocytic leukemia.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 2 mg/mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

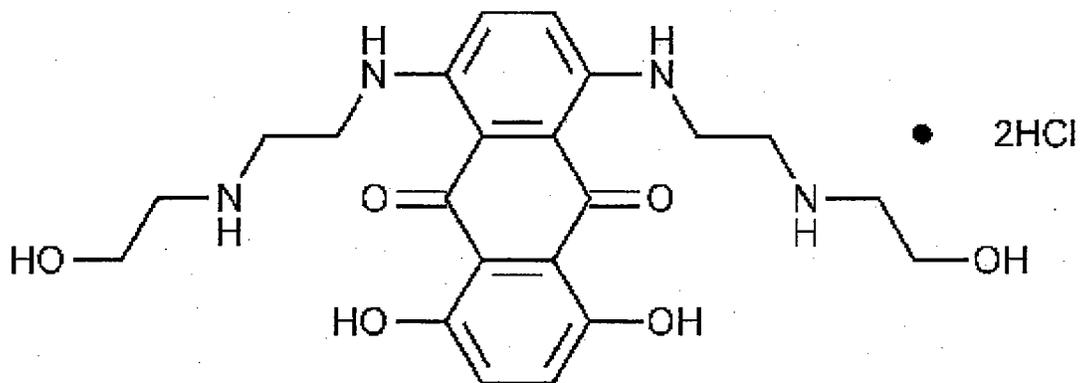
SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1,4-dihydroxy-5,8-bis((2-((2-hydroxyethyl)amino)ethyl)amino)-9,10-anthracenedione dihydrochloride  
MW: C<sub>22</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>6</sub>  
CAS number: 70476-82-3

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS: None

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	3	Adequate	1/12/2006	Reviewed by K. Furnkranz
	III			4	N/A		
	III			4	N/A		

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

**B. Other Documents: N/A**

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	3/20/06	M. Stevens-Riley
EES	Acceptable	5/28/03	J. D'Ambrogio (HFD-322)
Methods Validation	N/A		
Labeling	Acceptable	3/16/06	A. Payne
Bioequivalence	Acceptable	8/22/03	S. Shrivastava
EA	N/A		
Radiopharmaceutical	N/A		

### 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. \_\_\_ Yes  No If no, explain reason(s) below:

**APPEARS THIS WAY  
ON ORIGINAL**



The Chemistry Review for ANDA 76-611

The Executive Summary

**I. Recommendations**

- A. Recommendation and Conclusion on Approvability:** The ANDA is approvable.
- B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**  
N/A

**II. Summary of Chemistry Assessments**

**A. Description of the Drug Product(s) and Drug Substance(s)**

- The drug substance Mitoxantrone Hydrochloride USP as well as the drug product Mitoxantrone Injection USP, 2 mg/mL are both listed in USP. The product will be packaged in 10 mL, 12.5 mL, and 15 mL fill size.
- The DMF associated with this application (DMF —) was previously reviewed and found to be adequate, 1/12/2006.
- Bedford Laboratories is the applicant. The manufacturer of the drug product is Ben Venue Laboratories.
- Ben Venue has developed their own in-house methods for the drug substance assay and the drug product assay, residual oxygen content, and related substances. The method validations were submitted and found to be satisfactory.

**B. Description of How the Drug Product is Intended to be Used**

Mitoxantrone in combination with corticosteroids is indicated as initial chemotherapy for the treatment of patients with pain related to advance hormone refractory prostate cancer.

Dosage: 12 to 14 mg/m<sup>2</sup> given as a short intravenous infusion every 21 days.

Mitoxantrone in combination with other approved drug(s) is indicated in the initial therapy of acute nonlymphocytic leukemia in adults.

Dosage: For induction: 12 mg/m<sup>2</sup> daily on Days 1 to 3 given as an intravenous infusion, and 100 mg/m<sup>2</sup> of cytarabine for 7 days given as a continuous 24-hour infusion on days 1 to 7.

The product is to be stored between 15°-25°C (59° to 77°F). DO NOT FREEZE.



Executive Summary Section

**C. Basis for Approvability or Not-Approval Recommendation**

CMC, labeling, bioequivalence, micro, and EER are all acceptable.

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**APPEARS THIS WAY  
ON ORIGINAL**

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confidential commercial

information from

CHEMISTRY REVIEW #3

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## CHEMISTRY REVIEW



### Chemistry Assessment Section

30. **MICROBIOLOGY** Acceptable on 3-20-06 by M. Stevens-Riley

31. **SAMPLES AND RESULTS/METHODS VALIDATION STATUS**

The drug substance and drug product are both USP. Therefore no method validation was required.

32. **LABELING** Acceptable on 3-16-06 by A. Payne

33. **ESTABLISHMENT INSPECTION** Acceptable 5/28/03, J.D' Ambrigo

34. **BIOEQUIVALENCE** Acceptable on 8/22/03 by S. Shrivastava

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:**

Satisfactory RV#1

APPEARS THIS WAY  
ON ORIGINAL



# CHEMISTRY REVIEW



## Chemistry Assessment Section

cc: ANDA 76-611  
ANANDA DUP 76-611  
DIV FILE  
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/K.Woodland/ *K Woodland 3/29/06*  
HFD-620/R.Bykadi,Ph.D./ *R Bykadi 3-29-06*  
HFD-617/B.Danso,Pharm.D./ *B Danso 3/29/06*  
F/T by /

V:\FIRMSAMBEDFORD\LTRS&REV\76611.rv3.doc

**TYPE OF LETTER: APPROVABLE**

**APPEARS THIS WAY  
ON ORIGINAL**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 76-611**

**BIOEQUIVALENCE REVIEW(S)**

## DIVISION OF BIOEQUIVALENCE REVIEW

---

<b>ANDA No.</b>	<b>76-611</b>
<b>Drug Product Name</b>	Mitoxantrone Injection, USP
<b>Strength</b>	2 mg/mL; 10 mL, 12.5 mL and 15 mL vials
<b>Applicant Name</b>	Bedford Laboratories
<b>Address</b>	Bedford, OH
<b>Submission Date(s)</b>	December 26, 2002
<b>Amendment Date(s)</b>	N/A
<b>Reviewer</b>	<b>S. P. Shrivastava</b>
<b>First Generic</b>	<b>May be</b>
<b>File Location</b>	<b>V:\firmsam\bedford\ltrs&amp;rev\76611w1202</b>

---

### I. Executive Summary

The firm has submitted a request for waiver of *in vivo* bioavailability/bioequivalence study requirements based on 21 CFR 320.22(b)(1) for its proposed product mitoxantrone Injection, 2 mg/mL, 10 mL, 12.5 mL and 15 mL vials. The Test product, supplied in vials as 2 mg/mL (10 mL, 12.5 mL and 15 mL fill/vial) is bioequivalent to Novantrone® Injection (NDA #N19297, 12/23/87), manufactured by Serono Inc./Immunex Corp. The waiver of bioequivalence study requirements is granted.

### II. Table of Contents

I.	Executive Summary.....	1
II.	Table of Contents.....	1
III.	Submission Summary .....	2
A.	Drug Product Information.....	2
B.	PK/PD Information .....	2
C.	Contents of Submission .....	2
D.	Pre-Study Bioanalytical Method Validation---N/A .....	3
E.	In Vivo Studies---N/A .....	3
1.	Single-dose Fasting Bioequivalence Study ---N/A.....	3
2.	Single-dose Fed Bioequivalence Study---N/A .....	3
F.	Formulation (Not For Release Under FOI).....	3
G.	In Vitro Dissolution ---N/A .....	4
H.	Waiver Request(s).....	4
I.	Deficiency Comments --- None.....	4
J.	Recommendations.....	4
1.	WAIVER (WAI) Submission date: 12/26/02.....	6

### III. Submission Summary

#### A. Drug Product Information

<b>Test Product</b>	Mitoxantrone Injection
<b>Reference Product</b>	Novantrone® Injection
<b>RLD Manufacturer</b>	Serono Inc.
<b>NDA No.</b>	019297
<b>RLD Approval Date</b>	12/23/87
<b>Indication</b>	Initial chemotherapy for prostate cancer and acute non-lymphocytic leukemia

#### B. PK/PD Information

<b>Bioavailability</b>	99%
<b>Food Effect</b>	N/A
<b>T<sub>max</sub></b>	N/A
<b>Metabolism</b>	N/A
<b>Excretion</b>	11 and 25% of dose excreted in urine and feces, respectively, in 5 days.
<b>Half-life (Terminal)</b>	23-215 hrs. (median 75 hrs.)
<b>Relevant OGD or DBE History</b>	ANDAs, or Protocols: None were found in DBE files CD 02-243: Inquiry on inclusion of metabisulfite in the product
<b>Agency Guidance</b>	None
<b>Drug Specific Issues (if any)</b>	None

#### C. Contents of Submission

<b>Study Types</b>	<b>Yes/No?</b>	<b>How many?</b>
<b>Single-dose fasting</b>	No	
<b>Single-dose fed</b>	No	
<b>Steady-state</b>	No	
<b>In vitro dissolution</b>	No	
<b>Waiver requests</b>	No	
<b>BCS Waivers</b>	No	
<b>Vasoconstrictor Studies</b>	No	
<b>Clinical Endpoints</b>	No	
<b>Failed Studies</b>	No	
<b>Amendments</b>	No	

**D. Pre-Study Bioanalytical Method Validation---N/A**

**E. In Vivo Studies----N/A**

1. Single-dose Fasting Bioequivalence Study ----N/A

2. Single-dose Fed Bioequivalence Study----N/A

**F. Formulation (Not For Release Under FOI)**

<b>Location</b>	<b>See below</b>
<b>Inactive ingredients within IIG Limits (yes or no)</b>	<b>Yes, identical to the RLD</b>
<b>If yes, list ingredients outside of limits</b>	<b>None</b>
<b>If a tablet, is the product scored? (yes or no)</b>	<b>N/A</b>
<b>If yes, which strengths are scored?</b>	<b>N/A</b>
<b>Is scoring of RLD the same as test? (yes or no)</b>	<b>N/A</b>
<b>Formulation is acceptable (yes or no)</b>	<b>Yes</b>
<b>If not acceptable, why?</b>	<b>N/A</b>

Components and composition of the test and the reference products are given in Table 1.

