

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**Approval Package for:**

**APPLICATION NUMBER:**

**40-475**

Generic Name: Dihydroergotamine Mesylate Injection  
USP, 1mg/mL packaged in 1mL single-  
dose ampules

Sponsor: PharmaForce, Inc.

Approval Date: April 28, 2003

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:**

**40-475**

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**40-475**

**APPROVAL LETTER**

APR 28 2003

PharmaForce, Inc.  
U.S. Agent for: Paddock Laboratories, Inc.  
Attention: Marilyn A. Friedly  
1507 Chambers Road  
Columbus, OH 43212

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated February 28, 2002, 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 ampules.

Reference is also made to your amendments dated December 16, and December 30, 2002; and January 13, March 14, March 17, April 9, April 16 and April 25, 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<sup>®</sup> 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 4/28/03

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

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**40-475**

**FINAL PRINTED LABELING**

# Dihydroergotamine Mesylate Injection, USP

Rx Only



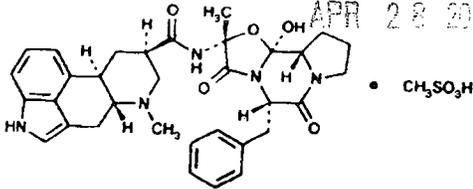
## WARNING

Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of DIHYDROERGOTAMINE with potent CYP3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP3A4 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 sections)

## DESCRIPTION

Dihydroergotamine Mesylate is ergotamine hydrogenated in the 9, 10 position as the mesylate salt. Dihydroergotamine Mesylate is known chemically as ergotaman-3',6',18-trione,9,10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-(5'-o)-monomethanesulfonate. Its molecular weight is 679.80 and its molecular formula is  $C_{33}H_{37}N_5O_5 \cdot CH_3SO_3$ .

The chemical structure is:



Dihydroergotamine Mesylate Injection, USP is a clear, colorless solution supplied in sterile ampoules for intravenous, intramuscular, or subcutaneous administration. Each mL contains 1 mg Dihydroergotamine Mesylate, USP; Alcohol, USP 6.1% by volume; Glycerin, USP 15% by weight; Water for Injection, USP; Methanesulfonic Acid and/or Sodium Hydroxide for pH adjustment. pH range is 3.4 - 4.9.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Dihydroergotamine binds with high affinity to 5-HT<sub>1D</sub> and 5-HT<sub>1B</sub> receptors. It also binds with high affinity to serotonin 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, and 5-HT<sub>2C</sub> receptors, noradrenergic  $\alpha_{2A}$ ,  $\alpha_{2B}$  and  $\alpha_1$  receptors, and dopamine D<sub>2L</sub> and D<sub>3</sub> receptors.

The therapeutic activity of dihydroergotamine in migraine is generally attributed to the agonist effect at 5-HT<sub>1B</sub> receptors. Two current theories have been proposed to explain the efficacy of 5-HT<sub>1B</sub> receptor agonists in migraine. One theory suggests that activation of 5-HT<sub>1D</sub> 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<sub>1B</sub> 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'- $\beta$ -hydroxydihydroergotamine, exhibits affinity equivalent to its parent for adrenergic and 5-HT receptors and demonstrates equivalent potency in several vasoconstrictor 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%-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%-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, USP 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 ergotamine) 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, USP 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, USP 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, USP may increase blood pressure, it should not be given to patients with uncontrolled hypertension.

Dihydroergotamine Mesylate Injection, USP, 5-HT<sub>1</sub> 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, USP should not be administered to patients with hemiplegic or basilar migraine.

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

Dihydroergotamine Mesylate Injection, USP 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

uterine vessels and/or increased myometrial tone.

Dihydroergotamine Mesylate Injection, USP 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, USP 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 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, USP should not be used by patients with documented ischemic or vasospastic coronary artery disease. (See CONTRAINDICATIONS.) It is strongly recommended that Dihydroergotamine Mesylate Injection, USP 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, USP 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, USP 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, USP in those patients with risk factors.

It is recommended that patients who are intermittent long-term users of Dihydroergotamine Mesylate Injection, USP 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, USP.

The systematic approach described above is currently recommended as a method to identify patients in whom Dihydroergotamine Mesylate Injection, USP 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, USP, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the Dihydroergotamine Mesylate Injection, USP 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, USP, 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, USP.

Dihydroergotamine Mesylate Injection, USP 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, USP 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, USP 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<sub>1</sub> agonist in a study evaluating subjects undergoing cardiac catheterization.

## PRECAUTIONS

### General

Dihydroergotamine Mesylate Injection, USP 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<sub>1</sub> agonist are candidates for further evaluation. (See WARNINGS)

Fibrotic Complications: See WARNINGS: Fibrotic Complication

### 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, USP, 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, USP 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, USP. Sumatriptan and Dihydroergotamine Mesylate Injection, USP should not be taken within 24 hours of each other. (See CONTRAINDICATIONS)

Boehringer-Ingelheim

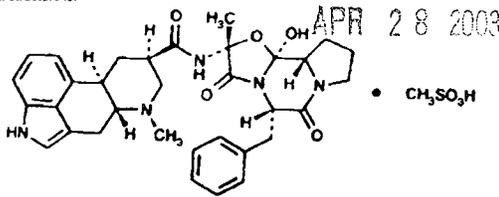
## DESCRIPTION

Dihydroergotamine Mesylate is ergotamine hydrogenated in the 9, 10 position as the mesylate salt. Dihydroergotamine Mesylate is known chemically as ergotaman-3',6',18-trione,9,10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-(5 $\alpha$ ), monomethanesulfonate. Its molecular weight is 679.80 and its molecular formula is C<sub>33</sub>H<sub>37</sub>N<sub>5</sub>O<sub>5</sub>•CH<sub>3</sub>SO<sub>3</sub>.

