CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

40-453

Generic Name:	Dihydroergotamine Mesylate Injection USP, 1mg/mL
Sponsor:	Bedford Laboratories
Approval Date:	June 9, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 40-453

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Reviews / Information Included in this ANDA Review.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

ANDA 40-453

JUN 9 2003

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

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated October 19, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Dihydroergotamine Mesylate Injection USP, 1 mg/mL, packaged in 1 mL single-dose vials.

Reference is also made to your amendments dated October 11 and October 25, 2002; and March 17, April 24, April 25, June 2, and June 3, 2003.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Dihydroergotamine Mesylate Injection USP, 1 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (D.H.E. 45® Injection of Xcel Pharmaceuticals).

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

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 6/9/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-453

FINAL PRINTED LABELING

BEDFORD LABORATORIES

DHE-P00B

DIHYDROERGOTAMINE MESYLATE INJECTION USP

Rx ONLY.

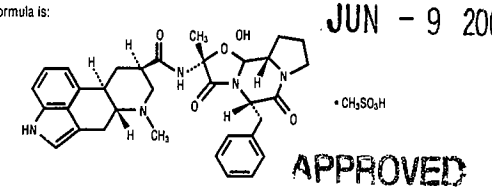
WARNING

Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of DIHYDROERGOTAMINE with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of DIHYDROERGOTAMINE, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated. (See also **CONTRAINDICATIONS** and **WARNINGS**.)

DESCRIPTION

Dihydroergotamine mesylate is ergotamine hydrogenated in the 9, 10 position as the mesylate salt. Dihydroergotamine mesylate is known chemically as dihydroergotamine monomethanesulfonate. Its molecular weight is 679.78 and its molecular formula is $C_{33}H_{37}N_5O_5{\cdot}CH_4O_3S$.

Its structural formula is:



JUN - 9 2003

APPROVED

Dihydroergotamine Mesylate Injection is a sterile, clear, colorless solution in sterile vials for IV, IM, or subcutaneous administration. Each mL contains dihydroergotamine mesylate USP 1 mg, alcohol 6% (v/v), glycerin 153.6 mg, and water for injection, qs. Methanesulfonic acid and/or sodium hydroxide added to adjust pH to a range of 3.4 to 4.9.

CLINICAL PHARMACOLOGY

Mechanism of Action

Dihydroergotamine binds with high affinity to 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors. It also binds with high affinity to serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors, noradrenaline α_{2A}, α_{2B} and α_1 receptors, and dopamine D_{2L} and D_3 receptors.

The therapeutic activity of dihydroergotamine in migraine is generally attributed to the agonist effect at 5-HT_{1D} receptors. Two current theories have been proposed to explain the efficacy of 5-HT_{1D} receptor agonists in migraine. One theory suggests that activation of 5-HT_{1D} receptors located on intracranial blood vessels, including those on arterio-venous anastomoses, leads to vasoconstriction, which correlates with the relief of migraine headache. The alternative hypothesis suggests that activation of 5-HT_{1D} receptors on sensory nerve endings of the trigeminal system results in the inhibition of pro-inflammatory neuropeptide release.

In addition, dihydroergotamine possesses oxytocic properties. (see **CONTRAINDICATIONS.**)

Pharmacokinetics

Absorption

Absolute bioavailability for the subcutaneous and intramuscular route have not been determined, however, no difference was observed in dihydroergotamine bioavailability from intramuscular and subcutaneous doses. Dihydroergotamine mesylate is poorly bioavailable following oral administration.

Distribution

Dihydroergotamine mesylate is 93% plasma protein bound. The apparent steady-state volume of distribution is approximately 800 liters.

Metabolism

Four dihydroergotamine mesylate metabolites have been identified in human plasma following oral administration. The major metabolite, 8'-β-hydroxydihydroergotamine, exhibits affinity equivalent to its parent for adrenergic and 5-HT receptors and demonstrates equivalent potency in several venoconstrictor activity models, *in vivo* and *in vitro*. The other metabolites, i.e., dihydrolysergic acid, dihydrolysergic amide, and a metabolite formed by oxidative opening of the proline ring are of minor importance. Following nasal administration, total metabolites represent only 20% to 30% of plasma AUC. Quantitative pharmacokinetic characterization of the four metabolites has not been performed.

Excretion

The major excretory route of dihydroergotamine is via the bile in the feces. The total body clearance is 1.5 L/min which reflects mainly hepatic clearance. Only 6% to 7% of unchanged dihydroergotamine is excreted in the urine after intramuscular injection. The renal clearance (0.1 L/min) is unaffected by the route of dihydroergotamine administration. The decline of plasma dihydroergotamine after intramuscular or intravenous administration is multi-exponential with a terminal half-life of about 9 hours.

Subpopulations

No studies have been conducted on the effect of renal or hepatic impairment, gender, race, or ethnicity on dihydroergotamine pharmacokinetics. Dihydroergotamine mesylate injection is contraindicated in patients with severely impaired hepatic or renal function. (See **CONTRAINDICATIONS.**)

Interactions

Pharmacokinetic interactions have been reported in patients treated orally with other ergot alkaloids (e.g., increased levels of ergtomine) and macrolide antibiotics, principally troleandomycin, presumably due to inhibition of cytochrome P450 3A metabolism of the alkaloids by troleandomycin. Dihydroergotamine has also been shown to be an inhibitor of cytochrome P450 3A catalyzed reactions and rare reports of ergotism have been obtained from patients treated with dihydroergotamine and macrolide antibiotics (e.g., troleandomycin, clarithromycin, erythromycin), and in patients treated with dihydroergotamine and protease inhibitors (e.g. ritonavir), presumably due to inhibition of cytochrome P450 3A metabolism of ergotamine (See **CONTRAINDICATIONS**). No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

INDICATIONS AND USAGE

Dihydroergotamine mesylate injection is indicated for the acute treatment of migraine headaches with or without aura and the acute treatment of cluster headache episodes.

CONTRAINDICATIONS

There have been a few reports of serious adverse events associated with the coadministration of dihydroergotamine and potent CYP 3A4 inhibitors, such as protease inhibitors and macrolide antibiotics, resulting in vasospasm that led to cerebral ischemia and/or ischemia of the extremities. The use of potent CYP 3A4 inhibitors (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, troleandomycin, ketoconazole, itraconazole) with dihydroergotamine is, therefore contraindicated (See **WARNINGS: CYP 3A4 Inhibitors.**)

Dihydroergotamine mesylate injection should not be given to patients with ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients who have clinical symptoms or findings consistent with coronary artery vasospasm including Prinzmetal's variant angina. (see **WARNINGS.**)

Because dihydroergotamine mesylate injection may increase blood pressure, it should not be given to patients with uncontrolled hypertension.

Dihydroergotamine mesylate injection, 5-HT_1 agonists (e.g., sumatriptan), ergotamine-containing or ergot-type medications or methysergide should not be used within 24 hours of each other.

Dihydroergotamine mesylate injection should not be administered to patients with hemiplegic or basilar migraine.

In addition to those conditions mentioned above, dihydroergotamine mesylate injection is also contraindicated in patients with known peripheral arterial disease, sepsis, following vascular surgery and severely impaired hepatic or renal function.

Dihydroergotamine mesylate injection may cause fetal harm when administered to a pregnant woman. Dihydroergotamine possesses oxytocic properties and, therefore, should not be administered during pregnancy. 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 hazard to the fetus.

There are no adequate studies of dihydroergotamine in human pregnancy, but developmental toxicity has been demonstrated in experimental animals. In embryo-fetal development studies of dihydroergotamine mesylate nasal spray, intranasal administration to pregnant rats throughout the period of organogenesis resulted in decreased fetal body weights and/or skeletal ossification at doses of 0.16 mg/day (associated with maternal plasma dihydroergotamine exposures (AUC) approximately 0.4 to 1.2 times the exposures in humans receiving the MRDD of 4 mg) or greater. A no effect level for embryo-fetal toxicity was not established in rats. Delayed skeletal ossification was also noted in rabbit fetuses following intranasal administration of 3.6 mg/day (maternal exposures approximately 7 times human exposures at the MRDD) during organogenesis. A no effect level was seen at 1.2 mg/day (maternal exposures approximately 2.5 times human exposures at the MRDD). When dihydroergotamine mesylate nasal spray was administered intranasally to female rats during pregnancy and lactation, decreased body weights and impaired reproductive function (decreased mating indices) were observed in the offspring at doses of 0.16 mg/day or greater. A no effect level was not established. Effects on development occurred at doses below those that produced evidence of significant maternal toxicity in these studies. Dihydroergotamine-induced intrauterine growth retardation has been attributed to reduced uteroplacental blood flow resulting from prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone.

Dihydroergotamine mesylate injection is contraindicated in patients who have previously shown hypersensitivity to ergot alkaloids.

Dihydroergotamine mesylate should not be used by nursing mothers. (See **PRECAUTIONS.**)

Dihydroergotamine mesylate should not be used with peripheral and central vasoconstrictors because the combination may result in additive or synergistic elevation of blood pressure.

WARNINGS

Dihydroergotamine mesylate injection should only be used where a clear diagnosis of migraine headache has been established.

CYP 3A4 Inhibitors (e.g. Macrolide Antibiotics and Protease Inhibitors)

There have been rare reports of serious adverse events in connection with the coadministration of dihydroergotamine and potent CYP 3A4 inhibitors, such as protease inhibitors and macrolide antibiotics, resulting in vasospasm that led to cerebral ischemia and/or ischemia of the extremities. The use of potent CYP 3A4 inhibitors with dihydroergotamine should therefore be avoided (see **CONTRAINDICATIONS.**) Examples of some of the more potent CYP 3A4 inhibitors include: anti-fungals ketoconazole and itraconazole, the protease inhibitors ritonavir, nelfinavir, and indinavir, and macrolide antibiotics erythromycin, clarithromycin, and troleandomycin. Other less potent CYP 3A4 inhibitors should be administered with caution. Less potent inhibitors include saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton, and clotrimazole. These lists are not exhaustive, and the prescriber should consider the effects on CYP 3A4 of other agents being considered for concomitant use with dihydroergotamine.

Fibrotic Complications

There have been reports of pleural and retroperitoneal fibrosis in patients following prolonged daily use of injectable dihydroergotamine mesylate. Rarely, prolonged daily use of other ergot alkaloid drugs has been associated with cardiac valvular fibrosis. Rare cases have also been reported in association with the use of injectable dihydroergotamine mesylate; however, in those cases, patients also received drugs known to be associated with cardiac valvular fibrosis.

Administration of dihydroergotamine mesylate injection should not exceed the dosing guidelines and should not be used for chronic daily administration (see **DOSAGE AND ADMINISTRATION.**)

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events

Dihydroergotamine mesylate injection should not be used by patients with documented ischemic or vasospastic coronary artery disease. (See **CONTRAINDICATIONS** is strongly recommended that dihydroergotamine mesylate injection not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, females who are surgically or physiologically postmenopausal, or males who are over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of or consistent with coronary artery vasospasm or myocardial ischemia, dihydroergotamine mesylate injection should not be administered. (See **CONTRAINDICATIONS.**)

For patients with risk factors predictive of CAD who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of dihydroergotamine mesylate injection take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received dihydroergotamine mesylate. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following dihydroergotamine mesylate injection, in those patients with risk factors.

It is recommended that patients who are intermittent long-term users of dihydroergotamine mesylate injection and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use dihydroergotamine mesylate injection.

The systematic approach described above is currently recommended as a method to identify patients in whom dihydroergotamine mesylate injection may be used to treat migraine headaches with an acceptable margin of cardiovascular safety.

Cardiac Events and Fatalities

The potential for adverse cardiac events exists. Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported to have occurred following the administration of dihydroergotamine mesylate injection. Considering the extent of use of dihydroergotamine mesylate in patients with migraine, the incidence of these events is extremely low.

Drug-Associated Cerebrovascular Events and Fatalities

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with dihydroergotamine mesylate injection; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the dihydroergotamine mesylate injection having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

Other Vasospasm Related Events

Dihydroergotamine mesylate injection, like other ergot alkaloids, may cause vasospastic reactions other than coronary artery vasospasm. Myocardial, peripheral vascular, and colonic ischemia have been reported with dihydroergotamine mesylate injection.

Dihydroergotamine mesylate injection associated vasospastic phenomena may also cause muscle pains, numbness, coldness, pallor, and cyanosis of the digits. In patients with compromised circulation, persistent vasospasm may result in gangrene or death. Dihydroergotamine mesylate injection should be discontinued immediately if signs or symptoms of vasoconstriction develop.