**Table 1. Comparative Composition of Test and Reference Products**

<b>Ingredient</b>	<b>Test, mg/mL*</b>	<b>Reference, mg/mL</b>
Mitoxantrone	2.328**	2.0
Sodium Chloride, USP	8.0	8.0
Sodium Acetate, USP	0.05, pH Adjuster	0.05
Glacial Acetic Acid, USP	0.46 pH Adjuster	0.46
Water for Injection, USP	q.s. to 1 mL	q.s.
	***	

\* Exhibit Batch = \_\_\_\_\_ Production Batch = \_\_\_\_\_

\*\* Hydrochloride salt eq. to 2 mg free base/mL (MW: Base = 444.49, HCl Salt = 517.41)

\*\*\*Used as \_\_\_\_\_

**COMMENTS**

1. The test drug product contains the same active and inactive ingredients.
2. The test drug product has the same route of administration (i.e., intravenous injection) and the same indications for use as that of the RLD.

**G. In Vitro Dissolution ---N/A**

**H. Waiver Request(s)**

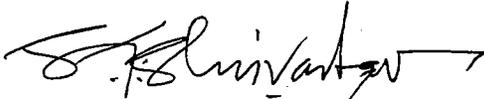
The Applicant requests a waiver of *in vivo* bioequivalence testing under 21 CFR 320.22(b)(1) for the following strength(s): 2 mg/mL, 10 mL, 12.5 mL and 15 mL vials

**I. Deficiency Comments --- None**

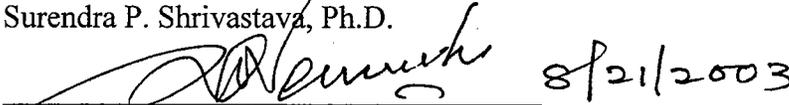
**J. Recommendations**

The Division of Bioequivalence agrees that the information submitted by Bedford Laboratories demonstrates that mitoxantrone injection, 2 mg/mL, 10 mL, 12.5 mL and 15 mL vials, falls under 21 CFR 320.22(b)(1) of the Bioavailability/Bioequivalence regulations. The waiver of an *in vivo* bioequivalence study requirement for mitoxantrone injection, 2 mg/mL, is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product to be bioequivalent to Novantrone® Injection, 2 mg/mL manufactured by Serono Inc.

The firm should be informed of the recommendation.



\_\_\_\_\_  
Surendra P. Shrivastava, Ph.D.



\_\_\_\_\_  
Shrinivas Nerurkar, Ph.D.

8/21/2003

SPS/sps/8-14-03/76611n1202

cc: ANDA #76-611 (Original, Duplicate), HFD-655 (SNerurkar, SShrivastava), Drug File, Division File.

CC: ANDA  
ANDA DUPLICATE  
DIVISION FILE  
HFD-651/ Bio Drug File  
HFD-650/ SShrivastava

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Printed in final on 8/14/03

*SW 8/21/03*

Endorsements: (Final with Dates)

HFD-655/ SShrivastava

HFD-655/ SNerurkar

HFD-650/ D. Conner

*S.S. 8/21/03  
D.C. 8/22/03*

*fr*

BIOEQUIVALENCY - ACCEPTABLE

1. WAIVER (WAI)

Submission date: 12/26/02

Strengths: 2 mg/mL, 10, 12.5 and 15 mL vials

✓ Outcome: AC

**APPEARS THIS WAY  
ON ORIGINAL**

BIOEQUIVALENCY COMMENTS

ANDA: 76-611

APPLICANT: Bedford Laboratories

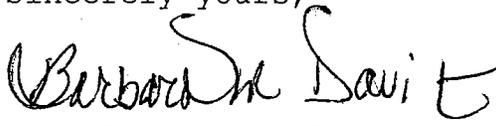
DRUG PRODUCT:

Mitoxantrone Injection USP, 2 mg/mL, 10 mL,  
12.5 mL and 15 mL vials

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

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

Sincerely yours,

*for* 

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

CC: ANDA  
ANANDA DUPLICATE  
DIVISION FILE  
HFD-651/ Bio Drug File  
HFD-650/ SShrivastava

V:\FIRMSAM\BEDFORD\ltrs&rev\76611W1202  
Printed in final on 8/14/03

Endorsements: (Final with Dates)  
HFD-655/ SShrivastava  
HFD-655/ SNerurkar  
HFD-650/ D. Conner

*8/21/03*  
*8/22/03*

*DN 8/21/03*

*Ja*

BIOEQUIVALENCY - ACCEPTABLE

**1. WAIVER (WAI)**

Submission date: 12/26/02

Strengths: 2 mg/mL, 10, 12.5 and 15 mL vials

✓ Outcome: AC

**APPEARS THIS WAY  
ON ORIGINAL**



**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 76-611**

**MICROBIOLOGY REVIEW(S)**

# Product Quality Microbiology Review

## Review for HFD-620

11 August 2003

**ANDA:** 76-611

**Drug Product Name**

**Proprietary:** Novantrone

**Non-proprietary:** Mitoxantrone Injection USP

**Drug Product Classification:** N/A

**Review Number:** 1

**Subject of this Review**

**Submission Date:** December 26, 2002 and August 5, 2003 (telephone amendment)

**Receipt Date:** December 30, 2002 and August 6, 2003

**Consult Date:** N/A

**Date Assigned for Review:** July 18, 2003

**Submission History (for amendments only)**

**Date(s) of Previous Submission(s):**

**Date(s) of Previous Micro Review(s):**

**Applicant/Sponsor**

**Name:** Bedford Laboratories

**Address:** 300 Northfield Road  
Bedford, Ohio 44146

**Representative:** Molly Rapp

**Telephone:** 440-201-3576

**Name of Reviewer:** Marla Stevens-Riley

**Conclusion:** Not recommended for approval on the basis on sterility assurance

---

## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUPPLEMENT:** N/A
  2. **SUPPLEMENT PROVIDES FOR:** N/A
  3. **MANUFACTURING SITE:** Ben Venue Laboratories  
270 Northfield Rd.  
Bedford, Ohio 44146
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** sterile solution, intravenous administration, 2 mg/mL as 10 mL (20 mg), 12.5 mL (25 mg), and 15 mL(30 mg) per vial
  5. **METHOD(S) OF STERILIZATION:** \_\_\_\_\_
  6. **PHARMACOLOGICAL CATEGORY:** chemotherapeutic agent for prostate cancer and acute non-lymphocytic leukemia
- B. **SUPPORTING/RELATED DOCUMENTS:** DMF 2315 (LOA in Appendix I)
- C. **REMARKS:** The applicant references the April 5, 2002 submission to DMF 2315; however, there has been a March 14, 2003 update and a June 9, 2003 amendment to DMF 2315. In addition, information provided in the August 5, 2003 telephone amendment will also be reviewed.

filename: v:microrev\76-611.doc

APPEARS THIS WAY  
ON ORIGINAL

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**Executive Summary**

**I. Recommendations**

- A. **Recommendation on Approvability** – Not recommended for approval on the basis of sterility assurance
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** –N/A

**II. Summary of Microbiology Assessments**

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – \_\_\_\_\_
- B. **Brief Description of Microbiology Deficiencies** –The DMF is deficient, and the ANDA submission has incomplete information regarding critical operations, environmental monitoring, and validation of the sterility test.
- C. **Assessment of Risk Due to Microbiology Deficiencies** -The risk to public health associated with these deficiencies is moderate.

**III. Administrative**

- A. **Reviewer's Signature** Mala Stevens-Riley
- B. **Endorsement Block**  
M. Stevens-Riley, Ph.D. 10/7/03  
N. J. Sweeney, Ph.D. N. J. Sweeney
- C. **CC Block**  
cc:  
Original ANDA 76-611  
Division File  
Field Copy  
10-7-03

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of trade secret and/or

confidential commercial

information from

*MICROBIOLOGY REVIEW #1*

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# **Product Quality Microbiology Review**

## **Review for HFD-620**

**5 December 2003**

**ANDA: 76-611**

### **Drug Product Name**

**Proprietary: Novantrone**

**Non-proprietary: Mitoxantrone Injection USP**

**Drug Product Classification: N/A**

**Review Number: 2**

### **Subject of this Review**

**Submission Date: October 28, 2003 and November 20, 2003 (telephone amendment)**

**Receipt Date: October 29, 2003 and November 21, 2003**

**Consult Date: N/A**

**Date Assigned for Review: November 3, 2003**

### **Submission History (for amendments only)**

**Date(s) of Previous Submission(s): December 26, 2002, August 5, 2003**

**Date(s) of Previous Micro Review(s): August 11, 2003**

### **Applicant/Sponsor**

**Name: Bedford Laboratories**

**Address: 300 Northfield Road  
Bedford, Ohio 44146**

**Representative: Molly Rapp**

**Telephone: 440-201-3576**

**Name of Reviewer: Marla Stevens-Riley**

**Conclusion: Recommended for approval on the basis on sterility assurance**

---

## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUPPLEMENT:** N/A
  2. **SUPPLEMENT PROVIDES FOR:** N/A
  3. **MANUFACTURING SITE:** Ben Venue Laboratories  
270 Northfield Rd.  
Bedford, Ohio 44146
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** sterile solution, intravenous administration, 2 mg/mL as 10 mL (20 mg), 12.5 mL (25 mg), and 15 mL(30 mg) per vial
  5. **METHOD(S) OF STERILIZATION:** \_\_\_\_\_
  6. **PHARMACOLOGICAL CATEGORY:** chemotherapeutic agent for prostate cancer and acute non-lymphocytic leukemia
- B. **SUPPORTING/RELATED DOCUMENTS:** DMFs 2315 (2315mic6a1) and \_\_\_\_\_
- C. **REMARKS:** The subject amendment provides responses for the deficiency letter dated October 10, 2003. In addition, the applicant provides revised bioburden specifications and refers to the October 20, 2003 submission (amendment) to DMF 2315. The November 20, 2003 telephone amendment regarding the depyrogenation of the stoppers is also reviewed.