The chemical structure is:



212761



C<sub>33</sub>H<sub>37</sub>N<sub>5</sub>O<sub>5</sub>•CH<sub>3</sub>SO<sub>3</sub>S

Dihydroergotamine mesylate

Mol. wt. 679.80

Dihydroergotamine Mesylate Injection, USP is a clear, colorless solution supplied in sterile ampoules for intravenous, intramuscular, or subcutaneous administration. Each mL contains 1 mg Dihydroergotamine Mesylate, USP; Alcohol, USP 6.1% by volume; Glycerin, USP 15% by weight; Water for Injection, USP; Methanesulfonic Acid and/or Sodium Hydroxide for pH adjustment. pH range is 3.4 - 4.9.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Dihydroergotamine binds with high affinity to 5-HT<sub>1A</sub> and 5-HT<sub>1D</sub> receptors. It also binds with high affinity to serotonin 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, and 5-HT<sub>2C</sub> receptors, noradrenaline  $\alpha_{2A}$ ,  $\alpha_{2B}$  and  $\alpha_1$  receptors, and dopamine D<sub>2L</sub> and D<sub>3</sub> receptors.

The therapeutic activity of dihydroergotamine in migraine is generally attributed to the agonist effect at 5-HT<sub>1D</sub> receptors. Two current theories have been proposed to explain the efficacy of 5-HT<sub>1D</sub> receptor agonists in migraine. One theory suggests that activation of 5-HT<sub>1D</sub> 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<sub>1D</sub> 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'- $\beta$ -hydroxydihydroergotamine, exhibits affinity equivalent to its parent for adrenergic and 5-HT receptors and demonstrates equivalent potency in several vasoconstrictor 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%-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%-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, USP 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 ergotamine) 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, USP 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, USP 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, USP may increase blood pressure, it should not be given to patients with uncontrolled hypertension.

Dihydroergotamine Mesylate Injection, USP, 5-HT<sub>1</sub> 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, USP should not be administered to patients with hemiplegic or basilar migraine.

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

Dihydroergotamine Mesylate Injection, USP 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 0.4-1.2 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

uteroplacental blood flow. 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, USP should not be used by patients with documented ischemic or vasospastic coronary artery disease. (See **CONTRAINDICATIONS**.) It is strongly recommended that Dihydroergotamine Mesylate Injection, USP 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, USP 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, USP 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, USP, in those patients with risk factors.

It is recommended that patients who are intermittent long-term users of Dihydroergotamine Mesylate Injection, USP 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, USP.

The systematic approach described above is currently recommended as a method to identify patients in whom Dihydroergotamine Mesylate Injection, USP 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, USP; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the Dihydroergotamine Mesylate Injection, USP 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, USP 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, USP.

Dihydroergotamine Mesylate Injection, USP 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, USP 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, USP 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<sub>1</sub> agonist in a study evaluating subjects undergoing cardiac catheterization.

## PRECAUTIONS

### General

Dihydroergotamine Mesylate Injection, USP 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<sub>1</sub> agonist are candidates for further evaluation. (See **WARNINGS**)

Fibrotic Complications: See **WARNINGS: Fibrotic Complication**

### 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, USP, 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, USP 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, USP. Sumatriptan and Dihydroergotamine Mesylate Injection, USP 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, USP 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<sub>1</sub> agonists have been coadministered 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, USP.

### Oral Contraceptives

The effect of oral contraceptives on the pharmacokinetics of Dihydroergotamine Mesylate Injection, USP 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, USP. There was no evidence of impairment of fertility in rats given intranasal doses of Dihydroergotamine Mesylate 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

**Pregnancy Category X. See CONTRAINDICATIONS.**

### Nursing Mothers

Ergot drugs are known to inhibit prolactin. It is likely that Dihydroergotamine Mesylate Injection, USP 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, USP, nursing should not be undertaken with the use of Dihydroergotamine Mesylate Injection, USP. (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, USP, 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, USP: vasospasm, paraesthesia, hypertension, 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, USP 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, USP 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, USP overdose are similar to those of an ergotamine overdose, although there is less pronounced nausea and vomiting with Dihydroergotamine Mesylate Injection, USP. 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 i.v. 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).\*

### DOSE AND ADMINISTRATION

Dihydroergotamine Mesylate Injection, USP 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.

### HOW SUPPLIED

#### Dihydroergotamine Mesylate Injection, USP

Available as a clear, colorless, sterile solution in single 1 mL sterile ampoules containing 1 mg of dihydroergotamine mesylate per mL.

- Packages of 5: NDC 0574-0850-05
- Packages of 10: NDC 0574-0850-10

Store below 25°C (77°F). Do not refrigerate or freeze.

To assure constant potency, protect the ampoules from light and heat. Use carton to protect contents from light until used. 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, USP 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, USP. Your pharmacist and/or health care provider can provide more detailed information.

#### Purpose of your Medication

Dihydroergotamine Mesylate Injection, USP 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 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, USP 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 troleandomycin, clarithromycin or erythromycin.

#### Important questions to consider before using Dihydroergotamine Mesylate Injection, USP

Please answer the following questions before you use your Dihydroergotamine Mesylate Injection, USP. 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, USP.