Increase in Blood Pressure

Significant elevation in blood pressure has been reported on rare occasions in patients with and without a history of hypertension treated with dihydroergotamine mesylate injection. Dihydroergotamine mesylate injection is contraindicated in patients with uncontrolled hypertension. (See **CONTRAINDICATIONS.**)

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT_1 agonist in a study evaluating subjects undergoing cardiac catheterization.

PRECAUTIONS

General

Dihydroergotamine mesylate injection may cause coronary artery vasospasm; patients who experience signs or symptoms suggestive of angina following its administration should, therefore, be evaluated for the presence of CAD or a predisposition to variant angina before receiving additional doses. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT agonist are candidates for further evaluation. (See **WARNINGS.**)

Fibrotic Complications: See **WARNINGS: Fibrotic Complications.**

Information for Patients

The text of a patient information sheet is printed at the end of this insert. To assure safe and effective use of dihydroergotamine mesylate injection, the information and instructions provided in the patient information sheet should be discussed with patients.

Patients should be advised to report to the physician immediately any of the following: numbness or tingling in the fingers and toes, muscle pain in the arms and legs, weakness in the legs, pain in the chest, temporary speeding or slowing of the heart rate, swelling, or itching.

Prior to the initial use of the product by a patient, the prescriber should take steps to ensure that the patient understands how to use the product as provided. (See **Patient Information Sheet and product packaging.**)

Administration of dihydroergotamine mesylate injection should not exceed the dosing guidelines and should not be used for chronic daily administration (see **DOSAGE AND ADMINISTRATION.**)

Drug Interactions

Vasoconstrictors

Dihydroergotamine mesylate injection should not be used with peripheral vasoconstrictors because the combination may cause synergistic elevation of blood pressure.

Sumatriptan

Sumatriptan has been reported to cause coronary artery vasospasm, and its effect could be additive with dihydroergotamine mesylate injection. Sumatriptan and dihydroergotamine mesylate injection should not be taken within 24 hours of each other. (See **CONTRAINDICATIONS.**)

Beta Blockers

Although the results of a clinical study did not indicate a safety problem associated with the administration of dihydroergotamine mesylate injection to subjects already receiving propranolol, there have been reports that propranolol may potentiate the vasoconstrictive action of ergotamine by blocking the vasodilating property of epinephrine.

Nicotine

Nicotine may provoke vasoconstriction in some patients, predisposing to a greater ischemic response to ergot therapy.

CYP 3A4 Inhibitors (e.g. Macrolide Antibiotics and Protease Inhibitors) See **CONTRAINDICATIONS** and **WARNINGS.**

SSRI's

Weakness, hyperreflexia, and incoordination have been reported rarely when 5-HT_1 agonists have been co-administered with SSRI's (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline). There have been no reported cases from spontaneous reports of drug interaction between SSRI's and dihydroergotamine mesylate injection.

Oral Contraceptives

The effect of oral contraceptives on the pharmacokinetics of dihydroergotamine mesylate injection has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Assessment of the carcinogenic potential of dihydroergotamine mesylate in mice and rats is ongoing.

Mutagenesis

Dihydroergotamine mesylate was clastogenic in two *in vitro* chromosomal aberration assays, the V79 Chinese hamster cell assay with metabolic activation and the cultured human peripheral blood lymphocyte assay. There was no evidence of mutagenic potential when dihydroergotamine mesylate was tested in the presence or absence of metabolic activation in two gene mutation assays (the Ames test and the *in vitro* mammalian Chinese hamster V79/HGPRT assay) and in an assay for DNA damage (the rat hepatocyte unscheduled DNA synthesis test). Dihydroergotamine was not clastogenic in the *in vivo* mouse and hamster micronucleus tests.

Impairment of Fertility

Impairment of fertility was not evaluated for dihydroergotamine mesylate injection. There was no evidence of impairment of fertility in rats given intranasal doses of Migranal® Nasal Spray up to 1.6 mg/day (associated with mean plasma dihydroergotamine mesylate exposures [AUC] approximately 9 to 11 times those in humans receiving the MRDD of 4 mg).

Pregnancy: Teratogenic Effects; Pregnancy Category X.
See **CONTRAINDICATIONS.**

Nursing Mothers

Ergot drugs are known to inhibit prolactin. It is likely that dihydroergotamine mesylate injection is excreted in human milk, but there are no data on the concentration of dihydroergotamine in human milk. It is known that ergotamine is excreted in breast milk and may cause vomiting, diarrhea, weak pulse, and unstable blood pressure in nursing infants. Because of the potential for these serious adverse events in nursing infants exposed to dihydroergotamine mesylate injection nursing should not be undertaken with the use of dihydroergotamine mesylate injection. (See **CONTRAINDICATIONS.**)

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following use of dihydroergotamine mesylate injection but are extremely rare. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS.**) Fibrotic complications have been reported in association with long term use of injectable dihydroergotamine mesylate (see **WARNINGS: Fibrotic Complications.**)

Post-Introduction Reports

The following events derived from postmarketing experience have been occasionally reported in patients receiving dihydroergotamine mesylate injection: vasospasm, paraesthesia, hyperten-sion, dizziness, anxiety, dyspnea, headache, flushing, diarrhea, rash, increased sweating, and pleural and retroperitoneal fibrosis after long-term use of dihydroergotamine. Extremely rare cases of myocardial infarction and stroke have been reported. A causal relationship has not been established.

Dihydroergotamine mesylate injection is not recommended for prolonged daily use. (See **DOSAGE AND ADMINISTRATION.**)

DRUG ABUSE AND DEPENDENCE

Currently available data have not demonstrated drug abuse or psychological dependence with dihydroergotamine. However, cases of drug abuse and psychological dependence in patients on other forms of ergot therapy have been reported. Thus, due to the chronicity of vascular headaches, it is imperative that patients be advised not to exceed recommended dosages.

OVERDOSAGE

To date, there have been no reports of acute overdosage with this drug. Due to the risk of vascular spasm, exceeding the recommended dosages of dihydroergotamine mesylate injection is to be avoided. Excessive doses of dihydroergotamine may result in peripheral signs and symptoms of ergotism. Treatment includes discontinuance of the drug, local application of warmth to the affected area, the administration of vasodilators, and nursing care to prevent tissue damage.

In general, the symptoms of an acute dihydroergotamine mesylate injection overdose are similar to those of an ergotamine overdose, although there is less pronounced nausea and vomiting with dihydroergotamine mesylate injection. The symptoms of an ergotamine overdose include the following: numbness, tingling, pain, and cyanosis of the extremities associated with diminished or absent peripheral pulses; respiratory depression; an increase and/or decrease in blood pressure, usually in that order, confusion, delirium, convulsions, and coma; and/or some degree of nausea, vomiting, and abdominal pain.

In laboratory animals, significant lethality occurs when dihydroergotamine is given at IV doses of 44 mg/kg in mice, 130 mg/kg in rats, and 37 mg/kg in rabbits.

Up-to-date information about the treatment of overdosage can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the Physician's Desk Reference® (PDR).*

DOSAGE AND ADMINISTRATION

Dihydroergotamine mesylate injection should be administered in a dose of 1 mL intravenously, intramuscularly or subcutaneously. The dose can be repeated, as needed, at 1 hour intervals to a total dose of 3 mL for intramuscular or subcutaneous delivery or 2 mL for intravenous delivery in a 24 hour period. The total weekly dosage should not exceed 6 mL. Dihydroergotamine mesylate injection should not be used for chronic daily administration.

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

HOW SUPPLIED

Dihydroergotamine Mesylate Injection USP is available as a clear, colorless, sterile solution in single 1 mL sterile vials; each mL containing 1 mg of dihydroergotamine mesylate, in cartons of 10 **(NDC 55390-013-10).**

Store at 20° to 25°C (68° to 77°F). See USP controlled room temperature. In light-resistant containers. Do not refrigerate or freeze.

To assure constant potency, protect the vials from light and heat. Administer only if clear and colorless.

INSTRUCTION FOR PATIENTS ON SUBCUTANEOUS SELF-INJECTION
Information for the Patient
Dihydroergotamine Mesylate Injection USP

Before self-injecting dihydroergotamine mesylate injection by subcutaneous administration, you will need to obtain professional instruction on how to properly administer your medication. Below are some of the steps you should follow carefully. Read this leaflet completely before using this medication.

This leaflet does not contain all of the information on dihydroergotamine mesylate injection. Your pharmacist and/or health care provider can provide more detailed information.

Purpose of your Medication

Dihydroergotamine mesylate injection is intended to treat an active migraine headache. Do not try to use it to prevent a headache if you have no symptoms. Do not use it to treat common tension headache or a headache that is not at all typical of your usual migraine headache. Administration of dihydroergotamine mesylate injection should not exceed the dosing guidelines and should not be used for chronic daily administration. There have been reports of fibrosis (stiffening) in the lung or kidney areas in patients following prolonged daily use of injectable dihydroergotamine mesylate. Rarely, prolonged daily use of other ergot alkaloid drugs (the class of drugs to which dihydroergotamine mesylate injection belongs) has been associated with heart valvular fibrosis. Rare cases have also been reported in association with the use of injectable dihydroergotamine mesylate; however, in those cases, patients also received drugs known to be associated with heart valvular fibrosis.

Do not use dihydroergotamine mesylate injection if you:

- are pregnant or nursing.
- have any disease affecting your heart, arteries, or circulation.
- are taking certain anti-HIV medications (protease inhibitors).
- are taking a macrolide antibiotic such as toleandomycin, clarithromycin or erythromycin.

Important questions to consider before using dihydroergotamine mesylate injection

Please answer the following questions before you use your dihydroergotamine mesylate injection. If you answer YES to any of these questions or are unsure of the answer, you should talk to your doctor before using dihydroergotamine mesylate injection.

- Do you have high blood pressure?
- Do you have chest pain, shortness of breath, heart disease, or have you had any surgery on your heart arteries?
- Do you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a male over 40)?
- Do you have any problems with blood circulation in your arms or legs, fingers, or toes?
- Are you pregnant? Do you think you might be pregnant? Are you trying to become pregnant? Are you sexually active and not using birth control? Are you breast feeding?
- Have you ever had to stop taking this or any other medication because of an allergy or bad reaction?
- Are you taking any other migraine medications, erythromycin or other antibiotics, or medications for blood pressure prescribed by your doctor, or other medicines obtained from your drugstore without a doctor's prescription?
- Do you smoke?
- Have you had, or do you have, any disease of the liver or kidney?
- Is this headache different from your usual migraine attacks?
- Are you using dihydroergotamine mesylate injection, spray or other dihydroergotamine mesylate containing drugs on a daily basis?
- Are you taking a protease inhibitor for HIV therapy?
- Are you taking a macrolide class of antibiotic?

Serious or potentially life-threatening reductions in blood flow to the brain or extremities have been reported rarely due to interactions between dihydroergotamine and protease inhibitors or macrolide antibiotics.

REMEMBER TO TELL YOUR DOCTOR IF YOU HAVE ANSWERED YES TO ANY OF THESE QUESTIONS BEFORE YOU USE DIHYDROERGOTAMINE MESYLATE INJECTION

Side Effects To Watch Out For

Although the following reactions rarely occur, they can be serious and should be reported to your physician immediately:

- Numbness or tingling in your fingers and toes.
- Pain, tightness, or discomfort in your chest.
- Muscle pain or cramps in your arms and legs.
- Weakness in your legs.
- Temporary speeding or slowing of your heart rate.
- Swelling or itching.

Dosage

Your doctor will have told you what dose to use for each migraine attack. Should you get another migraine attack in the same day as the attack you treated, you must not treat it with dihydroergotamine mesylate injection unless at least 6 hours have elapsed since your last injection. No more than 6 mL of dihydroergotamine mesylate injection should be injected during a one-week period. Dihydroergotamine mesylate injection is not intended to be used on a prolonged daily basis.

Learn what to do in case of an Overdose

If you have used more medication than you have been instructed, contact your doctor, hospital emergency department, or nearest poison control center immediately.