**filename:** v:microrev\76-611a1.doc

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**Executive Summary**

**I. Recommendations**

- A. **Recommendation on Approvability** – Recommended for approval on the basis of sterility assurance
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** –N/A

**II. Summary of Microbiology Assessments**

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – \_\_\_\_\_
- B. **Brief Description of Microbiology Deficiencies** –none
- C. **Assessment of Risk Due to Microbiology Deficiencies** -The risk to public health associated with this drug product is low.

**III. Administrative**

A. **Reviewer's Signature** Macla Stevens-Riley

B. **Endorsement Block**  
M. Stevens-Riley, Ph.D. 12/10/03  
N. J. Sweeney, Ph.D.

*N. J. Sweeney*  
12-10-03

C. **CC Block**  
cc:  
Original ANDA 76-611  
Division File  
Field Copy

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of trade secret and/or

confidential commercial

information from

*MICROBIOLOGY REVIEW #2*

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# Product Quality Microbiology Review

## Review for HFD-620

28 February 2006

ANDA: 76-611

### Drug Product Name

**Proprietary:** Novantrone

**Non-proprietary:** Mitoxantrone Injection USP

**Drug Product Priority Classification:** N/A

Review Number: 3

### Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
8/27/04 (gratuitous)	8/30/04		
2/24/06	2/27/06	N/A	2/10/06
3/7/06	3/15/06		

### Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
11/20/03	2	12/5/03
10/28/03		
8/5/03	1	8/11/03
12/26/02		

### Applicant/Sponsor

**Name:** Bedford Laboratories

**Address:** 300 Northfield Road  
Bedford, Ohio 44146

**Representative:** Molly Rapp, Manager Regulatory Affairs

**Telephone:** 440-201-3576

**Name of Reviewer:** Marla Stevens-Riley, Ph.D.

**Conclusion:** Recommended for approval on the basis of sterility assurance

---

## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** gratuitous amendment
  2. **SUBMISSION PROVIDES FOR:** addition of new filling line for drug product
  3. **MANUFACTURING SITE:** Ben Venue Laboratories  
270 Northfield Rd.  
Bedford, Ohio 44146
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** sterile solution, intravenous administration, 2 mg/mL as 10 mL (20 mg), 12.5 mL (25 mg), and 15 mL(30 mg) per vial
  5. **METHOD(S) OF STERILIZATION:** \_\_\_\_\_
  6. **PHARMACOLOGICAL CATEGORY:** Indicated as chemotherapeutic agent for prostate cancer and acute non-lymphocytic leukemia
- B. **SUPPORTING/RELATED DOCUMENTS:** DMF 2315 (see DMF review 2315mic20, dated 2/28/06). The LOA is dated March 18, 2003.
- C. **REMARKS:** The August 27, 2004 submission is a gratuitous amendment that adds the use of \_\_\_\_\_ Suite 13 as an option for \_\_\_\_\_ the drug product. The February 24, 2006 and March 7, 2006 amendments are telephone amendments providing more detailed information regarding the equipment associated with \_\_\_\_\_.

filename: 76-611a2.doc

**Executive Summary**

**I. Recommendations**

- A. **Recommendation on Approvability - Recommended for approval based on sterility assurance.**
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -N/A**

**II. Summary of Microbiology Assessments**

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - \_\_\_\_\_**
- B. **Brief Description of Microbiology Deficiencies-none**
- C. **Assessment of Risk Due to Microbiology Deficiencies -The public health risk associated with this drug product is minimal.**

**III. Administrative**

- A. **Reviewer's Signature** Marla Stevens-Riley
- B. **Endorsement Block**  
 Marla Stevens-Riley, Ph.D. 3/17/06  
 Team Leader: Neal Sweeney
- C. **CC Block**  
 cc:  
 Original ANDA 76-611  
 Division File  
 Field Copy

*Neal Sweeney*  
3-17-06

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confidential commercial

information from

MICROBIOLOGY REVIEW #3

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This information remains unchanged from previous review (76-611a1, dated 12/5/2003).

**F.3. Microbial Limits Testing-N/A**

**APPEARS THIS WAY  
ON ORIGINAL**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 76-611**

**ADMINISTRATIVE DOCUMENTS**

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE : January 28, 2003

TO : Director  
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch  
Office of Generic Drugs (HFD-615)

*JD* 28-JAN-2003

SUBJECT: Examination of the request for waiver submitted with an ANDA for Mitoxantrone Injection USP, 2 mg/mL; 10 mL, 12.5 mL and 15 mL vials determine if the application is substantially complete for filing.

Bedford Laboratories submitted ANDA 76-611 for Mitoxantrone Injection USP, 2mg/mL; 10 mL, 12.5 mL and 15 mL vials. The ANDA contains a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the request for waiver is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for waiver submitted by Bedford on December 26, 2002 for its Mitoxantrone product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

**BIOEQUIVALENCE CHECKLIST for First Generic ANDA  
FOR APPLICATION COMPLETENESS**

ANDA# 76-611 FIRM NAME BEDFORD LABORATORIES

DRUG NAME MITOXANTRONE

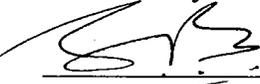
DOSAGE FORM INJECTION

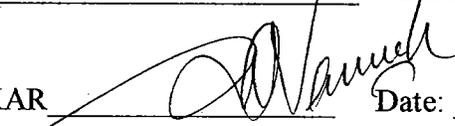
Requested by: GREG DAVIS  Date: 1/28/03  
Chief, Regulatory Support Team, (HFD-615)

Summary of Findings by Division of Bioequivalence	
	Study meets statutory requirements
	Study does NOT meet statutory requirements
	Reason:
X	Waiver meets statutory requirements
	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION:  X  COMPLETE   INCOMPLETE

Reviewed by: S. P. SHRIVASTAVA

  
Reviewer Date: 1/31/03

S. NERURKAR   
Team Leader Date: 2/5/2003

DALE CONNER   
Director, Division of Bioequivalence Date: 2/12/03

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	NA				
Assay Methodology					
Procedure SOP					
Methods Validation					
Study Results Ln/Lin					
Adverse Events					
IRB Approval					
Dissolution Data					
Pre-screening of Patients					
Chromatograms					
Consent Forms	↓				
Composition	YES				
Summary of Study	↑				
Individual Data & Graphs, Linear & Ln					
PK/PD Data Disk (or Elec Subm)					
Randomization Schedule					
Protocol Deviations	NA				
Clinical Site					
Analytical Site					
Study Investigators					
Medical Records					
Clinical Raw Data					
Test Article Inventory	↓				

BIO Batch Size	yes				
Assay of Active Content Drug	yes				
Content Uniformity	yes				
Date of Manufacture	yes				
Exp. Date of RLD	N/A				
BioStudy Lot Numbers	↓				
Statistics					
Summary results provided by the firm indicate studies pass BE criteria					
Waiver requests for other strengths / supporting data					

Additional Comments regarding the ANDA: *None*

**APPEARS THIS WAY  
ON ORIGINAL**

# TELEPHONE MEMO

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**ANDA/DMF#:** ANDA 76-611 and DMF 2315  
**FIRM:** Bedford  
**PARTICIPANTS:** Marla Stevens-Riley-FDA *M. Stevens-Riley 8/8/03*  
Molly Rapp-Bedford/Ben Venue  
**DATE:** 8/6/03  
**SUBJECT:** Mitoxantrone Injection  
**REQUESTED BY:** FDA

Dr. Stevens-Riley discussed the following:

1. The 8/5/03 fax stated slightly different information than what was stated in the voice mail message. Which information is correct? **Ms. Rapp stated that the 8/5/03 fax was correct.**
2. The information about the \_\_\_\_\_ in the March 14, 2003 submission to DMF 2315 is different from information seen in another application 76-461. Which is correct? **Ms. Rapp stated that she would check on this and get back with Dr. Stevens-Riley.**
3. The June 9, 2003 amendment to deficiencies in the March 14, 2003 submission to DMF 2315 contains what appears to be a DMF update dated May 19, 2003 in Attachment IX (without the associated appendices of data). Should this be a complete update to the DMF? If so, it should be submitted separately as an update and have the associated data. **Ms. Rapp stated that she would check on this and get back with Dr. Stevens-Riley.**
4. Dr. Stevens-Riley stated she has been reviewing several of their applications and has been trying to identify the repeated deficiencies. Dr. Stevens-Riley described the problems with referencing the DMF and the general review deficiencies that are continually encountered in Bedford's applications. Some of the problems are lack of specific information in the ANDA to direct the reviewer to the exact filling line and equipment to review in the DMF, the repeated absence of the general information in the DMF and ANDAs necessary for review, and slight differences in the information submitted to an ANDA and the DMF. Dr. Stevens-Riley stated that reviews could proceed more efficiently if information was submitted with the ANDA rather than to the DMF. She stated that when they receive the deficiencies, they should note the ones that apply to most all of the applications and attempt to correct those for future submissions.