- 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

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

### 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, USP unless at least 6 hours have elapsed since your last injection. No more than 6 mL of Dihydroergotamine Mesylate Injection, USP 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, USP

- Use available training materials.
  - Read and follow the instructions in the patient instruction booklet which is provided with the Dihydroergotamine Mesylate Injection, USP package before attempting to use the product.
  - If there are any questions concerning the use of your Dihydroergotamine Mesylate Injection, USP, ask your Doctor or pharmacist.
- Preparing for the Injection
  - Carefully examine the ampoule (glass vial) of Dihydroergotamine Mesylate Injection, USP for any cracks or breaks, and the liquid for discoloration, cloudiness, or particles. If any of these defects are present, use a new ampoule, make certain it is intact, and return the defective ampoule to your doctor or pharmacy. Once you open an ampoule, if it is not used within an hour, it should be thrown away.
- Locating an Injection Site
  - Administer your subcutaneous injection in the middle of your thigh, well above the knee.
- Drawing the Medication into the Syringe
  - Wash your hands thoroughly with soap and water.
  - Check the dose of your medication.
  - Look to see if there is any liquid at the top of the ampoule. If there is, gently flick the ampoule with your finger to get all the liquid into the bottom portion of the ampoule.
  - Hold the bottom of the ampoule in one hand. Clean the ampoule neck with an alcohol wipe using your other hand. Then place the alcohol wipe around the neck of the ampoule and break it open by pressing your thumb against the neck of the ampoule.

### Instructions for Use



One-point-cut ampoule with cut below colored line.



To break, place thumb on the color line and snap back.

- Tilt the ampoule down at a 45° angle. Insert the needle into the solution in the ampoule.
  - 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.
- 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.
  - 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 ampoule containing medication. If the expiration date has passed, do not use it.

### Answers to patients' questions about Dihydroergotamine Mesylate Injection, USP

#### What if I need help in using my Dihydroergotamine Mesylate Injection, USP?

If you have any questions or if you need help in opening, putting together, or using Dihydroergotamine Mesylate Injection, USP, speak to your doctor or pharmacist.

#### How much medication should I use and how often?

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If you have any other unanswered question about Dihydroergotamine Mesylate Injection, USP, consult your doctor or pharmacist.

\*Trademark of Medical Economics Company, Inc.

Manufactured by:  
Draxis Pharma Inc.  
16751 Trans-Canada Road  
Kirkland, Quebec H9H 4J4  
Canada

Manufactured for:  
Paddock Laboratories, Inc.  
3940 Quebec Avenue North  
Minneapolis, MN 55427

Revised April 2003

**Paddock**  
Laboratories, Inc.

MUJ of 4 mg).

#### Pregnancy

**Pregnancy Category X. See CONTRAINDICATIONS.**

#### Nursing Mothers

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Dihydroergotamine Mesylate Injection, USP is not recommended for prolonged daily use. (See DOSAGE AND ADMINISTRATION)

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

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#### HOW SUPPLIED

**Dihydroergotamine Mesylate Injection, USP**

Available as a clear, colorless, sterile solution in single 1 mL sterile ampoules containing 1 mg of dihydroergotamine mesylate per mL.

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Packages of 10: NDC 0574-0850-10

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To assure constant potency, protect the ampoules from light and heat. Use carton to protect contents from light until used. Administer only if clear and colorless.

#### INSTRUCTION FOR PATIENTS ON SUBCUTANEOUS SELF-INJECTION

##### Information for the Patient

##### Dihydroergotamine Mesylate Injection, USP

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This leaflet does not contain all of the information on Dihydroergotamine Mesylate Injection, USP. Your pharmacist and/or health care provider can provide more detailed information.

##### Purpose of your Medication

Dihydroergotamine Mesylate Injection, USP 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 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, USP 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 troleandomycin, clarithromycin or erythromycin.

##### Important questions to consider before using Dihydroergotamine Mesylate Injection, USP

Please answer the following questions before you use your Dihydroergotamine Mesylate Injection, USP. 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, USP.

- 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, nasal 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 mesylate and protease inhibitors or macrolide antibiotics.

have elapsed since your last injection. No more than 6 mL of Dihydroergotamine Mesylate Injection, USP 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, USP

1. Use available training materials.
  - Read and follow the instructions in the patient instruction booklet which is provided with the Dihydroergotamine Mesylate Injection, USP package before attempting to use the product.
  - If there are any questions concerning the use of your Dihydroergotamine Mesylate Injection, USP, ask your Doctor or pharmacist.
2. Preparing for the Injection
  - Carefully examine the ampoule (glass vial) of Dihydroergotamine Mesylate Injection, USP for any cracks or breaks, and the liquid for discoloration, cloudiness, or particles. If any of these defects are present, use a new ampoule, make certain it is intact, and return the defective ampoule to your doctor or pharmacy. Once you open an ampoule, 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.
  - Look to see if there is any liquid at the top of the ampoule. If there is, gently flick the ampoule with your finger to get all the liquid into the bottom portion of the ampoule.
  - Hold the bottom of the ampoule in one hand. Clean the ampoule neck with an alcohol wipe using your other hand. Then place the alcohol wipe around the neck of the ampoule and break it open by pressing your thumb against the neck of the ampoule.

#### Instructions for Use



One-point-cut ampoule with cut below colored line.



To break, place thumb on the color line and snap back.

- Tilt the ampoule down at a 45° angle. Insert the needle into the solution in the ampoule.
  - 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 ampoule containing medication. If the expiration date has passed, do not use it.