How to use the dihydroergotamine mesylate injection

1. Use available training materials.
   - Read and follow the instructions in the patient instruction leaflet which is provided with the dihydroergotamine injection package before attempting to use the product.
   - If there are any questions concerning the use of your dihydroergotamine mesylate injection, ask your doctor or pharmacist.
2. Preparing for the Injection
   - Carefully examine the vial of dihydroergotamine mesylate injection for any cracks or breaks, and the liquid for discoloration, cloudiness, or particles. If any of these defects are present, use a new vial, make certain it is intact, and return the defective vial to your doctor or pharmacy. Once you open a vial, if it is not used within an hour, it should be thrown away.
3. Locating an Injection Site
   - Administer your subcutaneous injection in the middle of your thigh, well above the knee.
4. Drawing the Medication into the Syringe
   - Wash your hands thoroughly with soap and water.
   - Check the dose of your medication.
   - Flip off the aluminum seal and wipe the stopper with alcohol wipe.
   - Insert the needle into the solution through the middle of the stopper.
   - Draw up the medication by pulling back the plunger slowly and steadily until you reach your dose.
   - Check the syringe for air bubbles. Hold it with the needle pointing upward. If there are air bubbles, tap your finger against the barrel of the syringe to get the bubbles to the top. Slowly and carefully push the plunger up so that the bubbles are pushed out through the needle and you see a drop of medication.
   - When there are no air bubbles, check the dose of the medication. If the dose is incorrect, repeat steps 6 through 8 until you draw up the right dose.
5. Preparing the Injection Site
   - With a new alcohol wipe, clean the selected injection site thoroughly with a firm, circular motion from inside to outside. Wait for the injection site to dry before injecting.
6. Administering the Injection
   - Hold the syringe/needle in your right hand.
   - With your left hand, firmly grasp about a 1-inch fold of skin at the injection site.
   - Push the needle shaft, bevel side up, all the way into the fold of skin at a 45° to 90° angle, then release the fold of skin.
   - While holding the syringe with your left hand, use your right hand to draw back slightly on the plunger.
   - If you do not see any blood coming back into the syringe, inject the medication by pushing down on the plunger. If you do see blood in the syringe, that means the needle has penetrated a vein. If this happens, pull the needle/syringe out of the skin slightly and draw back on the plunger again. If no blood is seen this time, inject the medication.
   - Use your right hand to pull the needle out of your skin quickly at the same angle you injected it. Immediately press the alcohol wipe on the injection site and rub.

Check the expiration date printed on the vial containing medication. If the expiration date has passed, do not use it.

Answers to patients' questions about dihydroergotamine mesylate injection

What if I need help in using my dihydroergotamine mesylate injection? If you have any questions or if you need help in opening, putting together, or using dihydroergotamine mesylate injection, speak to your doctor or pharmacist.

How much medication should I use and how often?

Your doctor will have told you what dose to use for each migraine attack. Should you get another migraine attack in the same day as the attack you treated, you must not treat it with dihydroergotamine mesylate injection unless at least 6 hours have elapsed since your last injection. No more than 6 mL of dihydroergotamine mesylate injection should be injected during a one-week period. Do not use more than this amount unless instructed to do so by your doctor. Dihydroergotamine mesylate injection is not intended for chronic daily use.

If you have any other unanswered question about dihydroergotamine mesylate injection, consult your doctor or pharmacist.

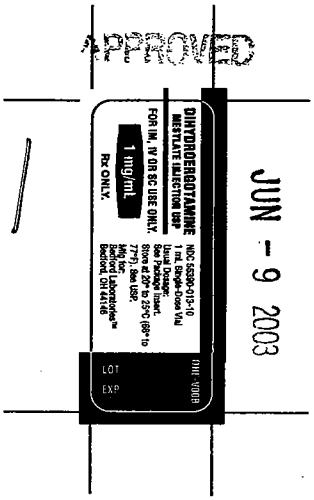
*Trademark of Medical Economics Company, Inc.

Manufactured by:
Ben Venue Laboratories, Inc.
Bedford, OH 44146

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146

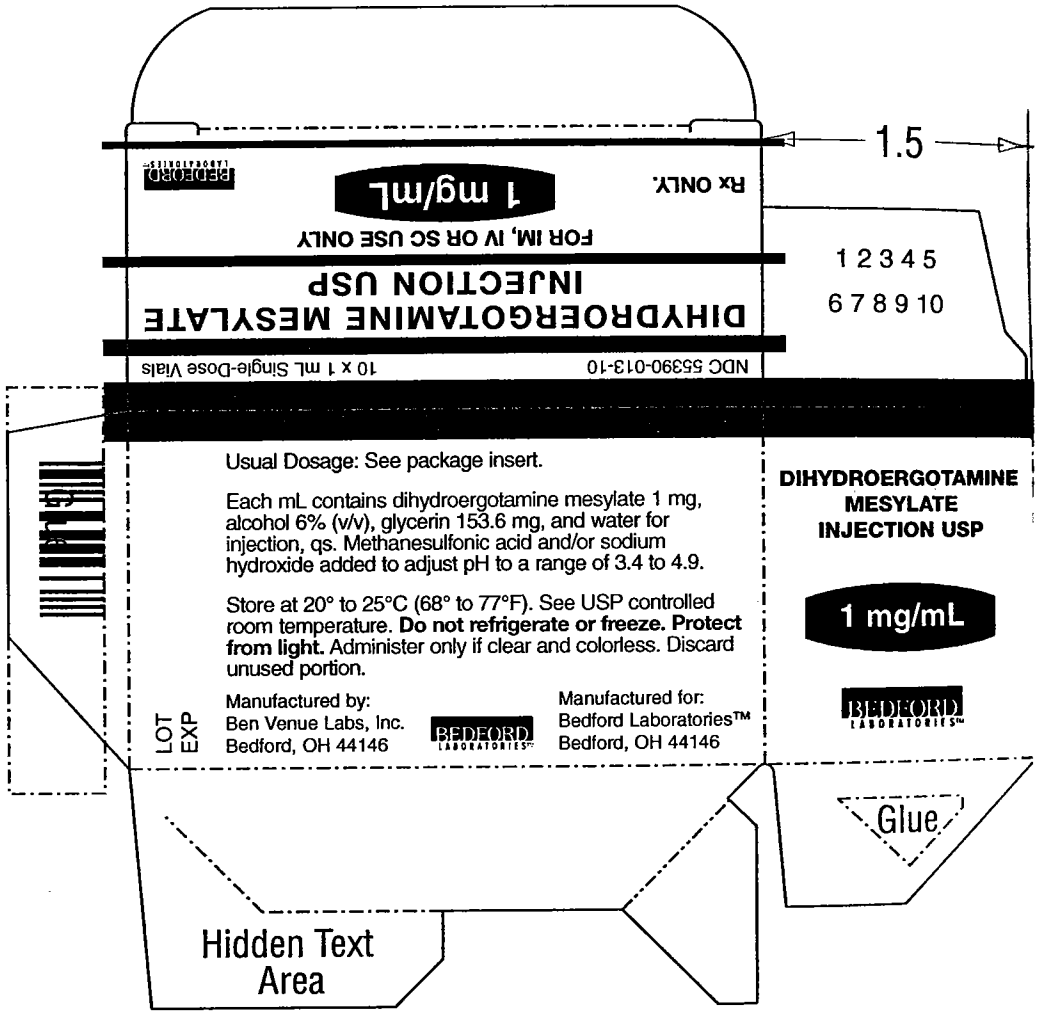
April 2003

DHE-P00B



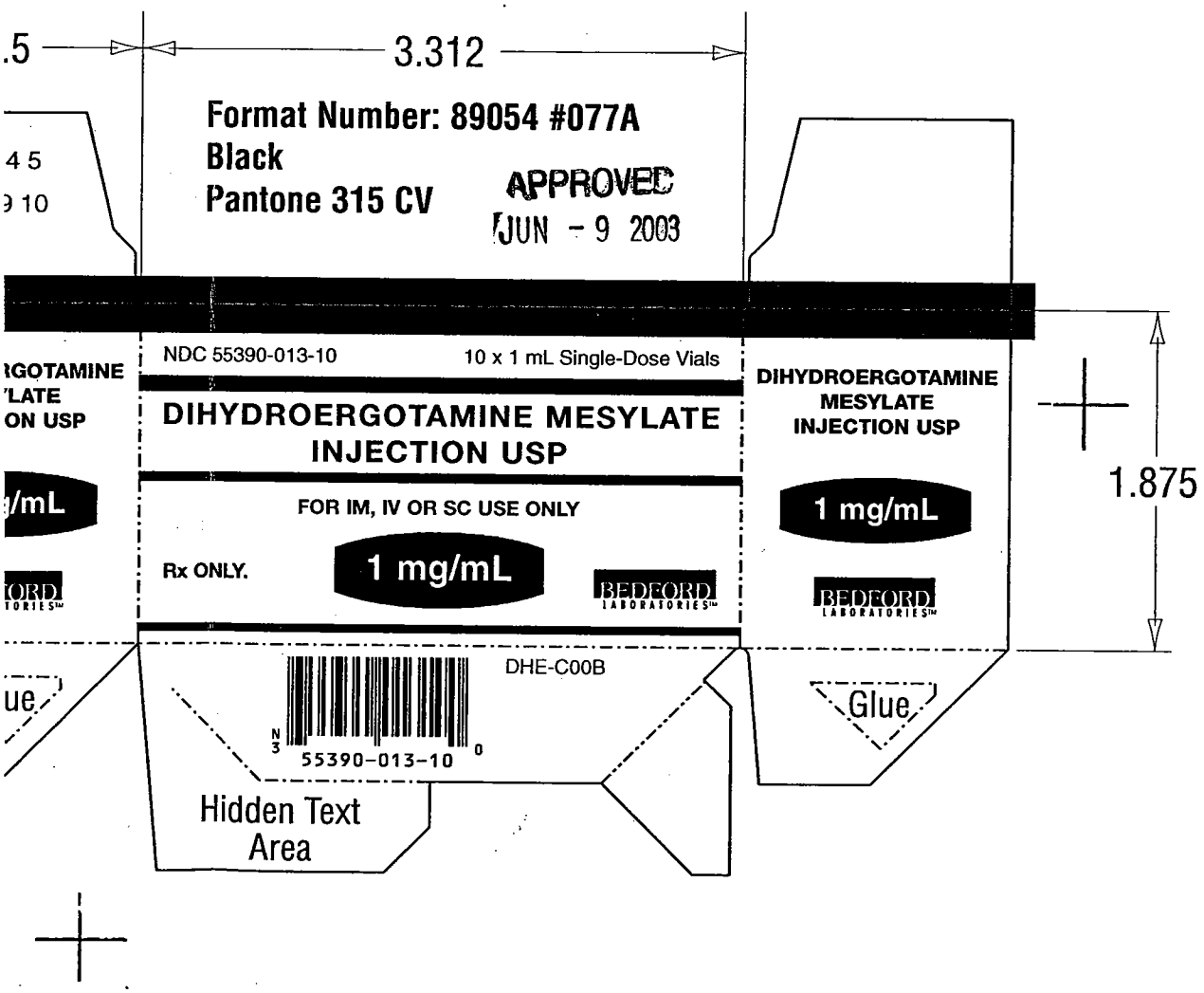
JUN - 9 2003

Note: Keyline does not print.



7633

Ben Venue
Printed Side
M081000B



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-453

CSO LABELING REVIEW(S)

[redacted]

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

ANDA Number: **40-453** Date of Submission: April 25, 2003

Applicant's Name: Bedford Laboratories

Established Name: **Dihydroergotamine Mesylate Injection USP, 1 mg/1 mL (1 mL vial)**

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? YES

	FPL/ Draft	Date of submission	Code	Vol.	Rev. Date	Recommendation
CONTAINER 1 mL vial	FPL	4/25/03	DHE-VOOB	3.1		Acceptable for approval
CARTON (10)	FPL	4/25/03	DHE-COOB	3.1		Acceptable for approval
INSERT	FPL	4/25/03	DHE-POOB	3.1	April 2003	Acceptable for approval

Revisions needed post-approval: Yes

1. **CARTON (10 X 1 mL Single-Dose Vials)**

   Add parenthesis around "See USP controlled room temperature" and delete the period that precedes it.

2. **INSERT (HOW SUPPLIED)**

   See comment 1.

BASIS OF APPROVAL:
Was this approval based upon a petition? no
What is the RLD on the 356(h) form: DHE 45 Injection
NDA Number: 5-929
NDA Drug Name: DHE 45 Injection
NDA Firm: Xcel Pharmaceuticals
Date of Approval of NDA Insert and supplement #: July 31, 2002; S-033
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? no
Basis of Approval for the Container Labels: side by side
Basis of Approval for the Carton Labeling: side by side
Other Comments

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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. USP 25	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	

Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? 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.		X	
Does the package proposed have any safety and/or regulatory concerns?		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	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? YES		X	
Are there any other safety concerns?		X	
Labeling			
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	
Labeling(continued)	Yes	No	N.A.
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	
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	
Inactive Ingredients: (FTR: List page # 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	
USP Issues: (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?		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? YES - TYPE 1 CLEAR GLASS IN INDIVIDUAL CARTONS	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	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T [] 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	
Patent/Exclusivity Issues?: 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.		X	

Questions for the Chemist:

E-mail from the chemist:

Koung,

I checked the ANDA for Dihydroergoatamine Mesylate Inj for pH. I have listed 3.4-4.9 in the ANDA which is the USP spec for stability. The release specs were tighter. I don't know what you read that had the specs different but perhaps if it is was in the label you should comment in your review if an error was made and the specs were wider. CMC looks ok.