**It was agreed that Ms. Rapp would call back with the information requested and fax the information as a telephone amendment and will send in a hard copy of the information.**

Filename: V/FirmsAM/Bedford/Telecons/76611MicroAug603.doc  
CC: ANDA 76-611  
CC: Division File

# TELEPHONE MEMO

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ANDA/DMF#: ANDA 76-611 and DMF 2315

FIRM: Bedford *M. Stevens-Riley 8-8-03*

PARTICIPANTS: Marla Stevens-Riley-FDA and Bonnie McNeal-FDA *B. McNeal 8/11/03*  
Molly Rapp-Bedford/Ben Venue

DATE: 8/8/03

SUBJECT: Mitoxantrone Injection

REQUESTED BY: FDA

Ms. Rapp had responses to previous issues:

1. The information about the \_\_\_\_\_ in the March 14, 2003 submission to DMF 2315 is different from information seen in another application 76-461. Which is correct? Ms. Rapp stated that the information in 76-461 is incorrect and the DMF 2315 March 14, 2003 update is correct. Dr. Stevens-Riley stated that it would be easier to make deficiencies regarding the \_\_\_\_\_ rather than have Ms. Rapp send in a telephone amendment because there are other deficiencies in the application.
2. The June 9, 2003 amendment to deficiencies in the March 14, 2003 submission to DMF 2315 contains what appears to be a DMF update dated May 19, 2003 in Attachment IX (without the associated appendices of data). Should this be a complete update to the DMF? If so, it should be submitted separately as an update and have the associated data. Ms. Rapp stated that this was meant to be an update as well as an answer the deficiency; however, the data pages were not included. Dr. Stevens-Riley, Ms. McNeal, and Ms. Rapp discussed the potentials problems with this "buried" information and decided that it would be better to submit a complete new update to the DMF. This update would not be submitted until after Ms. Rapp had received deficiencies from pending applications so she could incorporate the changes into the DMF update as well as prepare a response for the deficiencies.

Filename: V/FirmsAM/Bedford/Telecons/76611MicroAug803.doc

CC: ANDA 76-611

CC: Division File

## RECORD OF TELEPHONE CONVERSATION

<p>Reference is made to chemistry deficiency letter dated June 13, 2003. And Bedford Laboratories amendment dated July 3, 2003.</p> <p>FDA: Your response to deficiency A.2. is incomplete. Please clarify.</p> <p>A Deficiencies:</p> <p>2. Please test the drug substance for residual solvents and submit a revised drug substance COA. You should not use the vendor's test results before you have qualified your vendor based on your vendor qualification program.</p> <p>Bedford Labs: We did our qualification using the vendor's method.</p> <p>FDA: What is your vendor validation program?</p> <p>Bedford Labs: We normally do 3 lots, however we only had 1 lot at the time. We will gladly commit to qualifying two additional lots.</p> <p>FDA: You may send a commitment for the next two batches.</p>	<p style="text-align: center;"><b>DATE:</b></p> <p style="text-align: center;">September 3, 2003</p> <hr/> <p style="text-align: center;"><b>ANDA NUMBER</b></p> <p style="text-align: center;">76-611</p> <hr/> <p style="text-align: center;"><b>TELECON INITIATED BY AGENCY</b></p> <hr/> <p style="text-align: center;"><b>PRODUCT NAME:</b></p> <p style="text-align: center;">Mitoxantrone Injection</p> <hr/> <p style="text-align: center;"><b>FIRM NAME:</b></p> <p style="text-align: center;"><b>BEDFORD LABORATORIES</b></p> <hr/> <p style="text-align: center;"><b>FIRM REPRESENTATIVES:</b></p> <p style="text-align: center;">Molly Rapp</p> <hr/> <p style="text-align: center;"><b>TELEPHONE NUMBER:</b></p> <p style="text-align: center;">440-201-3576</p> <hr/> <p style="text-align: center;"><b>FDA REPRESENTATIVES</b></p> <p style="text-align: center;">Shing Liu, Ph.D. Kathy Woodland. Wanda Pamphile, Pharm.D.</p> <hr/> <p style="text-align: center;"><b>SIGNATURES:</b></p> <p style="text-align: center;">Shing Liu <i>S.H. Liu 9/3/03</i> Kathy Woodland <i>K Woodland 9/3/03</i> Wanda Pamphile <i>WP 9/3/03</i></p>
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Orig: ANDA 76-611  
 Cc: Division File  
 Chem. I Telecon Binder

V:\FIRMSAM\BEDFORD\TELECONS\76611.doc

Memorandum to the File

ANDA: 76-611

DRUG: Mitoxantrone Injection USP, 2 mg/mL, 10 mL,  
12.5 mL and 15 mL vials

SUBJECT: Clarification of error on Microbiology Deficiencies Fax  
Cover sheet sent to firm on October 10, 2003.

FIRM: Bedford Laboratories, Inc.

DATE: October 29, 2003

Please note that the fax cover sheet sent to the firm with Microbiology deficiencies contained errors. The fax sheet stated that the file on the application was closed with the issuing of these Microbiology deficiencies. **This is incorrect.** Only the issuance of Chemistry deficiencies can close the file on an application.

Therefore this memo should correct the file and clarify that the cover sheet was sent to the firm in error, and the file on this application should not be closed with the issuance of these deficiencies.

In the future a corrected cover sheet will be used to issue Microbiology deficiencies.

My apologies to the Document Room staff for this oversight.

*Bonnie McNeal 10/29/03*

Bonnie McNeal  
Project Manager, Microbiology Team, OGD

cc: ANDA 76-611  
Division file  
HFD-617/TAmes

File: V:\FIRMSAM\Bedford\MEMOS\76611Micro.doc

## RECORD OF TELEPHONE CONVERSATION

Upon ANDA 76-611 reaching the Division, Dr. Paul Schwartz pointed out that the drug product release specification does not include "other requirements" per USP <1>, per the current USP.

Bedford was asked to add this missing specification to their specification sheet for release, and to also update their specs for methods.

**APPEARS THIS WAY  
ON ORIGINAL**

**DATE:**

January 13, 2004

**ANDA NUMBER:**

76-611

**PRODUCT NAME:**

Mitoxantrone Injection  
USP, 2 mg/ mL

**INITIATED BY:**

Firm  Agency

**FIRM NAME:**

Bedford Labs

**FIRM REPRESENTATIVE:**

Pratima Patel

**TELEPHONE NUMBER:**

440-201-3469

**FDA REPRESENTATIVE:**

Shing Liu, Ph.D.  
Wanda Pamphile,  
Pharm.D.

**SIGNATURE**

Shing Liu *S.H. Liu 1/13/04*  
Wanda Pamphile *WP 1/13/04*

Orig: ANDA 76-611

Cc: Division File

Chem. I

V:\FIRMSAM\BEDFORD\TELECONS\76611Chem1.doc

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-611

Applicant Bedford Laboratories

Drug Mitoxantrone Injection USP

Strength(s) 2 mg/mL, 10 mL, 12.5 mL, and 15 ML

APPROVAL  TENTATIVE APPROVAL  SUPPLEMENTAL APPROVAL (NEW STRENGTH)  OTHER

REVIEWER:

DRAFT Package

FINAL Package

1. Martin Shimer  
Chief, Reg. Support Branch

Date 10/27/2003  
Initials MAS

Date 2/19/04  
Initials [Signature]

Contains GDEA certification: Yes  No   
(required if sub after 6/1/92)

Determ. of Involvement? Yes  No   
Pediatric Exclusivity System

Patent/Exclusivity Certification: Yes  No

RLD = NDA# 19297  
Date Checked 2/19/04

If Para. IV Certification- did applicant

Nothing Submitted

Notify patent holder/NDA holder Yes  No

Written request issued

Was applicant sued w/in 45 days: Yes  No

Study Submitted

Has case been settled: Yes  No

Date settled:

Is applicant eligible for 180 day

Generic Drugs Exclusivity for each strength: Yes  No

Type of Letter: TA

Comments: Eligible for TA only

2. Project Manager, Wanda Pamphile Team 5  
Review Support Branch

Date 12/19/03  
Initials WP

Date 1/1/04  
Initials WP

Original Rec'd date 12/26/02

EER Status Pending  Acceptable  OAI

Date Acceptable for Filing 12/30/02 ✓

Date of EER Status 5/28/03

Patent Certification (type) III

Date of Office Bio Review 8/22/03

Date Patent/Exclus. expires 4/11/06

Date of Labeling Approv. Sum 12/17/03

Citizens' Petition/Legal Case Yes  No

Date of Sterility Assur. App. 12/10/03

(If YES, attach email from PM to CP coord)

Methods Val. Samples Pending Yes  No

First Generic Yes  No

MV Commitment Rcd. from Firm Yes  No

Acceptable Bio reviews tabbed Yes  No

Modified-release dosage form: Yes  No

Interim Dissol. Specs in AP Ltr: Yes

Previously reviewed and tentatively approved  Date \_\_\_\_\_

Previously reviewed and CGMP def./NA Minor issued  Date \_\_\_\_\_

Comments:

3. Div. Dir./Deputy Dir.  
Chemistry Div. I or II  
Comments:

Date 1/21/04  
Initials RS

CAC acceptable  
review updated

4. Frank Holcombe First Generics Only  
Assoc. Dir. For Chemistry  
Comments: (First generic drug review) [Signature]

Date 2/1/04  
Initials FSH

REVIEWER:

FINAL ACTION

5. Gregg Davis  
Deputy Dir., DLPS

Date \_\_\_\_\_  
Initials \_\_\_\_\_

RCD = Novantrene <sup>injection</sup> (Concentrate)  
Serono Inc.

2mg (base) / mL  
NDA 19-297

20mg/10mL,  
25mg/12.5mL,  
30mg/15mL  
multi-dose vials

6. Peter Rickman  
Director, DLPS

Date 2/19/04  
Initials [Signature]

Para. IV Patent Cert: Yes  No ; Pending Legal Action: Yes  No ; Petition: Yes  No

Comments: Acceptable PDS dated 12/28/03 (verified 2/19/04) No OAT alerts

noted - Bioequivalence waiver granted under 21 CFR 320.22 (b)(1). The drug product is "ND" to the RLD. Office-level bio endorsed 8/22/03. Microbiology/sterility assurance found acceptable 12/10/03. Labeling found acceptable for TTA 12/17/03. CME found acceptable 1/21/04. Methods validation is not required - both the API and drug product are commercial. First generic CMC audit has been completed.

6. Robert L. West  
Acting Deputy Director, OGD

Date 2/19/2004  
Initials [Signature]

Para. IV Patent Cert: Yes  No ; Pending Legal Action: Yes  No ; Petition: Yes  No

Comments: At the time of filing Bedford made a paragraph III Certification

to both the '319 and '1738 patents. Bedford also addressed the NDA holder's orphan drug exclusivity pertaining to multiple sclerosis.