#### Answers to patients' questions about Dihydroergotamine Mesylate Injection, USP

##### What if I need help in using my Dihydroergotamine Mesylate Injection, USP?

If you have any questions or if you need help in opening, putting together, or using Dihydroergotamine Mesylate Injection, USP, 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, USP unless at least 6 hours have elapsed since your last injection. No more than 6 mL of Dihydroergotamine Mesylate Injection, USP 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, USP, consult your doctor or pharmacist.

\*Trademark of Medical Economics Company, Inc.

Manufactured by:  
Draxis Pharma Inc.  
16751 Trans-Canada Road  
Kirkland, Quebec H9H 4J4  
Canada

Manufactured for:  
Paddock Laboratories, Inc.  
3940 Quebec Avenue North  
Minneapolis, MN 55427

Revised April 2003

**Paddock**  
Laboratories, Inc.

R: X = 9.9176, Y = 5.9000  
 JM #: WGN3593D1.DWG  
 2/11/11

5 x 1 mL ampoules

**Dihydroergotamine Mesylate  
 Injection, USP**

**Paddock  
 Laboratories, Inc.**

NDC 0574-0850-05  
 Unit Dose Package

286941

Dihydroergotamine Mesylate  
 Injection, USP

**Paddock  
 Laboratories, Inc.**

5 x 1 mL ampoules  
 Unit Dose Package

**Dihydroergotamine Mesylate  
 Injection, USP**

5 x 1 mL ampoules  
 Unit Dose Package

**Paddock  
 Laboratories, Inc.**

NDC 0574-0850-05  
 Unit Dose Package

APR 28 2008

APPROVED

Manufactured by:  
 Paddock Laboratories, Inc.  
 Minneapolis, MN 55427

Manufactured by:  
 Draxis Pharma Inc.  
 Kirkland, Quebec H9H 4J4  
 Canada

Each 1 mL contains: 1mg Dihydroergotamine Mesylate, USP; Alcohol, USP 6.1% by volume; Glycerin, USP 15% by weight; Water for Injection, USP; Methanesulfonic Acid and/or Sodium Hydroxide for pH adjustment. pH range is 3.4 - 4.9.

Usual Adult Dose: 1mL to 2mL intravenously, vascular intramuscularly or subcutaneously to relieve vascular headache (e.g. migraine). See package insert for further dosage information.

Store and Dispense: Protect from light. Do not refrigerate. Below 25°C (77°F). Protect contents from light until used. or freeze. Use carton to protect contents from light until used. Administer only if clear and colorless.

**EPREUVE NUMERIQUE FINALE  
 FINAL DIGITAL PROOF**

AVIS

Cette épreuve est considérée comme finale et est faite à partir de fichiers électroniques. Wilco garantit que le visuel de cette-ci ne peut différer du résultat sur presse. Il est donc impératif que chaque tirage soit inspecté avec précaution avant d'y opposer votre approbation.

NOTE

This proof is considered as final and is made from the electronic file. Wilco guarantees that what you see on this proof is what you'll get on the press. It is of the utmost importance that this proof is examined with great care before you give your approbation.

Date:  Day/Yes  No/No

Corrections:  Approve/Approved

**WILCO**

6941

6941



Dihydroergotamine Mesylate Injection, USP

Each 1mL contains: 1mg Dihydroergotamine Mesylate, USP; Alcohol, USP 6.1% by volume; Glycerin, USP 1.5% by weight; Water for Injection, USP; Methanesulfonic Acid and/or Sodium Hydroxide for pH adjustment. pH range is 3.4 - 4.9.

Usual Adult Dose: 1mL to 2mL intravenously, intramuscularly or subcutaneously to relieve vascular headache (e.g. migraine). See package insert for further dosage information.

Store and Dispense: Protect from light. Do not refrigerate or freeze. Use carton to protect contents from light until used. Administer only if clear and colorless.

APPROVED  
APR 28 2003

Manufactured for:  
Paddock Laboratories, Inc.  
Minneapolis, MN 55427

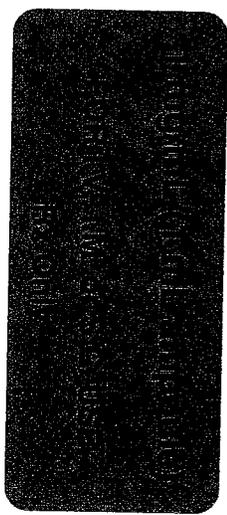
Manufactured by:  
Drexis Pharma Inc.  
Kirkland, Quebec H9H 4J4  
Canada



Dihydroergotamine Mesylate Injection, USP

5 x 1 mL ampoules  
Unit Dose Package

NDC 0574-0850-05  
Unit Dose Package  
5 x 1 mL ampoules  
**Dihydroergotamine Mesylate Injection, USP**



**Paddock**  
Laboratories, Inc.



PMS311



Date: \_\_\_\_\_  
Gentles: Q4/Vis   
Res/No   
Approved/Approved

**ÉPREUVE NUMÉRIQUE FINALE**  
**FINAL DIGITAL PROOF**

**NOTE**  
This proof is considered as final and is made from the electronic file. Wilco guarantees that what you see on the proof is what you'll get on the press. It is of the utmost importance that the proof is examined with great care before you give your approbation.