-----Original Message-----
From: Lee, Koung U
Sent: Monday, April 07, 2003 2:55 PM

To: Bernard, Karen A
Subject: ANDA 40-453, Bedford's Laboratories' Dihydroergotamine Mesylate Injection

Karen,
Bedford is proposing "Store below 25°C (77°F)" for their storage temperature statement for dihydroergotamine mesylate injection product. I was informed from the grapevine that this may be too open ended. Does Bedford's stability data support their proposed storage temperature statement, if not, how about "Store at 20-25 deg C (68 - 77 F) [see USP Controlled Room Temperature]"? Thanks for your help Karen.
Koung

4/9/03
After discussing the storage temperature statement with Richard Adam and Brenda Arnwine, Karen informed me that she will call the firm and ask them to change the storage temperature statement to "Store at 20° to 25° C (68° to 77°F)[see USP Controlled Room Temperature]."

Karen said that the chemist will now be paying more attention to the temperature statement and will include it in their reviews along with the stability data.

FOR THE RECORD:

1. **This review was based on supplement NDA 5-929/S-033 for the RLD - D.H.E.45 (SANDOZ; Approved July 31, 2002)**
2. **The ANDA proposes to market 1 mL amber vials cartons of 10's. The RLD markets their drug product in 1 mL amber glass ampules in cartons of 10.**
3. **Bedford is the sole manufacturer. Outside firms are utilized for testing only.**
4. **There are no outstanding patents or exclusivities for this drug product.**
5. **The inactive ingredients are accurately stated in the DESCRIPTION section (p. 59 vol 1.1).**
6. **Storage/dispensing recommendations:**
   ANDA: container - Store at 20° to 25° C (68° to 77°F). See USP.
   carton - Store at 20° to 25° C (68° to 77°F). See USP controlled room temperature. Do not refrigerate or freeze. Protect from light. Administer only if clear and colorless. Discard unused portion.
   insert - Store at 20° to 25° C (68° to 77°F). See USP controlled room temperature, in light-resistant containers. Do not refrigerate or freeze. To assure constant potency, protect the vials from light and heat. Administer only if clear and colorless.
   For the carton and insert labeling, firm is asked to add parenthesis around "See USP controlled room temperature" and delete the period that precedes it. Because the container label is too small to include the complete storage temperature statement, it was agreed to shorten it by deleting "controlled room temperature".
   NDA: container and carton - Below 25°C(77°F). Protect from light. Administer only if clear and colorless.
   Insert - Protect from light and heat. Below 77°F(25°C), in light-resistant containers. Administer only if clear and colorless.
   USP: Preserve in single-dose containers, preferably of Type 1 glass, protected from light.
7. **Subcutaneous route of administration was approved in S-025 supplement.**
8. **I called Ms. Martina Struck of Novartis at 973-781-3217 on 3/13/02 to ask about the "booklet" that the PPI refers to. Ms Struck confirmed that the "booklet" is actually the PPI. She assured me that they will considering changing the wording to make it more clear.**
9. **Alcohol Calculation: This product contains 49.3 mg of alcohol USP/mL.**

   ((1g/100mg X 49.3 mg/mL) / 0.814g/mL) X 0.955 X 100% = 5.8% (V/V)
   Firm rounds off to 6% (V/V).

Date of Review: May 6, 2003 **Date of Submission: April 25, 2003**

Primary Reviewer: Koung Lee **Date:** 5/9/03

Team Leader: Lillie Golson **Date:** 5/9/03

---

cc: ANDA 40-453

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

ANDA Number: **40-453** Date of Submission: March 17, 2003

Applicant's Name: Bedford Laboratories

Established Name: **Dihydroergotamine Mesylate Injection USP, 1 mg/1 mL (1 mL vial)**

Labeling Deficiencies

1. GENERAL

   Revise the storage temperature statement to read "Store at 20° to 25° C (68° to 77°F)[see USP Controlled Room Temperature]."

2. CONTAINER (1 mL)

   See GENERAL comment. If space is limited, you may omit "[see USP Controlled Room Temperature]".

3. CARTON (10)

   See GENERAL comment.

4. INSERT

   a. WARNINGS

      i. Risk of Myocardial Ischemia and/or Interaction and Other Adverse Cardiac Events

         Revise the beginning of the first paragraph to read "(See CONTRAINDICATIONS.) It is strongly recommended that..."

      ii. Increase in Blood Pressure

         Delete the [redacted] in "[redacted]... in the second sentence of the first paragraph.

   b. PRECAUTIONS (Beta Blockers)

      Delete the [redacted] in "[redacted]

   c. HOW SUPPLIED

      See GENERAL comment.

   d. INSTRUCTION FOR PATIENTS ON SUBCUTANEOUS SELF-INJECTION

      Important questions to consider before using dihydroergotamine mesylate injection

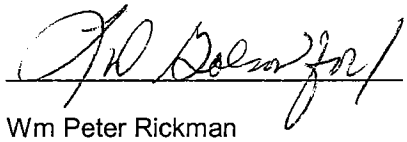
      Add a comma between "injection" and "spray" in the eleventh bulleted statement.

Please revise your labeling as instructed above and submit 12 final printed copies of labels and labeling for a full approval of this application.

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/ogd/rld/labeling_review_branch.html

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



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

BASIS OF APPROVAL:
Was this approval based upon a petition? no
What is the RLD on the 356(h) form: DHE 45 Injection
NDA Number: 5-929
NDA Drug Name: DHE 45 Injection
NDA Firm: Xcel Pharmaceuticals
Date of Approval of NDA Insert and supplement #: July 31, 2002; S-033
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? no
Basis of Approval for the Container Labels: side by side
Basis of Approval for the Carton Labeling: side by side
Other Comments

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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. USP 25	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? 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.		X	
Does the package proposed have any safety and/or regulatory concerns?		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	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? YES		X	
Are there any other safety concerns?		X	
Labeling			
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	
Labeling(continued)	Yes	No	N.A.
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	
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	
Inactive Ingredients: (FTR: List page # 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	
USP Issues: (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?		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? YES - TYPE 1 CLEAR GLASS IN INDIVIDUAL CARTONS	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	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T [] 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	
Patent/Exclusivity Issues?: 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.		X	

Questions for the Chemist:

E-mail from the chemist:

Koung,

I checked the ANDA for Dihydroergoatamine Mesylate Inj for pH. I have listed 3.4-4.9 in the ANDA which is the USP spec for stability. The release specs were tighter. I don't know what you read that had the specs different but perhaps if it is was in the label you should comment in your review if an error was made and the specs were wider. CMC looks ok.

-----Original Message-----
From: Lee, Koung U
Sent: Monday, April 07, 2003 2:55 PM
To: Bernard, Karen A
Subject: ANDA 40-453, Bedford's Laboratories' Dihydroergotamine Mesylate Injection

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Koung

4/9/03

After discussing the storage temperature statement with Richard Adam and Brenda Arnwine, Karen informed me that she will call the firm and ask them to change the storage temperature statement to "Store at 20° to 25° C (68° to 77°F)[see USP Controlled Room Temperature]."

Karen said that the chemist will now be paying more attention to the temperature statement and will include it in their reviews along with the stability data.

FOR THE RECORD:

1. **This review was based on supplement NDA 5-929/S-033 for the RLD - D.H.E.45 (SANDOZ; Approved July 31, 2002)**
2. **The ANDA proposes to market 1 mL amber vials cartons of 10's. The RLD markets their drug product in 1 mL amber glass ampules in cartons of 10.**
3. **Bedford is the sole manufacturer. Outside firms are utilized for testing only.**
4. **There are no outstanding patents or exclusivities for this drug product.**
5. **The inactive ingredients are accurately stated in the DESCRIPTION section (p. 59 vol 1.1).**
6. **Storage/dispensing recommendations:**

   ANDA: container - Store below 25°C(77°F)
   carton - Store below 25°C(77°F). Protect from light. Administer only if clear and colorless.
   insert - Store below 77°F(25°C) in light-resistant containers. Do not refrigerate or freeze. To assure constant potency, protect the vials from light and heat. Administer only if clear and colorless.

   NDA: container and carton - Below 25°C(77°F). Protect from light. Administer only if clear and colorless.

Insert - Protect from light and heat. Below 77°F(25°C), in light-resistant containers. Administer only if clear and colorless.

USP: Preserve in single-dose containers, preferably of Type 1 glass, protected from light.

7. **Subcutaneous route of administration was approved in S-025 supplement.**
8. **I called Ms. Martina Struck of Novartis at 973-781-3217 on 3/13/02 to ask about the "booklet" that the PPI refers to. Ms Struck confirmed that the "booklet" is actually the PPI. She assured me that they will considering changing the wording to make it more clear.**
9. **Alcohol Calculation: This product contains 49.3 mg of alcohol USP/mL.**

((1g/100mg X 49.3 mg/mL) / 0.814g/mL) X 0.955 X 100% = 5.8% (V/V)
Firm rounds off to 6% (V/V).

10. **Called Ms. Molly L. Rapp of Bedford Laboratories at 440-201-3576 on April 16, 2003, to discuss the storage temperature statement. She said that Karen Bernard called and requested the statement to be revised to** "Store at 20° to 25° C (68° to 77°F)[see USP Controlled Room Temperature]." She also informed me that the container (1 mL vial) was too small to fit both the established name and the full storage temperature statement. She asked whether she could just put "Store at 25° C". I recommended that she at least put the range and leave out "[See USP Controlled Room Temperature]". She agreed. She plans on submitting the amendment early next week.

Date of Review: April 9, 2003 **Date of Submission: March 17, 2003**

Primary Reviewer: Koung Lee Date: 4/16/03

Team Leader: Lillie Golson Date: 4/16/03

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cc: ANDA 40-453
DUP/DIVISION FILE
HFD-613/KLee/LGolson (no cc)
V:\FIRMSAM\BEDFORD\LTRS&REV\40453.NA2.LABELING
Review

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: **40-453** Date of Submission: October 25, 2002

Applicant's Name: Bedford Laboratories

Established Name: **Dihydroergotamine Mesylate Injection USP, 1 mg/1 mL (1 mL vial)**

Labeling Deficiencies:

1. CARTON

   Delete " [redacted] from " [redacted]. .

2. INSERT

   a. GENERAL

      There are numerous and significant differences between your proposed insert labeling and the reference listed drug insert labeling approved on July 31, 2002. Please review the attached reference listed drug insert labeling and revise your insert accordingly. In addition, we have the following comment.

   b. DESCRIPTION

      See CARTON comment.

Please revise your labeling as instructed above and submit 12 final printed copies of labels and labeling for a full approval of this application.

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/ogd/rld/labeling_review_branch.html

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

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

ATTACHMENT

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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. USP 25	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? 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.		X	
Does the package proposed have any safety and/or regulatory concerns?		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	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? YES		X	
Are there any other safety concerns?		X	
Labeling			
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	
Labeling(continued)	Yes	No	N.A.
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	
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	
Inactive Ingredients: (FTR: List page # 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	
USP Issues: (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?		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? YES - TYPE 1 CLEAR GLASS IN INDIVIDUAL CARTONS	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	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ 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	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents,		X	

exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. This review was based on supplement NDA 5-929/S-033 for the RLD - D.H.E.45 (SANDOZ; Approved July 31, 2002)
2. The ANDA proposes to market 1 mL amber vials cartons of 10's. The RLD markets their drug product in 1 mL amber glass ampules in cartons of 10.
3. Bedford is the sole manufacturer. Outside firms are utilized for testing only.
4. There are no outstanding patents or exclusivities for this drug product.
5. The inactive ingredients are accurately stated in the DESCRIPTION section (p. 59 vol 1.1).
6. Storage/dispensing recommendations:
   ANDA: container - Store below 25°C(77°F)
   carton - Below 25°C(77°F). Protect from light. Administer only if clear and colorless.
   insert - Store below 77°F(25°C) in light-resistant containers. Do not refrigerate or freeze. To assure constant potency, protect the vials from light and heat. Administer only if clear and colorless.
   NDA: container and carton - Below 25°C(77°F). Protect from light. Administer only if clear and colorless.
   Insert - Protect from light and heat. Below 77°F(25°C), in light-resistant containers. Administer only if clear and colorless.
   USP: Preserve in single-dose containers, preferably of Type 1 glass, protected from light.
7. Subcutaneous route of administration was approved in S-025 supplement.
8. I called Ms. Martina Struck of Novartis at 973-781-3217 on 3/13/02 to ask about the "booklet" that the PPI refers to. Ms Struck confirmed that the "booklet" is actually the PPI. She assured me that they will considering changing the wording to make it more clear.
9. E-mail from the chemist:
   Koung,
   I checked the ANDA for Dihydroergoatamine Mesylate Inj for pH. I have listed 3.4-4.9 in the ANDA which is the USP spec for stability. The release specs were tighter. I don't know what you read that had the specs different but perhaps if it is was in the label you should comment in your review if an error was made and the specs were wider.. CMC looks ok.
10. Alcohol Calculation: This product contains 49.3 mg of alcohol USP/mL.