This ANDA is recommended for tentative approval.

7. Gary Buehler  
Director, OGD

Date 2/19/04  
Initials GB

Comments: tentative  
First Generic Approval

PD or Clinical for BE

Special Scientific or Reg. Issue

8. Project Manager, Team  
Review Support Branch

Date \_\_\_\_\_  
Initials \_\_\_\_\_

Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:

45 Time notified of approval by phone 5P Time approval letter faxed

FDA Notification:

2/19/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

2/19/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-611 Applicant Bedford Laboratories

Drug Mitoxantrone Injection USP Strength(s) 2 mg/mL, 10 ml, 12.5 mL, and 15 mL

APPROVAL  TENTATIVE APPROVAL  SUPPLEMENTAL APPROVAL (NEW STRENGTH)  OTHER

REVIEWER:

DRAFT Package

FINAL Package

1. Martin Shimer  
Chief, Reg. Support Branch

Date 31 March 2006  
Initials MS

Date 4/4/06  
Initials [Signature]

Contains GDEA certification: Yes  No  Determ. of Involvement? Yes  No   
(required if sub after 6/1/92) Pediatric Exclusivity System  
Patent/Exclusivity Certification: Yes  No  RLD = NDA# 19-297  
If Para. IV Certification- did applicant Date Checked 4/4/06  
Nothing Submitted   
Notify patent holder/NDA holder Yes  No  Written request issued   
Was applicant sued w/in 45 days: Yes  No  Study Submitted   
Has case been settled: Yes  No  Date settled:  
Is applicant eligible for 180 day

Generic Drugs Exclusivity for each strength: Yes  No   
Date of latest Labeling Review/Approval Summary  
Any filing status changes requiring addition Labeling Review Yes  No   
Type of Letter: PIII to 73564P 4/11/06  
Comments: ODE carried out Eligible for Full Approval on 4/11/2006

2. Project Manager, Ben Danso Team 5  
Review Support Branch

Date 3-31-06  
Initials BD

Date  
Initials

Original Rec'd date 12-26-2002 EER Status Pending  Acceptable  OAI   
Date Acceptable for Filing 12-30-2002 Date of EER Status 2-8-2006  
Patent Certification (type) pIII Date of Office Bio Review 8-22-2003  
Date Patent/Exclus. expires 4-11-2006 Date of Labeling Approv. Sum 3-16-2006  
Citizens' Petition/Legal Case Yes  No  Labeling Acceptable Email Rec'd Yes  No   
(If YES, attach email from PM to CP coord) Labeling Acceptable Email filed Yes  No   
First Generic Yes  No  Date of Sterility Assur. App. \_\_\_\_\_  
Methods Val. Samples Pending Yes  No   
MV Commitment Rcd. from Firm Yes  No   
Acceptable Bio reviews tabbed Yes  No  Modified-release dosage form: Yes  No   
Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes   
Pediatric Waiver Request Accepted  Rejected  Pending   
Previously reviewed and tentatively approved  Date 2-19-2004  
Previously reviewed and CGMP def. /NA Minor issued  Date \_\_\_\_\_  
Comments:

3. David Read (PP IVs Only) Pre-MMA Language included   
OGD Regulatory Counsel, Post-MMA Language Included   
Comments:

Date  
Initials

N/A

4. Div. Dir./Deputy Dir.  
Chemistry Div. I II OR III  
Comments:

Date 4/3/06  
Initials RLS

CGMP section is OK for AP

REVIEWER:

FINAL ACTION

5. Frank Holcombe First Generics Only Date \_\_\_\_\_  
 Assoc. Dir. For Chemistry Initials \_\_\_\_\_  
 Comments: (First generic drug review)  
 N/A. The first generic CMC audit was completed at the time of the tentative approval.

6. Vacant RLD = Novantone Injection 2mg(base)/mL Date \_\_\_\_\_  
 Deputy Dir., DLPS Serono Inc. Initials \_\_\_\_\_  
NDA 19-297 (Multi-dose vials)  
20mg(base)/10mL  
25mg(base)/12.5mL  
30mg(base)/15mL

7. Peter Rickman Date 4/4/06  
 Director, DLPS Initials \_\_\_\_\_  
 Para. IV Patent Cert: Yes  No  Pending Legal Action: Yes  No  Petition  Yes  No

Comments: Acceptable EGS dated 2/8/06 (revised 4/4/06) No OAI alerts noted. This ANDA was tentatively approved on 2/19/06 pending expiration of the '738 patent. Refers to the administrative sign off form completed at the time of the tentative approval. On 2/21/06 Bedford amended this ANDA to provide for an alternate \_\_\_\_\_ site for the drug product. Updated OI and Labeling was submitted on 11/2/06. Microbiology facility assurance found acceptable 3/17/06. FPL found acceptable for approval 3/16/06 (sponsored 3/29/06). OI found acceptable for approval 3/29/06. Methods validation was not requested for this compendial drug product.

8. Robert L. West Date 4/4/2006  
 Deputy Director, Initials \_\_\_\_\_  
 Para. IV Patent Cert: Yes  No  Pending Legal Action: Yes  No  Petition  Yes  No

Comments: Bedford made a paragraph 3C certification to the '738 patent expiring on 4/11/06. All language pertaining to Serono's Orphan Drug Exclusivity covering use of the drug product in the treatment of multiple sclerosis has been "carved out" of the labeling. The ODE expires on 10/13/07. This ANDA is recommended for final approval upon the expiration of the '738 patent on April 11, 2006.

9. Gary Buehler Date 4/11/06  
 Director, OGD Initials GB  
 Comments:  
 First Generic Approval  PD or Clinical for BE  Special Scientific or Reg. Issue

10. Project Manager, Team Ben Danso Date 4/11/06  
 Review Support Branch Initials \_\_\_\_\_  
 N/A Date PETS checked for first generic drug (just prior to notification to Applicant notification: \_\_\_\_\_)  
 Applicant notification: \_\_\_\_\_  
 12 - Time notified of approval by phone 12:10 Time approval letter faxed  
 FDA Notification: \_\_\_\_\_  
 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list. 4/11/06  
 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

**MEMORANDUM****DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

---

**DATE:** April 11, 2006

**FROM:**

Gary Buehler

Director

Office of Generic Drugs



4/11/06

**SUBJECT:** ANDA Labeling for Mitoxantrone Injection.

**TO:**

ANDA 76-611 - Bedford Labs

ANDA 76-871 - Mayne Pharma

ANDA 77-496 - American Pharmaceutical Partners, Inc.

ANDA 77-356 - Sicor Pharmaceuticals, Inc.

Dr. Katz, Director of the Division of Neurology Products, reported to me that he received a phone call from someone at Serono, the manufacturer of Novantrone (mitoxantrone). This call was apparently prompted by two tentative approvals of mitoxantrone, pending the expiration of Serono's patent for the oncology indication on April 11. The MS indication is protected, due to orphan exclusivity, until 2007. There are extensive monitoring requirements in the label that pertain to the MS patients (cardiac monitoring before every dose, etc.), and the company was wondering how this gets incorporated into the generic labeling, given that they will not get the MS indication at this time, but given the likely (off-label) use in this population.

Further communications from the division indicated a concern about patient safety issues (particularly cardiotoxicity monitoring) for MS patients who may be receiving the new generic version of mitoxantrone, in particular that prescribers who might not have used the drug in the past for MS patients might decide to use the generic and would not know what to do (at least not from the labeling). Also, if patients don't get the patient leaflet they won't know what monitoring they are supposed to undergo. The division asked if safety information related to an off-label indication could be added to a generic drug, noting that sometimes pediatric safety information is sometimes added even when a generic is prevented by exclusivity from carrying the pediatric claim.

I contacted various people in OGD as well as Liz Dickinson in OCC to consider our regulatory options.

When reviewing whether it is appropriate to permit the omission of protected information from labeling, OGD is governed by 21 CFR 314.127(a)(7). That regulation directs that the scope of our inquiry regarding safety and effectiveness with labeling carve-outs is limited to determining whether the differences in the generic labeling would render the drug less safe or effective than the listed drug for "all remaining nonprotected conditions of use." The agency's inquiry does not extend to possible off-label uses of the drug product. The issue of orphan drug exclusivity, and the appropriateness of carving out orphan-protected information, was decided in the case of *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz* (4th Cir. 2002).

The agency's ability to include certain safety information pertaining to pediatric uses to labeling notwithstanding three year exclusivity is governed by the Best Pharmaceuticals Act provision that applies only to pediatric information.

In this instance, the exclusivity covers the MS indication and all of the related precautions and other labeling. The remaining indications are not protected and we have determined that the labeling with the protected information omitted provides appropriate information for use on these nonprotected indications.

This information was conveyed to Dr. Katz. Dr. Katz said he understood the situation and thanked us for looking into it. OGD therefore can proceed with approval of these ANDAs with the proposed labeling.

**APPEARS THIS WAY  
ON ORIGINAL**

cc: ANDA 76-611  
ANDA 76-871  
ANDA 77-496  
ANDA 77-356  
G. Buehler - HFD-600  
R. West - HFD-600  
D. Read - HFD-600  
C. Parise - HFD-600  
D. Hare - HFD-600  
R. Hassall - HFD-600  
P. Rickman - HFD-615  
J. Grace/ A. Payne - HFD-613  
T. Ames/P. Chen - HFD-617

v:\firmsam\bedford\memos\76611 mitoxantrone lab  
v:\firmsam\maynepharmam\memos\76871 mitoxantrone lab  
v:\firmsam\app\memos\77496 mitoxantrone lab  
v:\firmsnz\sicor\memos\77356 mitoxantrone lab

**APPEARS THIS WAY  
ON ORIGINAL**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 76-611**

**CORRESPONDENCE**



December 26, 2002

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

505 (j)(2)(A) OK  
13-FEB-2003  
[Signature]

**RE: Abbreviated New Drug Application**  
**PRODUCT: Mitoxantrone Injection USP; 2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial**

Dear Sir/Madam:

In accordance with Section 505 (j) (1) of the Federal Food, Drug and Cosmetic Act, Bedford Laboratories is submitting in triplicate (an archival copy, a review copy and a field copy) an Abbreviated New Drug Application for Mitoxantrone Injection, USP; 2 mg/mL, 10 mL, 12.5 mL and 15 mL per vial. Please note that the field copy has been sent directly to the FDA District Office in Cincinnati, Ohio.