**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**40-475**

**CSO LABELING REVIEW(S)**

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

ANDA Number: **40-475**

Dates of Submission: **March 17 and April 9, 2003**

Applicant's Name: **Paddock Laboratories, Inc.**

Established Name: **Dihydroergotamine Mesylate Injection USP, 1 mg/mL, 1 mL ampoules**

**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**

Container Labels: **1 mL ampoules**

*Satisfactory in FPL as of March 17, 2003 submission [vol 4.1].*

Carton Labeling: **5 x 1 mL and 10 x 1 mL**

*Satisfactory in FPL as of March 17, 2003 submission [vol 4.1].*

Professional Package Insert Labeling:

*Satisfactory in FPL as of April 9, 2003 submission [vol 4.1 - code # 212761 - rev. 4-03].*

Revisions needed post-approval: labels and labeling - Delete  after each inactive ingredient --

**Per fax from M. Friedly authorized agent for Paddock Labs after discussion with L. Golson - firm to revise their storage temperature recommendations to "Store at 20 to 25°C (68 to 77°F). Excursions permitted to 15 to 30°C (59 to 86°F). [See USP Controlled Room Temperature]." After approval at the time of next printing.**

**BASIS OF APPROVAL:**

**There are no patents or exclusivities for this drug product.**

Was this approval based upon a petition? **No**

What is the RLD on the 356(h) form: **D.H.E.45<sup>®</sup>**

NDA Number: **05-929**

NDA Drug Name: **D.H.E.45<sup>®</sup> (dihydroergotamine mesylate) Injection**

NDA Firm: **Novartis**

Date of Approval of NDA Insert and supplement # **7-31-02 (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-sides**

Basis of Approval for the Carton Labeling: **side-by-sides**

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 24	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? <b>NO</b>		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	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? NO - Issues for FTR: Innovator individually cartoned? NO - Light sensitive product which might require cartoning? YES Must the package insert accompany the product? YES - CARTONS OF 10 - PROTECT FROM LIGHT		X	
Are there any other safety concerns?		X	
<b>Labeling</b>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by..." statement needed?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
<b>Inactive Ingredients:</b> (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	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
<b>USP Issues:</b> (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? YES If so, is NDA and/or ANDA in a light resistant container? NO - CARTONED	X	X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
<b>Bioequivalence Issues:</b> (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
<b>Patent/Exclusivity Issues?:</b> FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

**FOR THE RECORD: (portions taken from previous review)**

1. Review based on the labeling of D.H.E.45®, approved 7-31-02.

2. Patent/ Exclusivities -  
**Patent Data - 05-929**

No	Expiration	Use Code	Use	File
None				II

**Exclusivity Data - 05-929**

Code/sup	Expiration	Use Code	Description	Labeling Impact
None			There is no unexpired exclusivity for this product	

3. Storage Conditions/Dispensing Recommendations:  
NDA - Below 25°C (77°F). Do not refrigerate or freeze. Protect from light. Administer only if clear and colorless.  
ANDA - Below 25°C (77°F). Do not refrigerate or freeze. Protect from light. Use carton to protect contents from light until used. Administer only if clear and colorless.  
USP - Preserve in single-dose containers, preferably of Type I glass, protected from light.  
**Per fax from M. Friedly authorized agent for Paddock Labs after discussion with L. Golson - firm to revise their storage temperature recommendations to "Store at 20 to 25°C (68 to 77°F). Excursions permitted to 15 to 30°C (59 to 86°F). [See USP Controlled Room Temperature]." After approval at the time of next printing.**
4. Draxis Pharma is the manufacturer (p 300 v 1.1).
5. Product Line:  
The innovator markets this product in cartons of 10 x 1 mL ampules  
The applicant proposes to market this product also in cartons of 5 x 1 mL and 10 x 1 mL ampoules
6. The ampules are made of Type 1 glass.
7. Inactive Ingredients:  
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 158 (Volume 1.1).
8. The firm's statement of alcohol content is correct. The alcohol content is 6.1% v/v.

~~EtOH USP~~ x 100% = 6.1% (see page 328 v 1.1 section 11)

The innovator expresses the alcohol content in terms of "alcohol, USP" (v/v) and after discussion with J. Grace it is satisfactory to have the generic express it in these terms as well.

9. The RLD has patient information which includes how to use this product at the end of the professional insert but it is not detachable and there is only one PI per 10 count box. This is what the ANDA will have and we find this acceptable (after discussion between L. Golson and A. Vezza).

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Date of Review: 4-11-03

Dates of Submission: 3-17-03 & 4-9-03

Primary Reviewer: Adolph Vezza

Date: 4/16/03

Team Leader: Lillie Golson

Date: 4/16/03

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cc: ANDA: 40-475  
DUP/DIVISION FILE  
HFD-613/AVezza/LGolson (no cc)  
aev/4/11/03|V:\FIRMSNZ\PADDOCK\LTRS&REV\40475.APL  
Review

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

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ANDA Number: **40-475**

Date of Submission: **December 16, 2002**

Applicant's Name: **Paddock Laboratories, Inc.**

Established Name: **Dihydroergotamine Mesylate Injection USP, 1 mg/mL, 1 mL ampoules**

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Labeling Deficiencies:

1. GENERAL COMMENTS

- a. We note that the insert of the reference listed drug (RLD) states that this product may not be refrigerated or frozen. Your product's insert labeling states that this product should not be frozen. Your drug product as well as the RLD states that this drug product should be stored below 25°C. Can your drug product be refrigerated? Please comment.
- b. If your product should not be refrigerated or frozen please indicate this on your carton and insert labeling.