    ((1g/100mg X 49.3 mg/mL) / 0.814g/mL) X 0.955 X 100% = 5.8% (V/V)
    Firm rounds off to 6% (V/V).

Date of Review: December 16, 2002 Date of Submission: October 25, 2002

Primary Reviewer: Koung Lee Date: 12/23/02

Team Leader: Lillie Golson Date: 12/23/02

cc: ANDA 40-453
DUP/DIVISION FILE
HFD-613/KLee/LGolson (no cc)
V:\FIRMSAM\BEDFORD\LTRS&REV\40453.NA2.LABELING
Review

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

ANDA Number: **40-453** Date of Submission: October 19, 2001

Applicant's Name: Bedford Laboratories

Established Name: **Dihydroergotamine Mesylate Injection USP, 1 mg/1 mL (1 mL vial)**

Labeling Deficiencies:

1. CONTAINER - 1 mL vial

   a. We note that you did not include alcohol in the description of the active ingredient. Alcohol must be declared in conjunction with the active ingredient. See 502(e)(1) of the FD&C Act for guidance.

   b. Express the alcohol content of your product in terms of percent volume (v/v) of absolute alcohol. Refer to 21 CFR 201.10(d)(2) for guidance.

   c. We encourage you to revise the net quantity statements to read "1 mL Single-Dose Vial".

   d. Add "Discard Unused Portion" if space permits.

2. CARTON

   a. See comments 1a and 1b.

   b. We encourage the relocation of the statement "Discard Unused Portion" after the storage statement.

   c. We encourage you to revise the net quantity statements to read "10 x 1 mL Single-Dose Vials".

   d. The pH range for Dihydroergotamine Mesylate Injection in the USP Monograph is 3.4 to 4.9. The pH range for your proposed product is 3.2 to 4.9. Please explain the difference.

3. INSERT

   a. GENERAL

      Add "injection" after "dihydroergotamine" throughout the insert where ever the dosage form is specified as "injection" in the reference listed drug labeling.

   b. DESCRIPTION

      i. See comment 1b.

      iii. Revise the last paragraph to read "Dihydroergotamine Mesylate Injection is a sterile, clear, colorless solution for IV, IM or subcutaneous administration. Each mL..."

   c. CLINICAL PHARMACOLOGY (Mechanism of Action)

      i. Revise the first sentence of the first paragraph to read "...affinity to 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors..."

      ii. Revise the second sentence to read (α_{2A}, α_{2B}, α_1 receptors, and..."

   d. WARNINGS (Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events)

      Replace " ——— with "patients" in the second sentence of the first paragraph.

e. HOW SUPPLIED

Delete "[redacted]" or replace "below" with "at" if you intend your product to be stored at controlled room temperature. If your product should be stored at controlled room temperature, the storage temperature statement on the carton labeling and container label should also be the same as the insert labeling.

4. INSTRUCTION FOR PATIENTS ON SUBCUTANEOUS SELF-INJECTION (How to use the dihydroergotamine injection)

a. Relocate the following to be the first statement.

"Check the expiration date printed on the vial containing medication. If the expiration date has passed, do not use it."

b. Use available training materials

Add the following as the first bulleted statement.

- Read and follow the instructions in the patient instruction leaflet which is provided with the dihydroergotamine injection package before attempting to use the product.

c. Drawing the Medication into the Syringe

Replace the third and fourth statements with the following.

- Flip off the aluminum seal and wipe the stopper with an alcohol wipe.
- Insert the needle into the solution through the middle of the stopper.

d. Please indicate the number of patient instruction leaflet(s) you intend to include in your packaging.

Please revise your labeling as instructed above and submit 4 draft labels and package insert labeling for a tentative approval or 12 final printed copies of labels and labeling for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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

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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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. USP 23	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? 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.		X	
Does the package proposed have any safety and/or regulatory concerns?		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	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? YES		X	
Are there any other safety concerns?		X	
Labeling			
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	
Labeling (continued)	**Yes**	**No**	**N.A.**
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	
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	
Inactive Ingredients: (FTR: List page # 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	
USP Issues: (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?		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? YES - TYPE 1 CLEAR GLASS IN INDIVIDUAL CARTONS	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	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ 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	
Patent/Exclusivity Issues?: 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.		X	

FOR THE RECORD:

1. This review was based on supplements NDA 5-929(S-019 & 025) for the RLD - D.H.E.45 (SANDOZ; Approved January 29, 1998)
2. The ANDA proposes to market 1 mL amber vials cartons of 10's. The RLD markets their drug product in 1 mL amber glass ampules in cartons of 10.
3. Bedford is the sole manufacturer. Outside firms are utilized for testing only.
4. There are no outstanding patents or exclusivities for this drug product.
5. The inactive ingredients are accurately stated in the DESCRIPTION section (p. 59 vol 1.1).
6. Storage/dispensing recommendations:
   ANDA: container - Store below 25°C(77°F)
   carton - Below 25°C(77°F). Protect from light. Administer only if clear and colorless.
   insert - Store below 77°F(25°C), excursions permitted 15° to 30° C (59° to 86° F) [see USP Controlled Room Temperature], in light-resistant containers. Do not refrigerate or freeze. To assure constant potency, protect the vials from light and heat. Administer only if clear and colorless.
   NDA: container and carton - Below 25°C(77°F). Protect from light. Administer only if clear and colorless.
   Insert - Protect from light and heat. Below 77°F(25°C), in light-resistant containers. Administer only if clear and colorless.
   USP: Preserve in single-dose containers, preferably of Type 1 glass, protected from light.
8. Subcutaneous route of administration was approved in S-025 supplement.
9. I called Ms. Martina Struck of Novartis at 973-781-3217 on 3/13/02 to ask about the "booklet" that the PPI refers to. Ms Struck confirmed that the "booklet" is actually the PPI. She assured me that they will considering changing the wording to make it more clear.

Date of Review: March 13, 2002 Date of Submission: October 19, 2001

Primary Reviewer: Koung Lee Date: 3/13/02

Team Leader: Charlie Hoppes Date: 3/14/02

cc: ANDA 40-453
DUP/DIVISION FILE
HFD-613/KLee/CHoppes (no cc)
V:\FIRMSAM\BEDFORD\LTRS&REV\40453.NA.LABELING
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-453

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 40-453

3. NAME AND ADDRESS OF APPLICANT
Bedford Laboratories
Attention: Molly L. Rapp
300 Northfield Road
Bedford, Ohio 44146

4. BASIS OF SUBMISSION
Reference Listed drug product: D.H.E. 45 Injection by Novartis approved in NDA #05-929.

The firm filed a Paragraph I patent certification. There is no patent in effect.

The proposed drug product contains the same active ingredients and has same strength, dosages form, route of administration, indications and usage as the listed drug.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
NA

7. NONPROPRIETARY NAME
Dihydroergotamine Mesylate Injection, USP

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

9. AMENDMENTS AND OTHER DATES:
Original submission: 10-19-01
Acceptable for Filing: 10-23-01
Acknowledgement: 12-12-01

10. PHARMACOLOGICAL CATEGORY
Antimigraine

11. Rx or OTC
Rx

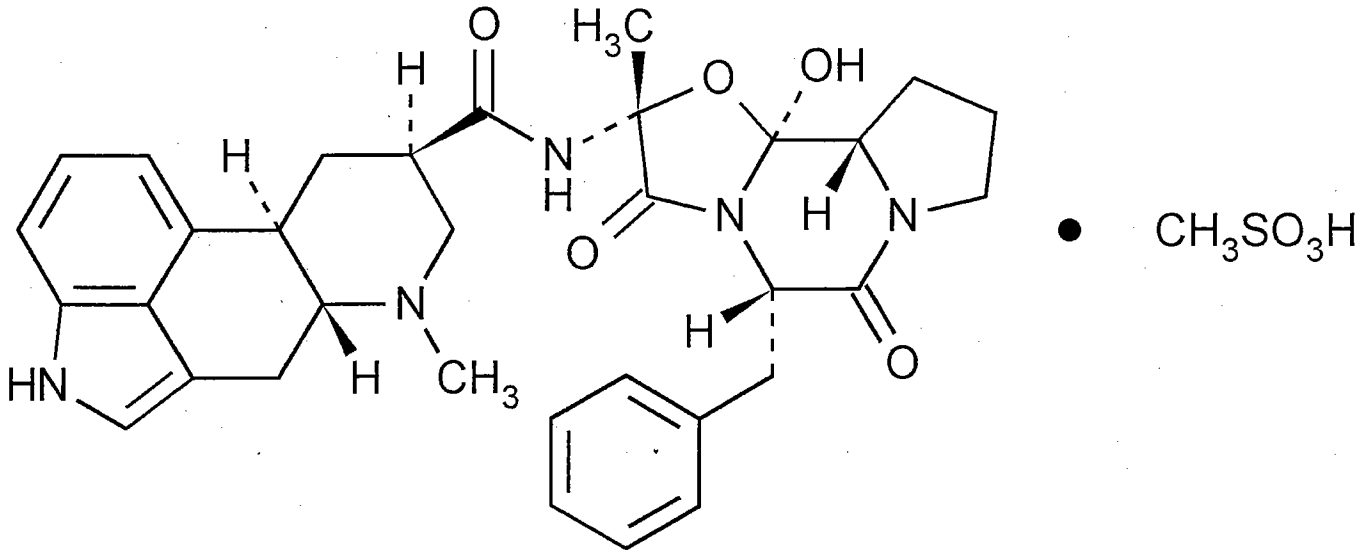
12. RELATED IND/NDA/DMF(s)
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM
Injection

14. POTENCY
1 mg/mL - 1 ml Vials

15. CHEMICAL NAME AND STRUCTURE

Generic name: Dihydroegotamine Mesylate
Chemical name:



16. RECORDS AND REPORTS
N/A

17. COMMENTS
Chemistry is deficient.
Bioequivalence is acceptable (waiver granted) by H.Nguyen on 1/03/02.
Labeling is deficient 3/14/02.
Microbiology is pending.
EER is pending.

18. CONCLUSIONS AND RECOMMENDATIONS
The application is unapprovable. Minor amendment.

19. REVIEWER: Karen A. Bernard, Ph.D.
DATE COMPLETED: 3-11-02

Redacted 13

Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-453

3. NAME AND ADDRESS OF APPLICANT
Bedford Laboratories
Attention: Molly L. Rapp
300 Northfield Road
Bedford, Ohio 44146

4. BASIS OF SUBMISSION
Reference Listed drug product: D.H.E. 45 Injection by Novartis approved in NDA #05-929.

The firm filed a Paragraph I patent certification. There is no patent in effect.