The drug product subject to this application will be manufactured by Ben Venue Laboratories, Inc., located at 270 Northfield Road, Bedford, Ohio, 44146.

This abbreviated new drug application contains the information required by Section 505 (j)(2)(A)(i), (ii)(I), (iv), (v) and (vi). The application is provided in the format suggested by your office, and contains a copy of the package insert of the "listed drug" (Immunex Corporation; Novantrone®, NDA 019297). The application consists of three volumes.

In accordance with Title 21 CFR 320.22, Bedford Laboratories requests a waiver of the requirement for submission of evidence demonstrating the *in vivo* bioavailability/bioequivalence for the drug product that is the subject of this application (Mitoxantrone Injection, USP; 2 mg/mL, 10 mL, 12.5 mL and 15 mL per vial). The drug product is a sterile solution intended for intravenous administration and it contains active and inactive ingredients in the same concentration as in the listed drug.

Bedford Laboratories certifies that the methods used in, and the facilities and controls used for the manufacture, processing, packaging and holding of the drug product are in conformity with current Good Manufacturing Practices in accordance with Title 21 CFR 210 and 211. Ben Venue's signed statement is provided in Section IX (MANUFACTURING FACILITY) Subsection 3 (cGMP Certification).

RECEIVED  
DEC 30 2002  
OGD / CDER

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264



Bedford Laboratories commits to provide full cooperation to resolve any problem which may arise during the methods validation testing as part of the "Post-Approval" process for the above listed drug product.

Bedford Laboratories acknowledges that the subject drug product is an official article in the United States Pharmacopeia (USP), and in the event of a dispute, only the results obtained by the official methods and procedures mentioned in the USP XXIV will be considered conclusive.

Section XXII of this application, provided as Volume III, contains the Sterilization Assurance Data and Information as well as the following: a copy of the labeling and package insert, a summary of the manufacturing process including the components and composition statement, copies of the executed batch record containing holding times, and sterilization records.

If the Agency has any comments or further requests, or, if we could be of any assistance in your review, the phone numbers for contact are (440)-201-3576 (direct) and (440)-232-2772 (facsimile).

Sincerely,  
for Bedford Laboratories™

A handwritten signature in black ink, appearing to read "Molly Rapp".

Molly Rapp  
Manager, Regulatory Affairs  
Ben Venue Laboratories, Inc.



February 5, 2003

TELEPHONE AMENDMENT

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

NOV LO PRESS

NC

**RE: Abbreviated New Drug Application**  
**PRODUCT: Mitoxantrone Injection USP; 2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial**

Dear Emily:

We would like to revise our unaccepted Abbreviated New Drug Application for Mitoxantrone Injection, USP; 2 mg/mL, 10 mL, 12.5 mL and 15 mL per vial in response to a February 4, 2003 telephone correspondence from Ms. Emily Thomas from the FDA.

The original application incorrectly referred to Immunex Corporation as the holder of the listed drug. The current holder of the listed drug (Novantrone®, NDA 019297) is Serono Inc. The sections affected by this change are provided. This amendment consists of one volume.

In addition, Eda Howard from the FDA contacted us on January 29, 2003 requesting a new label for one of the original ANDA submission volumes. That label is provided in this amendment.

Please note that the labeling is not affected by the change in the holder of the listed drug.

If the Agency has any comments or further requests, or, if we could be of any assistance in your review, the phone numbers for contact are (440)-201-3576 (direct) and (440)-232-2772 (facsimile).

Sincerely,  
for Bedford Laboratories™

Molly Rapp  
Manager, Regulatory Affairs  
Ben Venue Laboratories, Inc.

RECEIVED

FEB 06 2003

OGD / CDER



ANDA 76-611

cc: DUP/Jacket

Division File

Field Copy

HFD-610/R.West

HFD-610/P.Rickman

HFD-92

HFD-615/M.Bennett

HFD-600/

Endorsement:

HFD-615/GDavis, Chief, RSB *Davis* 13-FEB-2003 date

HFD-615/ETHomas, CSO *Anthony Thomas* 2/6/03 date

Word File V:\Firmsam\bedford\ltrs&rev\76611.ack

F/T EST02/06/03

ANDA Acknowledgment Letter!



March 18, 2003

NEW CORRESPONDENCE

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

NEW CORRESP

NC

RE: ANDA 76-611

PRODUCT: Mitoxantrone Injection USP; 2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial

Dear Sir/Madam:

Bedford Laboratories would like to amend their unapproved above listed ANDA by providing revised DMF authorization letter for recently updated DMF 2315.

FDA 356H Form is provided in this amendment along with revised DMF authorization letter.

If you need any assistance in reviewing this Application, the phone numbers for contact are (440)-201-3576 (direct) and (440)-232-2772 (facsimile).

Sincerely,  
for Bedford Laboratories™

*Molly Rapp*

Molly Rapp  
Manager, Regulatory Affairs  
Ben Venue Laboratories, Inc.

RECEIVED

MAR 20 2003

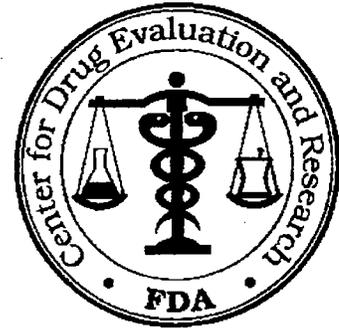
OGD / CDER

# MINOR AMENDMENT

ANDA 76-611

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773 (301-594-0320)

JUN 13 2003



APPLICANT: Bedford Laboratories

TEL: 440-201-3576

ATTN: Molly L. Rapp

FAX: 440-232-2772

FROM: Wanda Pamphile

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 20, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mitoxantrone Injection USP, 2 mg/mL, 10 mL, 12.5 mL and 15 mL vials.

Reference is also made to your amendment(s) dated: December 26, 2002.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (4 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120; which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

## SPECIAL INSTRUCTIONS:

Chemistry and labeling comments included. Please include in response.

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

WF 6/13/03

JUN 13 2003

**36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

ANDA: 76-611

APPLICANT: Bedford Laboratories

DRUG PRODUCT: Mitoxantrone Injection, 2 mg/mL; 10 mL, 12.5 mL and 15 mL vials

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The Drug Master File #  Mitoxantrone Hydrochloride USP, is currently inadequate. The DMF holder has been notified. Please do not respond to this letter until the DMF holder has informed you that a complete response to the DMF deficiencies has been submitted to the agency.
2. Please test the drug substance for residual solvents and submit a revised drug substance COA. You should not use the vendor's test results before you have qualified your vendor based on your vendor qualification program.

3.



4.



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

1. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.
2. Your Sterility Assurance information is pending review. Deficiencies, if any, will be communicated separately.

3. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.
4. Please submit any updated stability data.

Sincerely yours,



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

**REVIEW OF PROFESSIONAL LABELING #1  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH**

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ANDA Number: **76-611**

Dates of Submission: December 26, 2002 (original)

Applicant's Name: Bedford Laboratories

Established Name: Mitoxantrone Injection USP, 2 mg/mL; 10 mL, 12.5 mL and 15 mL MDV vials

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Labeling Deficiencies:

**1. CONTAINER** (2 mg/mL: 10 mL, 12.5 mL and 15 mL):

- a. Add an "Each mL contains Mitoxantrone HCl equivalent to 2 mg Mitoxantrone free base.
- b. If space permits add "cytotoxic agent".
- c. Add, "(concentrate)" to the main panel. This word is seen on the reference listed drug labels and would give added emphasis that this product **must** be diluted before injection.

**2. CARTON** (1s: 20 mg/10mL; 25 mg/12.5 mL or 30 mg/15 mL): - See comments under Container.

**3. INSERT:**

a. GENERAL COMMENT

Please be advise that your proposed labeling will need to be revised according to the most recently approved labeling for Novantrone Injection (Mitoxantrone HCl; NDA 19-297/S-027; Approved 1/13/03; Serono, Inc). The current label for this drug product is not available in electronic format from FDA. To obtain a current label, please contact the Company, We note the revised RLD labeling is not available to our office at this time. Review of your proposed labeling is pending.

b. DESCRIPTION

"Acetic acid" should be replace by the proper USP name which is Glacial Acetic Acid' and sterile water, USP should be added as an inactive ingredient to be consistent with your component/composition statement.

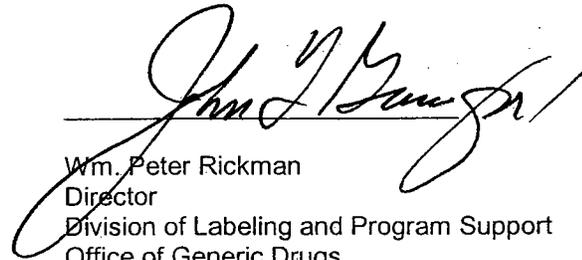
**4. PATIENT INFORMATION SHEET** - See comments under INSERT.

Please revise your labels and labeling, as instructed above, and submit in final print container labels and draft patient and insert labeling.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

<http://www.fda.gov/cder/cdernew/listserv.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 the most recent Novantrone labeling with all differences annotated and explained.

A handwritten signature in black ink, appearing to read "Wm. Peter Rickman", is written over a horizontal line. The signature is cursive and somewhat stylized.

Wm. Peter Rickman  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**APPEARS THIS WAY  
ON ORIGINAL**

July 3, 2003

**Minor Amendment/  
Chemistry and Labeling**

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

ORIG AMENDMENT  
NAM

**RE: ANDA 76-611/Minor Amendment - Chemistry and Labeling**  
**PRODUCT: Mitoxantrone Injection USP; 2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial**

Dear Sir/Madam:

Bedford Laboratories™ would like to amend their unapproved above listed ANDA by responding the Agency's deficiency dated June 11, 2003. FDA 356H Form is provided.