2. CONTAINER 1 mL

Much of the text printed on the blue background is not easily legible. Please improve the readability..

3. CARTON 5 x 1 mL

See GENERAL COMMENTS (1)(b) above.

4. INSERT

- a. We note that there is information at the end of the insert labeling which explains the usage of this product to the patient. How will this be provided to the patient? We suggest that this information appear on a separate sheet of paper as well as at the end of the insert for ease of distribution to the end user (patient). Please comment.
- b. See GENERAL COMMENTS (1)(b) above.

Please revise your container labels and and carton and insert labeling, as instructed above, and submit 12 copies of each labeling piece in final print (or 4 copies of draft labeling if you prefer)..

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/rid/labeling\\_review\\_branch.html](http://www.fda.gov/cder/ogd/rid/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:**

**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:

Container Labels: 1 mL ampoules

Carton Labeling: 10 x 1 mL

Professional Package Insert Labeling:

Revisions needed post-approval:

**BASIS OF APPROVAL:**

**There are no patents or exclusivities for this drug product.**

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: D.H.E.45®

NDA Number: 05-929

NDA Drug Name: D.H.E.45® (dihydroergotamine mesylate) Injection

NDA Firm: Novartis

Date of Approval of NDA Insert and supplement # 7-31-02 (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-sides

Basis of Approval for the Carton Labeling: side-by-sides

Other Comments

**REVIEW OF PROFESSIONAL LABELING CHECK LIST**

<b>Established Name</b>	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 24	X		
Is this name different than that used in the Orange Book?		X	
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? NO		X	
<b>Packaging</b>			
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	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? NO - Issues for FTR: Innovator individually cartoned? NO - Light sensitive product which might require cartoning? YES Must the package insert accompany the product? YES - CARTONS OF 10 - PROTECT FROM LIGHT		X	
Are there any other safety concerns?		X	
<b>Labeling</b>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
<b>Labeling(continued)</b>			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?	X		
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	

<b>Inactive Ingredients:</b> (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	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
<b>USP Issues:</b> (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? YES If so, is NDA and/or ANDA in a light resistant container? NO - CARTONED			
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
<b>Bioequivalence Issues:</b> (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
<b>Patent/Exclusivity Issues?:</b> FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

**NOTES TO THE CHEMIST:**

- Can this firm's product be frozen and/or refrigerated? The storage recommendations are: "Store below 25°C" - as are the innovator's. The innovator's PI states the product should not be refrigerated or frozen while this ANDA's PI states that it should not be frozen only. I have discussed it with the chemist, M. Selvam, and he believes that the storage temperature implies that the generic product can be refrigerated. He will ask the firm about this as I have in this review.
- Is the pH accurate as described in the DESCRIPTION section? Per M. Selvam - the product is "USP" and the USP monograph pH range is 3.4 - 4.9, the same as that which is in the DESCRIPTION section. He feels this is sufficient.

**FOR THE RECORD: (portions taken from previous review)**

- Review based on the labeling of D.H.E.45®, approved 7-31-02.
- Patent/ Exclusivities -  
Patent Data – 05-929

No	Expiration	Use Code	Use	File
None				II

**Exclusivity Data - 05-929**

Code/sup	Expiration	Use Code	Description	Labeling Impact
None			There is no unexpired exclusivity for this product	

3. Storage Conditions/Dispensing Recommendations:  
 : NDA - Below 25°C (77°F). Protect from light. Administer only if clear and colorless  
 : ANDA - Below 25°C (77°F). Protect from light. Use carton to protect contents from light until used.  
 : Administer only if clear and colorless.  
 : USP - Preserve in single-dose containers, preferably of Type I glass, protected from light.

The NDA PI states that the product should not be refrigerated or frozen while the ANDA PI says that the product cannot be frozen. After discussing this with the chemist, M. Selvam, it was decided that we both would ask the firm about this in our respective reviews.

4. Draxis Pharma is the manufacturer (p 300 v 1.1).
5. Product Line:  
 The innovator markets this product in cartons of 10 x 1 mL ampules  
 The applicant proposes to market this product also in cartons of 5 x 1 mL and 10 x 1 mL ampoules
6. The ampules are made of Type 1 glass.
7. Inactive Ingredients:  
 The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 158 (Volume 1.1).
8. The firm's statement of alcohol content is correct. The alcohol content is 6.1% v/v.

~~\_\_\_\_\_~~ USP x 100% = 6.1% (see page 328 v 1.1 section 11)

The innovator expresses the alcohol content in terms of "alcohol, USP" (v/v) and after discussion with J. Grace it is satisfactory to have the generic express it in these terms as well.

9. The RLD has patient information which includes how to use this product at the end of the professional insert but it is not detachable and there is only one PI per 10 count box. This is what the ANDA will have and we find this acceptable (after discussion between L. Golson and A. Vezza).