The proposed drug product contains the same active ingredients and has same strength, dosages form, route of administration, indications and usage as the listed drug.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
NA

7. NONPROPRIETARY NAME
Dihydroergotamine Mesylate Injection, USP

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

9. AMENDMENTS AND OTHER DATES:
Original submission: 10-19-01
Acceptable for Filing: 10-23-01
Acknowledgement: 12-12-01
FDA Minor Deficiency Letter: April 30, 2002
Amendment Response: October 25, 2002
Amendment: March 17, 2003
T-con: April 19, 2003
Amendment: April 24, 2003
Amendment: April 25, 2003
Amendment: June 2, 2003 Mail 6/13/03
Amendment: June 3, 2003

10. PHARMACOLOGICAL CATEGORY
Antimigraine

11. Rx or OTC
Rx

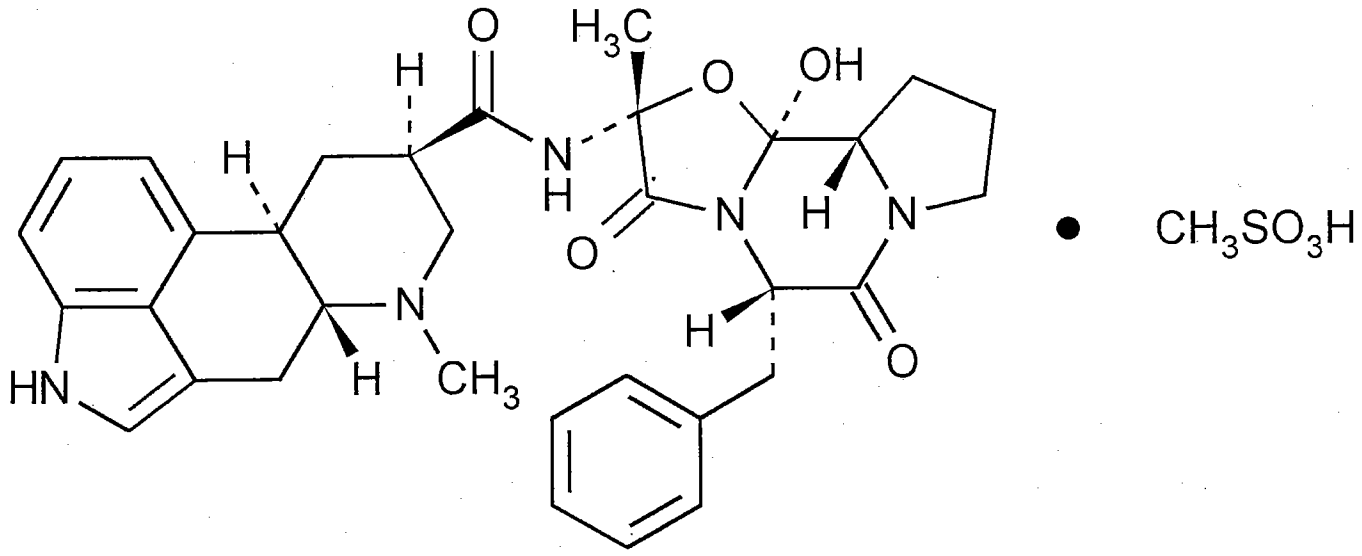
12. RELATED IND/NDA/DMF(s)
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM
Injection

14. POTENCY
1 mg/mL - 1 ml Vials

15. CHEMICAL NAME AND STRUCTURE

Generic name: Dihydroegotamine Mesylate
Chemical name:



16. RECORDS AND REPORTS
N/A

17. COMMENTS
Chemistry is now acceptable.
Bioequivalence is acceptable (waiver granted) by H.Nguyen on 1/03/02.
Labeling is acceptable as of 5/9/03
Microbiology is acceptable as of 5/1/03
EER is acceptable 7/8/02

18. CONCLUSIONS AND RECOMMENDATIONS
Approval

Redacted 12

Page(s) of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-453

MICROBIOLOGY REVIEW

Product Quality Microbiology Review
Review for HFD-640

November 12, 2002

ANDA: 40-453

Drug Product Name
Proprietary: N/A
Non-proprietary: Dihydroergotamine Mesylate Injection, USP
Drug Product Classification: N/A

Review Number: #1

Subject of this Review
Submission Date: October 19, 2001 (Original) and October 11, 2002 (Telephone Amendment)
Receipt Date: October 23, 2001 (Original) and October 15, 2002 (Telephone Amendment)
Consult Date: N/A
Date Assigned for Review: October 3, 2002

Submission History (for amendments only)
Date(s) of Previous Submission(s): N/A
Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor
Name: Bedford Laboratories (A Division of Ben Venue Laboratories, Inc.)
Address: 300 Northfield Road, Bedford, Ohio 44146
Representative: Molly L. Rapp
Telephone: 440-201-3576

Name of Reviewer: Lisa S.G. Shelton

Conclusion: The submission is **not recommended** for approval on the basis of 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, Inc.
270 Northfield Road
Bedford, OH 44146

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile injection, IM, IV, and subcutaneous, packaged as 1 mg/mL in a 1 mL vial

5. **METHOD(S) OF STERILIZATION:** [redacted]

6. **PHARMACOLOGICAL CATEGORY:** Vascular Agent

B. **SUPPORTING/RELATED DOCUMENTS:**

[redacted] DMF [redacted]
[redacted] DMF [redacted]
[redacted] – DMF [redacted]
[redacted]

C. **REMARKS:** A request for submission of legible floor plans was made by telephone on 10/8/02. A telephone amendment was received on 10/11/02.

Note to Field: While there was no significant impact on the outcome of the study, the Container/Closure Integrity Testing Validation Report (Study # PV-S18200M) is misleading in that it fails to clearly state that the original positive controls did not meet specifications and it does not cross reference the Investigation Report which is appended to the Validation Report in this application. Of note, the applicant incorrectly states that there were no deviations from the protocol (p. 262, Section XXII).

filename: V:\MICROREV\40-453.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability –
The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments are provided in the "Product Quality Microbiology Assessment" and "H. List of Microbiology Deficiencies and Comments" sections.

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 –
The subject drug product is [redacted] filled into 1 mL vials with stoppers [redacted]

B. Brief Description of Microbiology Deficiencies –
Clarification of which rooms are used for filling is needed. [redacted] validation parameters are based on an incorrect batch size for production. The application is confusing regarding which equipment will be used for [redacted] of vials and production parameters are not clearly stated. Validation data is missing for [redacted] stoppers as well as for sterilization of equipment. [redacted] data is insufficient; and comparison with production parameters is not provided.

C. Assessment of Risk Due to Microbiology Deficiencies –
The safety risk associated with the microbiology deficiencies is moderate.

III. Administrative

A. Reviewer's Signature Lisa S.B. Shelton

B. Endorsement Block
Microbiologist, Lisa S.G. Shelton, Ph.D. 11/12/02
Microbiology Team Leader, Neal J. Sweeney, Ph.D.

C. CC Block Neal J. Sweeney 11/13/02

cc:
Original ANDA 40-453
Division File
Field Copy

APPEARS THIS WAY
ON ORIGINAL

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Page(s) of trade secret and /or confidential commercial information

Product Quality Microbiology Review
Review for HFD-640

April 29, 2002

ANDA: 40-453

Drug Product Name
Proprietary: N/A
Non-proprietary: Dihydroergotamine Mesylate Injection, USP
Drug Product Classification: N/A

Review Number: #2

Subject of this Review
Submission Date: March 17, 2003 (Minor Amendment) and April 24, 2003 (Telephone Amendment)
Receipt Date: March 20, 2003 (Minor Amendment) and April 24, 2003 (Telephone Amendment)
Consult Date: N/A
Date Assigned for Review: April 1, 2003

Submission History (for amendments only)
Date(s) of Previous Submission(s): October 19, 2001 (Original) and October 11, 2002 (Telephone Amendment)
Date(s) of Previous Micro Review(s): November 19, 2002

Applicant/Sponsor
Name: Bedford Laboratories (A Division of Ben Venue Laboratories, Inc.)
Address: 300 Northfield Road, Bedford, Ohio 44146
Representative: Molly L. Rapp
Telephone: 440-201-3576

Name of Reviewer: Lisa S.G. Shelton

Conclusion: The submission is **recommended** for approval on the basis of 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, Inc.
270 Northfield Road
Bedford, OH 44146

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile injection, IM, IV, and subcutaneous, packaged as 1 mg/mL in a 1 mL vial

5. **METHOD(S) OF STERILIZATION:** [redacted]

6. **PHARMACOLOGICAL CATEGORY:** Vascular Agent

B. **SUPPORTING/RELATED DOCUMENTS:**
[redacted] - DMF [redacted]
[redacted] DMF [redacted]
[redacted] – DMF [redacted]
[redacted]

C. **REMARKS:** Clarifying questions discussed by telephone (4/23/03), regarding filter validation, are addressed in a Telephone Amendment, dated 4/24/03.

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APPEARS THIS WAY
ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation on Approvability –
The submission is **recommended** for approval on the basis of sterility assurance. Specific comments are provided in the "Product Quality Microbiology Assessment" section.

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 –
The subject drug product is [redacted] filled into 1 mL vials with stoppers. [redacted]

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies –
The safety risk is considered minimal.

III. Administrative

A. Reviewer's Signature Lisa S.P. Shelton

B. Endorsement Block
Microbiologist, Lisa S.G. Shelton, Ph.D. 4/29/03
Microbiology Team Leader, Neal J. Sweeney, Ph.D.
Neal J Sweeney 5/1/03

C. CC Block
cc:
Original ANDA 40-453
Division File
Field Copy

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Page(s) of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-453

BIOEQUIVALENCE REVIEW(S)

#1

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 40-453 SPONSOR : Bedford Laboratories
DRUG AND DOSAGE FORM : Dihydroergotamine Mesylate Injection USP
STRENGTH(S) : 1 mg/mL (in 1 mL vials)
TYPES OF STUDIES : N/A
CINICAL STUDY SITE(S) : N/A
ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : N/A
DISSOLUTION : N/A.
WAIVER REQUEST: Acceptable

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : HN DATE : 1/3/02

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : YCH DATE : 1/3/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
for
INITIAL : N Gahwaiti DATE : 1/3/2002

Dihydroergotamine Mesylate Injection USP
1 mg/mL, 1 mL vials
ANDA # 40-453
Reviewer: Hoainhon Nguyen
W # 40453wo01.doc

Bedford Laboratories
Bedford, OH
Submission Date:
October 19, 2001

Review of a Waiver Request

The firm has requested a waiver from *in vivo* bioavailability requirements for its Dihydroergotamine Mesylate Injection USP, 1 mg/mL in 1 mL vials, in accordance with 21 CFR 320.22 (b) (1).

Comments:

1. The test product is a sterile solution intended for intravenous, intramuscular and subcutaneous administration.

2. The formulation of the test product is identical to that of the currently approved D.H.E. 45® Injection (NDA # 05-929), 1 mg/mL, manufactured by Novartis, as shown below:

Ingredients	Test Formulation (per mL)	D.H.E. 45's Formulation (per mL)
Dihydroergotamine Mesylate	1 mg	1 mg
Dehydrated Alcohol	49.3 mg*	6.1% v/v
Glycerin	153.6 mg**	15% w/v
Methanesulfonic Acid	to adjust pH	to adjust pH
Sodium Hydroxide	to adjust pH	to adjust pH
Water for Injection	q.s.	q.s.

*Equivalent to 6.1% v/v
**Equivalent to 15% w/v

Recommendations:

The Division of Bioequivalence agrees that the information submitted by Bedford

Laboratories demonstrates that its Dihydroergotamine Mesyltate Injection USP, 1 mg/mL in 1 mL vials, falls under 21 CFR 320.22 (b) (1) of the Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of *in vivo* bioavailability study be granted. The test product Dihydroergotamine Mesyltate Injection USP, 1 mg/mL in 1 mL vials, is deemed bioequivalent to the currently approved D.H.E. 45® Injection, 1 mg/mL, manufactured by Novartis.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 1/3/2002

Concur: Date: 1/3/2002
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 40-453 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File

Hnguyen/12-27-01/W #40453wo01.doc
Also under v:\firmsam\bedford\ltrs&rev\40453wo01.doc

Attachments: None

BIOEQUIVALENCY COMMENTS

ANDA: 40-453 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Dihydroergotamine Mesylate Injection USP, 1 mg/mL in 1 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

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 40-453
ANDA DUPLICATE
DIVISION FILE
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen

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Printed in final on / /00

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang 1/3/2002
HFD-617/K. Scardina 1/4/02
HFD-650/ D. Conner for 1/3/2002

BIOEQUIVALENCY - ACCEPTABLE Submission Date: 10-19-01

WAIVER (WAI) 01c

Strengths: 1 mg/mL
Outcome: AC

Outcome Decisions:
AC - Acceptable

WINBIO COMMENTS:

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 40-453 SPONSOR : Bedford Laboratories
DRUG AND DOSAGE FORM : Dihydroergotamine Mesylate Injection USP
STRENGTH(S) : 1 mg/mL (in 1 mL vials)
TYPES OF STUDIES : N/A
CINICAL STUDY SITE(S) : N/A
ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : N/A
DISSOLUTION : N/A.
WAIVER REQUEST: Acceptable

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : HN DATE : 1/3/02

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : YCH DATE : 1/3/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
for
INITIAL : Mo Gallaire DATE : 1/3/2002

RECORD OF TELEPHONE CONVERSATION

DATE: **4/23/03 (Initial Contact)**

INITIATED BY: **Lisa S.G. Shelton, Review Microbiologist** Lisa S.G. Shelton 4/25/03

Applicant/Sponsor

Name: Bedford Laboratories (A Division of Ben Venue Laboratories, Inc.)
Address: 300 Northfield Road, Bedford, Ohio 44146
Representative: Molly L. Rapp, Manager, Regulatory Affairs
Telephone: 440-201-3576

Questions regarding:

ANDA 40-453 Dihydroergotamine Mesylate Injection, USP
Amendment dated 3/17/03

With regard to the repeat filter validation described in Response to Microbiology Deficiency #2:

The response states that the [redacted] validation was repeated using different [redacted] and [redacted] times in order to support the [redacted] maximum batch size. The response goes on to present the rationale for the flow rate that would result in a [redacted] batch being [redacted] s, stated as a rate in excess of what would be used in production. The anticipated [redacted] for production is not provided. In the referenced Attachment II, the Pall Report # 10730FM on page 6, in Table 1, presents a production batch size of [redacted] and a duration of [redacted]

1. Please clarify what is the maximum batch size and duration of [redacted] planned for production.

2. Were the [redacted] validation test conditions modified to support the [redacted] batch size or the [redacted] batch size?