A. Chemistry Deficiency Response: The number associated with the responses given below correspond to the number identifying the deficiencies in your communication.

1. The DMF holder has responded to the deficiencies for DMF # ——— Please see Attachment I for a copy of the DMF holder's acknowledgement of a complete response to the DMF deficiencies dated July 2, 2003.
2. The confirmational residual solvent testing was provided in the original application on pages 133 to 139; a copy has been provided for your convenience in Attachment II.

3. 

4. 

RECEIVED  
JUL 07 2003  
OGD/CDER

*Handwritten initials and numbers:*  
MPL  
7-5-03

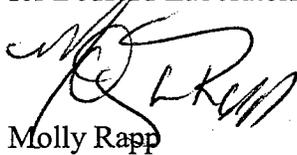
B. Labeling Deficiencies: The responses to the labeling deficiencies will be submitted when the RLD labeling becomes available.

C. Acknowledgements:

1. Bedford Laboratories™ acknowledges that all facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval.
2. Bedford Laboratories™ acknowledges that the sterility assurance information is pending review.
3. Bedford Laboratories™ acknowledges that the bioequivalence information is pending review.
4. Please refer to Attachment IV for updated stability data.

If you need any assistance in reviewing this Application, the phone numbers for contact are (440)-201-3576 (direct) and (440)-232-2772 (facsimile) or via email at [mrapp@cle.boehringer-ingelheim.com](mailto:mrapp@cle.boehringer-ingelheim.com).

Sincerely,  
for Bedford Laboratories™



Molly Rapp  
Manager, Regulatory Affairs  
Ben Venue Laboratories, Inc.



August 5, 2003

**Telephone Amendment**

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

ORIG AMENDMENT  
N/AM

**RE: ANDA 76-611/Telephone Amendment**  
**PRODUCT: Mitoxantrone Injection USP; 2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial**

Dear Ms. McNeil:

Bedford Laboratories™ would like to amend their unapproved above listed ANDA by responding to the Agency's telephone communication of August 4, 2003. FDA 356H Form is provided.

The specific equipment to be used for future manufacturing of Mitoxantrone is provided. Please note that the stoppers are pre-washed and therefore stopper washing equipment is not listed.

If you have any questions or comments the phone numbers for contact are (440)-201-3576 (direct) and (440)-232-2772 (facsimile) or via email at [mrapp@cle.boehringer-ingelheim.com](mailto:mrapp@cle.boehringer-ingelheim.com).

Sincerely,  
for Bedford Laboratories™

Molly Rapp  
Manager, Regulatory Affairs  
Ben Venue Laboratories, Inc.

RECEIVED  
AUG 06 2003  
OGD/CD

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264



September 3, 2003

ORIG AMENDMENT

N/AM

**Telephone Amendment**

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

**RE: ANDA 76-611/Telephone Amendment**  
**PRODUCT: Mitoxantrone Injection USP; 2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial**

Dear Sir/Madam:

Bedford Laboratories™ would like to amend their unapproved above listed ANDA by responding to the Agency's telephone communication of September 3, 2003. FDA 356H Form is provided.

Bedford Laboratories™ commits to performing confirmational residual solvent qualification on two additional lots of drug substance and reporting these results to the Office of Generic Drugs. Please note that results have been already submitted for one lot of drug substance.

If you have any questions or comments the phone numbers for contact are (440)-201-3576 (direct) and (440)-232-2772 (facsimile).

Sincerely,  
for Bedford Laboratories™

  
Molly Rapp  
Manager, Regulatory Affairs  
Ben Venue Laboratories, Inc.

RECEIVED  
SEP 04 2003  
OGD/CDEH

## MINOR AMENDMENT- Microbiology

ANDA 76-611

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773 (301-594-0320)

OCT 10 2003



APPLICANT: Bedford Laboratories

TEL: 440-201-3576

ATTN: Molly Rapp

FAX: 440-232-2772

FROM: Bonnie McNeal

PROJECT MANAGER: 301-827-0530

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 26, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mitoxantrone Mesylate Injection USP, 2 mg/mL.

Reference is also made to your amendment dated: August 5, 2003

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT-RESPONSE TO MICROBIOLOGY DEFICIENCIES should appear prominently in your cover letter. You have been/will be notified in separate communications from our Divisions of Chemistry Bioequivalence and Labeling of any deficiencies identified during our review of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

### SPECIAL INSTRUCTIONS:

Please respond to this letter as soon as possible. However, should you also have other outstanding deficiencies, for review purposes, please attempt to consolidate your responses into a single submission for this application.

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

B. Mc  
10/9/03

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

10/10/2003 FDA FAX

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December 1, 2003

**Minor Amendment - Labeling**

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

**ORIG AMENDMENT**

*N/AFI*

**RE: ANDA 76-611/Minor Amendment - Labeling**  
**PRODUCT: Mitoxantrone Injection USP; 2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial**

Dear Sir/Madam:

Bedford Laboratories™ would like to amend their unapproved above listed ANDA by responding the Agency's deficiency dated June 13, 2003. FDA 356H Form is provided.

The number assigned to each response listed below corresponds to the deficiencies communicated as per the Agency's correspondence dated June 13, 2002.

1. The size of the 10 mL container label does not allow for inclusion of the statement, "cytotoxic agent." All other recommended revisions to the container labels have been completed as requested.
2. All recommended revisions to the carton labeling have been completed as requested.
3. All recommended revisions to the package insert have been completed as requested. Reference is made to the Agency's correspondence dated October 1, 2003 in which the current reference listed drug labeling was provided. This correspondence has been utilized as the basis for revisions made to the Bedford Laboratories™ package insert.
4. Please note that the Bedford Laboratories™ package insert does not contain indications for use in patients with multiple sclerosis, and all references for use of the drug product in multiple sclerosis patients have been removed from the Bedford Laboratories™ labeling. The multiple sclerosis indications are protected by an Orphan Drug Exclusivity expiring October 13, 2007 (refer to section III of the original ANDA). Therefore, a patient information sheet is not provided as the information supplied is specific to this indication.

Side-by-side comparisons of the final printed container labels and cartons and draft package insert labeling versus that last submitted are provided under Attachment I. Twelve copies of each final printed container labels and cartons are provided under Attachment II. In addition, 4 copies of the draft package insert labeling are provided under Attachment III.

RECEIVED

DEC 03 2003

OGD/CDEr

A DIVISION OF BEN VENUE LABORATORIES, INC.



If you need any assistance in reviewing this Application, the phone numbers for contact are (440)-201-3576 (direct) and (440)-232-2772 (facsimile) or via email at [mrapp@cle.boehringer-ingenelheim.com](mailto:mrapp@cle.boehringer-ingenelheim.com).

Sincerely,  
for Bedford Laboratories™

A handwritten signature in black ink, appearing to read "Molly Rapp". The signature is written in a cursive style with a large, sweeping initial "M".

Molly Rapp  
Manager, Regulatory Affairs  
Ben Venue Laboratories, Inc.

**APPEARS THIS WAY  
ON ORIGINAL**



December 17, 2003

**Telephone Amendment - Labeling**

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

**RE: ANDA 76-611/Telephone Amendment - Labeling**  
**PRODUCT: Mitoxantrone Injection USP; 2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial**

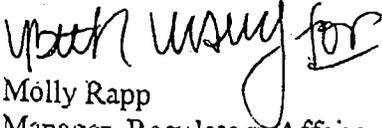
Dear Sir/Madam:

This amendment is submitted in response to a December 17, 2003 telephone contact from Angela Payne from the Agency concerning our Abbreviated new Drug Application, ANDA 76-611 for Mitoxantrone Injection, USP; 2 mg/mL, 10 mL, 12.5 mL and 15 mL per vial.

Bedford Laboratories™ commits to make the changes sent by the Agency to our package insert regarding the "Geriatric Use" and "Drug Interaction" sub-sections. Final printed labeling will be submitted prior to the final approval of Mitoxantrone Injection, USP.

If you need any assistance in reviewing this Application, the phone numbers for contact are (440)-201-3576 (direct) and (440)-232-2772 (facsimile) or via email at [mrapp@cle.boehringer-ingenelheim.com](mailto:mrapp@cle.boehringer-ingenelheim.com).

Sincerely,  
for Bedford Laboratories™

  
Molly Rapp  
Manager, Regulatory Affairs  
Ben Venue Laboratories, Inc.

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264



January 13, 2004

TELEPHONE AMENDMENT

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

ORIG AMENDMENT  
N/AM

**RE: ANDA 76-611/ Telephone Amendment**  
**PRODUCT: Mitoxantrone Injection, USP; 2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial**

Dear Emily:

This amendment is submitted in response to a January 13, 2004 telephone between Wanda Pamphile and Dr, Shing Liu from the Agency, and Pratima Patel from Ben Venue Labs concerning our Abbreviated new Drug Application, ANDA 76-611, for Mitoxantrone Injection, USP; 2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial.

As suggested by the Agency, a specification for "Other Requirements", according to the current USP, has been added to Ben Venue's Finished Product Release Specifications. An updated copy of Section XIV.B. has been attached for your review.

If the Agency has any comments or further requests, or, if we could be of any assistance in your review, the phone numbers for contact are (440)-201-3576 (direct) and (440)-232-2772 (facsimile).

Sincerely,  
for Bedford Laboratories™

*Molly Rapp*  
Molly Rapp  
Manager, Regulatory Affairs  
Ben Venue Laboratories, Inc.

RECEIVED  
JAN 14 2004  
OGD/CDER

A DIVISION OF BEN VENUE LABORATORIES, INC.



August 27, 2004

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

Gratuitous Amendment

ORIG AMENDMENT  
N/A

*To be reviewed  
by HCO upon  
approval*

**RE: ANDA 76-611/Gratuitous Amendment**  
**PRODUCT: Mitoxantrone Injection USP; 2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial**

Dear Sir/Madam:

Bedford Laboratories™ would like to amend our tentatively approved above listed ANDA to add \_\_\_\_\_ suite. FDA 356H Form is provided.