Date of Review: 2-7-03

Date of Submission: 12-16-02

Primary Reviewer: Adolph Vezza

Date:

*A. Vezza*

*2/24/03*

Team Leader: Lillie Golson

Date:

*L. Golson*

*2/24/03*

cc: ANDA: 40-475  
 DUP/DIVISION FILE  
 HFD-613/AVezza/LGolson (no cc)  
 aev/2/7/03\V:\FIRMSNZ\PADDOCK\LTRS&REV\40475na2.l



- ii. Chemical structure
  - A). Improve the legibility of the "3"s in the methyl groups.
  - B). Improve the legibility of the "mesylate" molecular formula as seen in the chemical structure.

c. CLINICAL PHARMACOLOGY

Revise the "Interactions" subsection as follows:

**Interactions**

Pharmacokinetic interactions have been reported in patients treated orally with other ergot alkaloids (e.g., increased levels of ergotamine) 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.

d. CONTRAINDICATIONS

Add the following text as the first paragraph:

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)

e. WARNINGS

Add the following two subsections immediately after the first sentence:

**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 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).

f. PRECAUTIONS

- i. Add the following text immediately after the first paragraph of the "General" subsection:

Fibrotic Complications: see WARNINGS: Fibrotic Complication

- ii. Information for Patients - Add the following paragraph as the last in this subsection:

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

- iii. \_\_\_\_\_ ..." - Revise this subsection and its title as follows:

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

- iv. SSRI's, first sentence - "coadministered" (delete hyphen)

g. ADVERSE REACTIONS

First paragraph - Add the following text as the last sentence:

Fibrotic complications have been reported in association with long term use of injectable dihydroergotamine mesylate (see WARNINGS: Fibrotic Complications).

h. DOSAGE AND ADMINISTRATION

Add the following text as the last sentence:

Dihydroergotamine mesylate injection should not be used for chronic daily administration.

i. INSTRUCTION FOR PATIENTS ON SUBCUTANEOUS SELF-INJECTION, Information for the Patient

- i. Purpose of your Medication - Add the following text to the end of this subsection:

"... 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 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.

ii. Do not use Dihydroergotamine Mesylate Injection if you: - Add the following text as the last two bullets in this subsection:

- are taking certain anti-HIV medications (protease inhibitors).
- are taking a macrolide antibiotic such as troleandomycin, clarithromycin or erythromycin.

iii. Important questions to consider before using Dihydroergotamine Mesylate Injection - Add the following bullets and text to the end of this subsection:

- Are you using dihydroergotamine mesylate injection, nasal 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 mesylate and protease inhibitors or macrolide antibiotics.

#### **REMEMBER TO TELL YOUR DOCTOR IF YOU HAVE ...**

iv. Dosage - Add the following text as the last sentence:

"... period. Dihydroergotamine mesylate injection is not intended to be used on a prolonged daily basis."

v. How to use the Dihydroergotamine Mesylate Injection - Add two pictures to the fourth bullet as the innovator does to illustrate to the patient how to break the ampoule. It is not necessary to include the dot on the ampoule as seen in the innovator's labeling. A copy of these pictures are attached for your convenience.

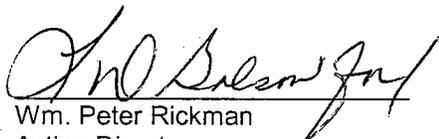
vi. How much medication should I use and how often? - Add the following text to the end of the first paragraph:

"... your doctor. Dihydroergotamine mesylate injection is not intended for chronic daily use."

Please revise your container labels and carton and insert labeling, as instructed above, and submit 12 copies of each labeling piece in final print (or 4 copies of draft labeling if you prefer)..

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](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

**APPEARS THIS WAY  
ON ORIGINAL**

**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 No If no, list why:

Container Labels: 1 mL ampoules

Carton Labeling: 10 x 1 mL

Professional Package Insert Labeling:

Revisions needed post-approval:

**BASIS OF APPROVAL:**

**There are no patents or exclusivities for this drug product.**

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: D.H.E.45®

NDA Number: 05-929

NDA Drug Name: D.H.E.45® (dihydroergotamine mesylate) Injection

NDA Firm: Novartis

Date of Approval of NDA Insert and supplement # 7-31-02 (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-sides

Basis of Approval for the Carton Labeling: side-by-sides

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 24	X		
Is this name different than that used in the Orange Book?		X	
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? NO		X	
<b>Packaging</b>			
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	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? NO - Issues for FTR: Innovator individually cartoned? NO - Light sensitive product which might require cartoning? YES Must the package insert accompany the product? YES - CARTONS OF 10 - PROTECT FROM LIGHT		X	
Are there any other safety concerns?		X	
<b>Labeling</b>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
<b>Labeling(continued)</b>			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult, Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?	X		
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note:		X	

Chemist should confirm the data has been adequately supported.			
<b>Inactive Ingredients:</b> (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	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
<b>USP Issues:</b> (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? YES If so, is NDA and/or ANDA in a light resistant container? NO - CARTONED			
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
<b>Bioequivalence Issues:</b> (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
<b>Patent/Exclusivity Issues?:</b> FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

**FOR THE RECORD:**

- Review based on the labeling of D.H.E.45®, approved 7-31-02.
- Patent/ Exclusivities -  
**Patent Data -**

No	Expiration	Use Code	Use	File
None				II

**Exclusivity Data -**

Code/sup	Expiration	Use Code	Description	Labeling Impact
None			There is no unexpired exclusivity for this product	

- Storage Conditions/Dispensing Recommendations:  
 NDA - Below 25°C (77°F). Protect from light. Administer only if clear and colorless  
 ANDA - Below 25°C (77°F). Protect from light. Use carton to protect contents from light until used. Administer only if clear and colorless.  
 USP - Preserve in single-dose containers, preferably of Type I glass, protected from light.
- Draxis Pharma is the manufacturer (p 300 v 1.1).
- Product Line:  
 The innovator markets this product in cartons of 10 x 1 mL ampules  
 The applicant proposes to market this product also in cartons of 10 x 1 mL ampoules
- The ampules are made of Type 1 glass.
- Inactive Ingredients:  
 The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 158 (Volume 1.1).