RESPONSE:

The maximum batch size is [redacted]. Molly will check to find out if the [redacted] validation report stated [redacted] as a worst case, possibly to cover [redacted]. Also, she will ascertain if the validation study conditions were modified to support the [redacted] or the [redacted] batch size. A detailed response will be sent by Telephone Amendment to be FAXed on 4/24/03, to be followed by hardcopy.

Drafted by L.Shelton 4/25/03
Filename V:\FIRMSAM\BEDFORD\TELECONS\40453micro.04-24-03.doc
CC: ANDA 40-453
Division File

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-453

ADMINISTRATIVE DOCUMENTS

DIVISION REVIEW SUMMARY

ANDA: 40-453

DRUG PRODUCT: Dihydroergotamine Mesylate Injection, USP

FIRM: Bedford Laboratories

DOSAGE FORM: Injection

STRENGTH: 1 mg/mL, 1 mL vial

CGMP STATEMENT/EIR UPDATE STATUS:
EER Acceptable 7/8/02

BIO INFORMATION:
The Division of Bioequivalence have found the application to be acceptable. The waiver was granted by HNguyen on 1/03/02.

VALIDATION-DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S)
USP product, methods validation not required.

STABILITY-ARE CONTAINERS USED IN THE STUDY IDENTICAL TO THOSE USED IN THE CONTAINER SECTION?
The revised future stability protocol the firm proposes is as follows:

Test	Limit
Physical Appearance	Clear, colorless solution, free of particles and contamination
pH	3.4-4.9
Assay	[redacted]
Chromatographic Purity (in-house [redacted] and	[redacted]

	Highest Individual Unknown NMT 0.5% Total Impurities NMT [redacted]
[redacted]	Content [redacted] of labeled amount [redacted]
Color of Solution	NMT [redacted] units
[redacted] USP	NMT [redacted]
Particulate Matter (HIAC)	Meets USP
Sterility	Meets USP
Bacterial Endotoxin	NMT [redacted] of DHE mesylate

Whereby testing will be designated by schedules:

Schedule A: every test station
Schedule B: annually
Schedule C: annually
Schedule D: initial and expiry

The firm included 3 months of accelerated data (40°C/75% RH) in the proposed container and 3 months of room temperature data (25°C ± 2°C) 60%RH for lot #0787-40-298523. As noted above, Particulate Matter, Sterility and Endotoxin testing will be performed using reduced testing stations. Data were collected in the upright and inverted container orientations. The firm proposes a 24 month expiration dating period with storage at 25°C ± 2°C 60%RH.

No admixture study is needed. No diluents are used with this drug product. The applicant did submit an elastomeric closure study. The sudy performed was derived from USP 24 <381> which is an extraction study. The firm utilized the drug product as the extraction vehicle. The study indicated that no significant amount of extractables were obtained from interaction of the DHE and the rubber stopper.

Also included is a future stability commitment in accordance with FDA Guidelines.

LABELING
The labeling review is acceptable 5/9/03

STERILIZATION VALIDATION
Acceptable 5/1/03

SIZE OF DEMONSTRATION BATCH

A general description of the manufacturing process is provided on page 106. The product is The compounding step

The firm manufactured an exhibit batch (#078740 298523) of The batch was single filled into 1 mL vials. The batch was manufactured on 5/21/01. The equipment is specified. The bulk accountability yield was recorded as The final batch reconciliation data (page 490) showed a 100% accountability yield after filling. units were filled into the 1 mL vials. The reconciliation was acceptable. The batch quantity was revised to reflect the actual amount of vials filled not the theoretical amount of vials projected to be filled. Therefore, the firm revised the batch quantity to be vials. See T-con with firm dated 11/27/01 in
Vol. 2.1.

Blank batch records are included for future production batches. The maximum intended production size is . The firm has scaled up their Master batch to vials. See T-con dated 11/27/01. The firm includes a holding policy that is in accordance with FDA guidelines. A reprocessing statement is also included.

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

RECOMMENDATION: Approve

SIGNATURE: DATE: December 5, 2002

RECORD OF TELEPHONE CONVERSATION

DATE: April 16, 2003

ANDA: 40-453

DRUG PRODUCT: Dihydroergotamine Mesylate Injection USP, 1 mg/1mL (1 mL vial)

FIRM: Bedford Laboratories.

CONVERSATION WITH: Molly Rapp

PHONE NUMBER: 440-201-3576

TOPIC: Labeling

Called Ms. Rapp and asked her to make the following changes.

1. GENERAL

   Revise the storage temperature statement to read "Store at 20° to 25° C (68° to 77°F)[see USP Controlled Room Temperature]."

2. CONTAINER (1 mL)

   See GENERAL comment. If space is limited, you may omit "[see USP Controlled Room Temperature]".

3. CARTON (10)

   See GENERAL comment.

4. INSERT

   a. WARNINGS

      i. Risk of Myocardial Ischemia and/or Interaction and Other Adverse Cardiac Events

         Revise the beginning of the first paragraph to read "(See CONTRAINDICATIONS.) It is strongly recommended that..."

      ii. Increase in Blood Pressure

         Delete the ' [redacted] in ' [redacted] in the second sentence of the first paragraph.

   b. PRECAUTIONS (Beta Blockers)

Delete the [redacted] in "[redacted]

c. HOW SUPPLIED

See GENERAL comment.

d. INSTRUCTION FOR PATIENTS ON SUBCUTANEOUS SELF-INJECTION

Important questions to consider before using dihydroergotamine mesylate injection

Add a comma between "injection" and "spray" in the eleventh bulleted statement.

I also asked her to add "Do not refrigerate or freeze" on the carton labeling to be consistent with the insert and RLD labeling.

Koung Lee 4/16/03

cc: ANDA 40-453

V:\FIRMSAM\BEDFORD\TELECON\40453.April16.2003.TEL

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-453

CORRESPONDENCE

BEDFORD
LABORATORIES™

June 3, 2003

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 C

RE: ANDA 40-453/ Telephone Amendment
PRODUCT: Dihydroergotamine Mesylate Injection, USP; 1 mg/mL, 1 mL vials

Dear Sir/Madam,

We wish to amend our unapproved Abbreviated New Drug Application 40-453 for Dihydroergotamine Mesylate Injection, USP, 1 mg/mL, 1 mL vials, by responding to the telephone communication of June 3, 2003 from Dr. Vilayat Sayeed. FDA 356h Form is provided.

This letter is in response to your inquiries concerning the APHA color limits established for DHE. Based on our conversation of June 3, 2003, we request to delete the color test from the finished product release testing and the stability testing. The basis for this request is this drug product is a clear and colorless solution and a test for color is unnecessary.

Please note that the product is inspected visually for color at each time point, just as it would be by a pharmacist prior to preparation.

We trust this meets with your approval. If the Agency has any comments or further requests, the phone numbers for contact are (440)201-3576 (direct) and (440)232-2772 (facsimile).

Sincerely,
for Bedford Laboratories™

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

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June 2, 2003

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/AA

RE: ANDA 40-453/ Telephone Amendment
PRODUCT: Dihydroergotamine Mesylate Injection, USP; 1 mg/mL, 1 mL vials

Dear Sir/Madam,

We wish to amend our unapproved Abbreviated New Drug Application 40-453 for Dihydroergotamine Mesylate Injection, USP, 1 mg/mL, 1 mL vials, by responding to the telephone communication of May 30, 2003 from Dr. Vilayat Sayeed FDA 356h Form is provided.

This letter is in response to your inquiries concerning the APHA color limits established for DHE. I have compiled a table of other Bedford Laboratories' products which require this test in order to provide a point of reference for the numerical limits set for DHE.

Product	ANDA #	Description	Stability Limit
			NMT — APHA
Amiodarone HCl Injection	76-299 (Approved)	Clear light yellow to yellow	NMT — APHA
Leucovorin Calcium Injection	40-347 (Approved)	Clear yellow solution	NMT — PHA

Many of our products which are clear and colorless require only a — analysis in a — with the limit set at a specific number of — units. Typically we apply the APHA color test to solutions that have color. I believe this test was chosen in error in regards to our typical practice, however, it is appropriate for demonstrating the absence of color just as well as a straightforward — analysis method would be. Also, the product is inspected visually for color at each time point, just as it would be by a pharmacist prior to preparation, and is limited by this visual test as well as the by the APHA test.

We trust this meets with your approval. If the Agency has any comments or further requests, the phone numbers for contact are (440)201-3576 (direct) and (440)232-2772 (facsimile).

Sincerely,
for Bedford Laboratories™

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

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April 25, 2003

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

Labeling Amendment

FPL

ORIG AMENDMENT
N/AF

RE: ANDA 40-453/ Labeling Amendment
PRODUCT: Dihydroergotamine Mesylate Injection, USP; 1 mg/mL, 1 mL vials

Dear Sir/Madam,

We wish to amend our unapproved Abbreviated New Drug Application 40-453 for Dihydroergotamine Mesylate Injection, USP, 1 mg/mL, 1 mL vials, by responding to the telephone communication of April 9, 2003 from Ms. Karen Bernard. FDA 356h Form is provided.

As requested by the Agency, we have revised that vial label, carton labeling and insert labeling to read "Store at 20 – 25°C (68 – 77°F). See USP controlled room temperature.". We have enclosed 12 copies of final printed labeling.

We trust this meets with your approval. If the Agency has any comments or further requests, the phone numbers for contact are (440)201-3576 (direct) and (440)232-2772 (facsimile).

Sincerely,
for Bedford Laboratories™

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

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~~1 of 5~~
EZ 4/24/03

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April 24, 2003

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
Nam

RE: ANDA 40-453/ Telephone Amendment
PRODUCT: Dihydroergotamine Mesylate Injection, USP; 1 mg/mL, 1 mL vials

Dear Ms. Lisa Shelton,

We wish to amend our unapproved Abbreviated New Drug Application 40-453 for Dihydroergotamine Mesylate Injection, USP, 1 mg/mL, 1 mL vials, by responding to the your telephone communication of April 23, 2003. FDA 356h Form is provided.

1. **Requested: the ANDA maximum batch size and the estimated duration of [redacted] for a routine manufacture of that batch size.** Response: The ANDA maximum batch size is [redacted]. The estimated [redacted] time during routine production for a [redacted] batch would be about [redacted]. This would be an intermittent [redacted] because the production department can only filter [redacted] at a time, the limitation being the post- [redacted] holding [redacted]

2. **Requested: clarification if the [redacted] validation was modified to support a [redacted] batch or a [redacted] batch size. You referenced page 6 of the [redacted] validation report which lists the batch size as [redacted]** Response: The [redacted] validation was repeated using [redacted], and [redacted] times in order to support the [redacted] maximum batch size. The actual [redacted] validation batch size was calculated with the primary factor being the [redacted] time of [redacted] which represents a worst-case [redacted] time. The [redacted] batch size stated in the [redacted] validation was a projected volume calculated from the [redacted] time [redacted] and the assumed minimum flow rate of approximately [redacted]

We trust this meets with your approval. If the Agency has any comments or further requests, the phone numbers for contact are (440)201-3576 (direct) and (440)232-2772 (facsimile).