We would like to add \_\_\_\_\_ Suite 13 as an optional \_\_\_\_\_ suite for this product. \_\_\_\_\_ Suite 13 is in the process of being dedicated for cytotoxic and genotoxic products and Mitoxantrone is categorized as a genotoxic drug product.

The current Process Simulation Test Data for this \_\_\_\_\_ suite is provided in Ben Venue Laboratories DMF 2315. A copy of the DMF authorization letter is provided.

If you have any questions or comments the phone numbers for contact are (440)-201-3576 (direct) and (440)-232-2772 (facsimile).

Sincerely,  
for Bedford Laboratories™

Molly Rapp  
Manager, Regulatory Affairs  
Ben Venue Laboratories, Inc.

*Mitoxantrone  
440-201-3576*

RECEIVED  
AUG 30 2004  
OGD/CDER



ORIGINAL <sup>1 of 2</sup>

ORIG AMENDMENT

N/AM

ANDA 76-611  
January 12, 2006

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

**Minor Amendment -  
Final Approval  
Requested**

**RE: ANDA 76-611 / Minor Amendment - Final Approval Requested**  
**PRODUCT: Mitoxantrone Injection USP; 2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial**

Dear Sir/Madam:

Bedford Laboratories™ would like to amend our tentatively approved ANDA, listed above, to request final approval. FDA 356H Form is provided in **Attachment I**.

1. **Labeling:** The package insert labeling for Mitoxantrone Injection USP has been revised to match the current Reference Listed Drug insert labeling, including the current language in the "Geriatric Use" and "Drug Interaction" sub-sections. The carton labeling for the 12.5 mL dosage has been revised to correct "10 mL" under the NDC number to "12.5 mL" (correction made in two places on the carton). No changes have been made to the 10 mL and 15 mL carton labeling or to any of the vial labeling although the label codes have been updated (for commercial use) for all labeling. A side-by-side comparison of the current insert labeling versus the previously-submitted insert labeling is provided in **Attachment II**. An electronic copy of the labeling is also provided.

2. **Chemistry:**

a. Drug Substance and Excipient Testing:

The specifications for drug substance and excipients testing remain unchanged from the specifications tentatively approved on February 19, 2004. Also, in accordance with Bedford Laboratories' September 3, 2003 commitment, a report providing confirmational residual solvent qualification on two additional lots of drug substance is provided in **Attachment III** (Report #02-0162.ad1).

b. Drug Product Release and Stability Testing:

The specifications for final product and stability testing of the drug product remain unchanged from the specifications tentatively approved on February 19, 2004.

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JAN 13 2006

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1/12/2006 BEDFORD LETTER

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February 24, 2006

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

Telephone Amendment

ORIG AMENDMENT

N/A

RE: ANDA 76-611

PRODUCT: Mitoxantrone Injection USP; 2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial

Dear Ms. Riley:

Bedford Laboratories™ would like to amend our tentatively approved above listed ANDA by providing additional information regarding equipments and \_\_\_\_\_ Suite 13. This is in reference to my recent conversation with Ms. Marla Steven-Riley.

FDA 356H Form is provided.

The Gratuitous Amendment was filed to add \_\_\_\_\_ Suite 13 as an optional \_\_\_\_\_ suite for this product on August 27, 2004. We would like to point out that the additional equipments are \_\_\_\_\_



I hope this helps in reviewing the amendment. However, if you have any questions or comments the phone numbers for contact are (440)-201-3576 (direct) and (440)-439-6080 (facsimile).

Sincerely,  
for Bedford Laboratories™

Molly Rapp  
Associate Director, Regulatory Affairs  
Ben Venue Laboratories, Inc.

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FEB 27 2006

OGD/CDER

# Fax Cover Sheet



Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Generic Drugs  
Rockville, Maryland

Date: 2-27-06

To: Laura Bedford Mitocentine

Phone: 440-201-3293 Fax: 440-439-6080 Fax

From: Angela Payne

Phone: (301) 827-5846 Fax: (301) ~~443-3847~~

827-7884

Number of Pages: \_\_\_\_\_  
(Including Cover Sheet)

Comments: for ANDA # 76611

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, this communication is not authorized. If you have received this document in error,

Upon further review of Mitoxantrone Injection USP labels the following changes should be made and resubmitted to the agency as a telephone amendment for labeling

The container and carton :

1. The established name should be revised to include some tall man letters to help avoid medications errors with other sound alike- look alike products MitoXANTrone or MitoXANTRONE.
2. Put parenthesis around the word "concentrate"-(Concentrate).
3. Recommend include the language: Open vials may be stored no longer than 7 days at 15-25C (59- 77F) or 14 days under refrigeration. DO NOT FREEZE . CONTAINS NO PRESERVATIVES
4. Usual Dosage: See package....

**APPEARS THIS WAY  
ON ORIGINAL**



ANDA 76-611  
March 2, 2006

ORIG AMENDMENT

N/AF

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

Telephone Amendment -  
Labeling

**RE: ANDA 76-611/Telephone Amendment - Labeling**  
**PRODUCT: Mitoxantrone Injection USP; 2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial**

Bedford Laboratories™ would like to amend our tentatively approved ANDA, cited above, to respond to the February 27, 2006 labeling deficiency. A copy of the deficiency is provided in **Attachment I** and FDA 356H Form is provided as **Attachment II**.

The number associated with the responses given below corresponds to the number identifying the deficiencies in your communication.

1. The drug product name in all the labeling has been revised to include some tall man letters to help avoid medication errors. Please note that the title in the package insert labeling has also been changed to include tall man letters according to our standard procedure.
2. The container and carton labeling have been revised to put parentheses around the word "Concentrate".
3. Language regarding storage for open vials has been added to the carton labeling. This change could not be made to the container labeling due to limited space.
4. No changes made. The proposed labeling already complies with comment #4 of the deficiency.

An electronic copy of the revised labeling is provided. A side-by-side comparison with the previously approved carton and container labeling is provided in **Attachment III**. Please note that the only change to the package insert was to include tall man letters in the title and therefore a side-by-side comparison for the insert is not provided.

If you have any questions or comments to help in your review, the phone numbers for contact are (440)-201-3576 (direct) and (440)-439-6080 (facsimile).

Sincerely, for Bedford Laboratories™

  
Molly Rapp  
Associate Director, Regulatory Affairs  
Ben Venue Laboratories, Inc.

RECEIVED  
MAR 03 2006  
OGD / CDER

ORIG AMENDMENT  
N/A S

March 7, 2006

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

**Telephone Amendment**

**RE: ANDA 76-611**  
**PRODUCT: Mitoxantrone Injection USP; 2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial**

Dear Ms. Riley:

Bedford Laboratories™ would like to amend our tentatively approved above listed ANDA in reference to February 28, 2006, and March 7, 2006 telephone conversations with Ms. Marla Stevens-Riley.

FDA 356H Form is provided.

In our February 24, 2006 telephone amendment, we erroneously listed \_\_\_\_\_ has been removed from service (Nov. 2005) and cannot be used \_\_\_\_\_ in the manufacture of the drug product, regardless of whether it is \_\_\_\_\_ Suite 11 or 13. This information was provided by fax on February 28, 2006, however a formal amendment was not submitted.

If you have any questions or comments the phone numbers for contact are (440)-201-3576 (direct) and (440)-439-6080 (facsimile).

Sincerely,  
for Bedford Laboratories™



Molly Rapp  
Associate Director, Regulatory Affairs  
Ben Venue Laboratories, Inc.

**RECEIVED**  
**MAR 15 2006**  
**OGD / CDER**



ORIGINAL 1 of 1

ANDA 76-611  
March 24, 2006

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

Telephone Amendment  
- Chemistry

ORIG AMENDMENT  
N/AM

**RE: ANDA 76-611/ Telephone Amendment - Chemistry**  
**PRODUCT: Mitoxantrone Injection USP; 2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial**

Dear Sir/Madam,

Bedford Laboratories™ would like to amend our tentatively approved above listed ANDA in reference to March 23, 2006 telephone conversation with the Agency's Kathy Woodland. FDA 356H Form is provided.

Bedford Laboratories has revised the drug substance individual unknown impurity specification from NMT — % to NMT —%. A copy of the revise drug substance specification is provided.

If you have any questions or comments the phone numbers for contact are (440)-201-3576 (direct) and (440)-439-6080 (facsimile).

Sincerely,  
for Bedford Laboratories™

Molly Rapp  
Associate Director, Regulatory Affairs  
Ben Venue Laboratories, Inc.

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MAR 27 2006  
OGD / CDER

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

ANDA 76-611  
March 28, 2006

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

ORIG AMENDMENT  
N/A  
Gratuitous Amendment  
- Chemistry

**RE: ANDA 76-611/ Gratuitous Amendment - Chemistry**  
**PRODUCT: Mitoxantrone Injection USP; 2 mg/mL; 10 mL, 12.5 mL and 15 mL per vial**

Dear Sir/Madam,

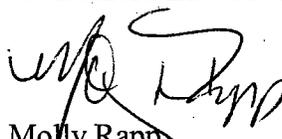
Bedford Laboratories™ would like to amend our tentatively approved ANDA, cited above, in reference to our March 24, 2006 telephone amendment. FDA 356H Form is provided in **Attachment I**.

To assist in the review of the revised drug substance specifications, a full description of the drug substance testing and corresponding specifications is provided in **Attachment II**.

Furthermore, Bedford Laboratories has changed the stability individual unknown impurity limit to NMT — 1/2%; the stability protocol is in the process of being revised to this limit.

If you have any questions or comments the phone numbers for contact are (440)-201-3576 (direct) and (440)-439-6080 (facsimile).

Sincerely,  
for Bedford Laboratories™

  
Molly Rapp  
Associate Director, Regulatory Affairs  
Ben Venue Laboratories, Inc.

RECEIVED  
MAR 29 2006  
OGD / CDER