Sincerely,
for Bedford Laboratories™

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

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5-5-03

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March 17, 2003 **Microbiology/Chemistry/Labeling Deficiency**

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 FPL

RE: ANDA 40-453/ Microbiology and Labeling Deficiency
PRODUCT: Dihydroergotamine Mesylate Injection, USP; 1 mg/mL, 1 mL vials

Dear Sir/Madam:

We wish to amend our unapproved Abbreviated New Drug Application 40-453, for Dihydroergotamine Mesylate Injection, USP, 1 mg/mL, 1 mL vials, by responding to the Agency's letter dated November 18, 2002 and the labeling deficiency dated December 24, 2002. We would also like to provide amended drug substance specifications.

FDA 356h Form is provided in Attachment I.

A. Chemistry: The drug substance manufacturer has amended the drug substance specifications by lowering the acetone limit to NMT [redacted], lowering the [redacted] limit to NMT [redacted], and adding a [redacted] specification of NMT [redacted] Please see Attachment IX for the revised drug substance specifications and revised specifications from the drug substance manufacturer.

B. Response to Microbiology Deficiency dated November 18, 2002: The number associated with the responses given below corresponds to the number identifying the deficiencies in your communication.

1. The commercial batches of this drug product will be filled only in [redacted] using [redacted] This [redacted]

2. The [redacted] validation was repeated using [redacted] times in order to support the [redacted] maximum batch size. Please refer to Attachment II. Ben Venue uses two [redacted] however in order to provide the worst case for validation purposes, we will assume only a [redacted]. The minimum [redacted] used during the [redacted]

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At this rate a batch would be in about , which exceeds the rates that would be seen in routine production. In addition, the total throughput used in the validation was . Again, using the , the total volume of drug product would be , which exceeds the maximum batch size by a factor of .

3. Once the of this drug product is completed, each sterilized vial filled with the product. Then, each product-filled vial is and then is The drug product is exposed to this

4a. The vials will be sterilized in the The information regarding is irrelevant to this Application and was included in error; will not be used for this product.

4b. Following are the production parameters for the vial sterilization in the Vial Sterilization:

4c. The validation data for the vial sterilization in the was provided in the original application on pages 173 to 176A.

4d. i. Annual performance audits of do not involve an endotoxin challenge. This routine qualification audit serves to verify the operation and functionality of the units. The routine qualification of the and production parameters mentioned on page 112 of the original application are not applicable to the The routine verification of the verifies the See Attachment III for a routine qualification of the Study #S11502M).

ii. Every three years a verification, which utilizes an endotoxin challenge, is performed. This routine verification demonstrates that a minimum of a reduction in endotoxin is achieved. Since the this cycle verification has not yet been conducted.

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5a. Stoppers will be sterilized in the [redacted] will not be used and was included in error. Validation data for [redacted] sterilization of stoppers in [redacted] has been provided in the original application on pages 177 to 182 (and inadvertently a second copy of this same data was provided on pages 204 to 209). Validation data for [redacted] is provided in Attachment IV.

5b. The annual routine qualification (also called "Performance Audit") of sterilizers includes a biological challenge as a portion of the qualification process. The routine cycle [redacted]

6a. Equipment will be sterilized in the [redacted] Autoclave #12 will not be used and was included in error. Validation data for [redacted] sterilization of equipment [redacted] has been provided in the original application on pages 187 to 202. Validation data for [redacted] is provided in Attachment IV.

6b. The annual equipment sterilization cycle verification of sterilizers includes a biological challenge. This verification serves to demonstrate the continued operational effectiveness of the sterilizer unit and to verify that the [redacted] will deliver a [redacted] input to all areas of a maximum equipment load that will result in a predictable log reduction of microorganisms having a D-value of at least [redacted]. Routine equipment sterilization cycle verifications for both [redacted] are provided in Attachment V.

7a. The [redacted] will be used to fill this drug product. The last [redacted] for this filling line are provided in Attachment VI.

7b. It was a typographical error. Ben Venue [redacted]

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7c. All relevant filling parameters for a maximum production batch of Dihydroergotamine Mesylate Injection USP have been compared with parameters used in [redacted]. For the comparison, see the following table:

Lot	Vial Size (cc)	Vial Opening Size (mm)	Fill Volume (g)	Filling Speed (vials/min)	Filling Duration
PST # 1009-51-372877	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PST # 1010-71-348905	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0787-40 (DHE Inj. USP) Scale-Up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

C. Acknowledgement of Comments in the Microbiology Deficiency dated November 18, 2002. The number associated with the responses given below corresponds to the number identifying the comments in your communication.

1a. i. The reference on page 241 of the original application made to the "Positive/Negative Control Data" refers to a file folder title used for internal filing of our container closure study. This "Positive/Negative Control Data" section is composed of pages 277 - 288 in the original application. We apologize for the confusion.
ii. In the study, an investigation report was initiated and written regarding the failure of five positive controls. Please see Attachment VII for a Test Occurrence report that was initiated, written, and added to Container Closure Study PV-S18200M after we submitted the application to the Agency. In our procedures for documentation of validation reports, there is a difference between deviations and occurrences. It was determined that this issue of impeded challenge pathways was considered a test occurrence as opposed to a deviation. The initiation and addition of the test occurrence report to Study PV-S18200M acknowledges our further review of the report and our effort to document this issue more clearly.

1b. [redacted]

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D. Response to the Labeling Deficiency dated December 24, 2002: All deficiencies have been addressed; please refer to Attachment VIII for a side-by-side comparison. Also, 12 copies of the proposed carton and insert labeling are provided in Attachment VIII.

We trust this meets with your approval. 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), or, via email at mrapp@cle.boehringer-ingelheim.com.

Sincerely,
for Bedford Laboratories™

P. Patel for

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

APPEARS THIS WAY
ON ORIGINAL

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October 25, 2002

ORIG AMENDMENT
N/AM

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 40-453/ Minor Amendment
PRODUCT: Dihydroergotamine Mesylate Injection, USP; 1 mg/mL, 1 mL vials

Dear Sir/Madam:

We wish to amend our unapproved Abbreviated New Drug Application 40-453, for Dihydroergotamine Mesylate Injection, USP, 1 mg/mL, 1 mL vials, to remove the Chemistry and Labeling deficiencies cited in the letter of April 30, 2002. Form FDA 356h is located in Attachment I.

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

Chemistry Deficiencies

1. Bedford Laboratories™ acknowledges that ANDA 40-453 will not be approved until DMF [redacted] has been deemed satisfactory.

2. & 3. Revised Test Specifications have been provided for your review in Attachment II. Attachment II includes updated Raw Material, Finished Product, and Stability Specifications. Please note that the impurity specifications have been updated to include all of the known impurities listed in the current test method. An updated copy of method 787-00-024 has been provided in Attachment III for your review. Also provided for your review are Addendums to both the Raw Material Certificate of Analysis, and the Final Product Certificate of Analysis. These Addendums, along with a table summarizing the impurity results can be found in Attachment IV

4. The testing and release of Glycerin, USP, BVL Lot 01-0633, was completed on May 4, 2001; the USP revisions became effective on January 1, 2002. Bedford Laboratories has updated the specifications for Glycerin, USP to be in accordance with those of the USP, current revision, and commits to testing all future lots of Glycerin, USP to these specifications.

5. Please refer to Attachment V for the revised Description of the Manufacturing Process, Page 106 of the original application, which includes the use of [redacted] manufacturing.

6. Bioburden specifications are located in both the [redacted] Process Validation Package, page 134, and also in the In-Process Specifications, page 511. The specifications are:

Response Level 1: Total Microbial Count and Fungi: [redacted]
Response Level 2: Total Microbial Count and Fungi: [redacted]

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A DIVISION OF BEN VENUE LABORATORIES, INC.

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

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7. For your convenience, a list of all testing and specifications has been included in Attachment VI in tabular form. Please note that fill volume checks are routinely performed on each batch. The results for the exhibit batch were provided on page 475 of the original application.

[redacted] is not monitored as an In-Process parameter; however, the testing has been added to the Final Product Release specifications with a limit of Not More Than [redacted] The revised specifications are provided in Attachment II.

8. Report 02-0094.1 is provided in Attachment VII which establishes the solution stability for one week.

9. Both Pre- and Post Approval Stability Protocols have been included in Attachment VIII. Please refer to the response to deficiency point #2 and 3.

Labeling Deficiencies

1. The size of the container label does not allow for the inclusion of the description of the product or the inclusion of, "Discard Unused Portion." The size of the container label also does not allow for alcohol to be included in the description of the active ingredient. The net quantity statement has been revised as recommended.

2. All recommended revisions to the carton labeling have been completed, including the revision of the pH range from 3.2 – 4.9 to 3.4 – 4.9 (current USP specification). The proposed pH range of 3.2 – 4.9 came from the RLD's labeling, which reads, "3.6 ± 0.4" which yields a lower pH limit of 3.2.

3. All recommended revisions to the package insert labeling have been completed as requested. Please note, Bedford Laboratories™ has integrated the "patient leaflet" information into the text of the package insert labeling. Therefore, no separate patient leaflets will be included with the drug product.

Side-by-side comparisons of the proposed vial label, carton labeling and package insert labeling versus that last submitted are provided in Attachment IX. Also, 12 copies of all final printed labeling are also provided in Attachment X.

We trust this meets with your approval. 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 L. Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.

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October 11, 2002

Microbiology Deficiency

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/AS

RE: ANDA 40-453/ Telephone Amendment
PRODUCT: Dihydroergotamine Mesylate Injection, USP; 1 mg/mL, 1 mL vials

Dear Sir/Madam:

We wish to amend our unapproved Abbreviated New Drug Application 40-453, for Dihydroergotamine Mesylate Injection, USP, 1 mg/mL, 1 mL vials, in response to a October 7, 2002 telephone conversation between Ms. Lisa Shelton of the Agency and Ms. Molly Rapp from Ben Venue Laboratories, Inc. Form FDA 356h is provided. Please find attached the facility CADD drawings. Every attempt has been made to obtain darker copies with visible walls and floor plan details.

We trust this meets with your approval. 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 L. Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.

RECEIVED
OCT 15 2002
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ANDA 40-453

DEC 12 2001

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

Dear Madam:

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

Reference is made to the telephone conversation dated November 27 ,2001 and to your correspondence dated November 28, 2001.

NAME OF DRUG: Dihydroergotamine Mesylate Injection USP, 1 mg/mL, 1 mL vials

DATE OF APPLICATION: October 19, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 23, 2001

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

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

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

Gregory S. Davis for

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

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LABORATORIES™

November 27, 2001

NC
NEW CORRESP

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 40-453/ Telephone Amendment
PRODUCT: Dihydroergotamine Mesylate Injection, USP; 1 mg/mL, 1 mL vials

Dear Sir/Madam:

We wish to amend our unapproved Abbreviated New Drug Application 40-453, for Dihydroergotamine Mesylate Injection, USP, 1 mg/mL, 1 mL vials, to remove the deficiencies discussed in the telephone conversation of November 27, 2001, between Mr. Paras Patel of the Agency and Ms. Molly Rapp of Ben Venue Laboratories, Inc. Form FDA 356h is located in Attachment I.

Attachment II contains the revised Process Control Specification from the executed exhibit lot of Dihydroergotamine Mesylate Injection, USP, Lot 0787-40-2098523. The Batch Quantity, in vials, has been revised to reflect the actual amount of vials filled, not the theoretical amount of vials projected to be filled. Therefore, the batch quantity has been revised to [redacted] vials.

We trust this meets with your approval. 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 L. Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.

CENTER FOR DRUG
NOV 2 8 2001
EVALUATION AND RESEARCH

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October 19, 2001

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)(i) OK
12-DEC-2001
Gregory B. Davis

RE: Abbreviated New Drug Application
PRODUCT: Dihydroergotamine Mesylate Injection, USP; 1 mg/mL, 1 mL vials

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 Dihydroergotamine Mesylate Injection (DHE), USP, 1 mg/mL; 1 mL vials. 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" (Novartis' D.H.E. 45®). 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 (DHE Injection, USP, 1 mg/mL; 1 mL vials). The drug product is a solution intended solely for intramuscular, intravenous or subcutaneous administration and it contains the active ingredient 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 C (cGMP Certification).

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.

Two copies of the analytical methods, which were used to test this product, as well as an analytical method validation package, are enclosed separately along with this application.

The proposed drug product is being claimed as "USP", although Bedford Laboratories utilized alternate methodology than that in the DHE and DHE Injection monographs. Bedford Laboratories acknowledges that in the event of a dispute, only the compendial results obtained by the official methods and procedures of the USP/NF will be considered conclusive.

Section XXII of this application, located in Volume 3, 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, and copies of the executed batch record sterilization information. This product is ———————

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 L. Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.