8 The firm's statement of alcohol content is correct. The alcohol content is 6.1% v/v.

~~\_\_\_\_\_~~, USP x 100% = 6.1% (see page 328 v 1.1 section 11)

The innovator expresses the alcohol content in terms of "alcohol, USP" (v/v) and after discussion with J. Grace it is satisfactory to have the generic express it in these terms as well.

9. The RLD has patient information which includes how to use this product at the end of the professional insert but it is not detachable and there is only one PI per 10 count box. This is what the ANDA will have and we find this acceptable (after discussion between L. Golson and A. Vezza).

---

Date of Review: 8-2-02 •

Dates of Submission: 4-~~20~~ and 6-7-02

Primary Reviewer: Adolph Vezza

Date:

*A. Vezza*

*8-19-02*

Team Leader: Lillie Golson

Date:

*L. Golson*

*8/19/02*

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cc: ANDA: 40-475  
DUP/DIVISION FILE  
HFD-613/AVezza/LGolson (no cc)  
aev/8/2/02\V:\FIRMSNZ\PADDOCK\LTRS&REV\40475na1.l  
Review

**APPEARS THIS WAY  
ON ORIGINAL**

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**40-475**

**CHEMISTRY REVIEW(S)**



**ANDA 40-475**

**Drug Name**

Dihydroergotamine Mesylate Injection USP, 1.0 mg/mL.

**Firm Name**

**PADDOCK LABORATORIES, INC.**

**Chemistry Reviewer's Name**

**Mouna P. Selvam, Ph.D.,**

**Chemistry Division Name**

**Division of Chemistry II**

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III. List Of Deficiencies To Be Communicated.....	

# Chemistry Review Data Sheet

1. ANDA # 40-475
2. REVIEW #: 1
3. REVIEW DATE: 13-SEP-2002
4. REVIEWER: Mouna P. Selvam, Ph.D.,
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

**Firm:**

Original Submission.  
Original Amendment

02-28-2002  
07-19-2002

**FDA:**

Refuse to receive  
Acceptable for Filing  
Acknowledgement.  
Bio-Review  
Labeling Review

04-08-2002  
04-30-2002  
05-03-2002  
08-05-2002  
08-19-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original Submission

02-28-2002

**APPEARS THIS WAY  
ON ORIGINAL**

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Paddock Laboratories.  
Address: 3940 Quebec Ave North  
Minneapolis, MN 55427  
Representative: Marilyn A. Friedly  
PharmaForce  
Telephone: 614-486-7360

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A  
b) Non-Proprietary Name (USAN): Dihydroergotamine Mesylate Injection

## 9. LEGAL BASIS FOR 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 or Exclusivity 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.

## 10. PHARMACOL. CATEGORY:

Antimigraine

## 11. DOSAGE FORM:

Injection

## 12. STRENGTH/POTENCY:

1.0 mg/mL

## 13. ROUTE OF ADMINISTRATION:

IM, IV

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note23]:

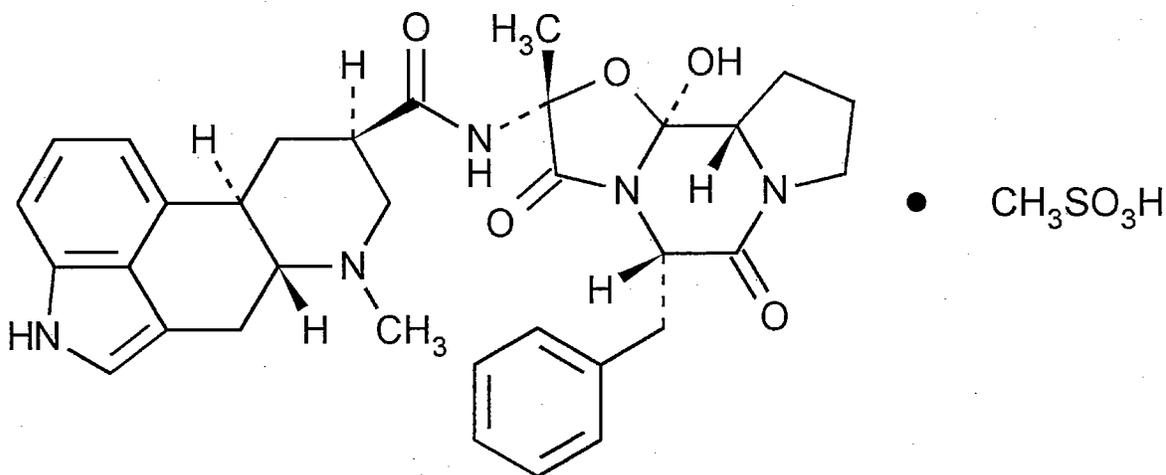
\_\_\_\_\_SPOTS product – Form Completed

x   Not a SPOTS product

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

Generic name: Dihydroergotamine Mesylate

Chemical name: Ergotaman-3 $\alpha$ ,6 $\alpha$ ,18-trione, 9,10-dihydro-12 $\alpha$ -hydroxy-2 $\alpha$ -methyl-5 $\alpha$ -(phenylmethyl)-, (5 $\alpha$ )-, monomethanesulfonate (salt).



C<sub>33</sub>H<sub>37</sub>N<sub>5</sub>O<sub>5</sub>·CH<sub>4</sub>O<sub>3</sub>S; Mol. Wt. 679.78

Dihydroergotamine monomethanesulfonate [6190-39-2].

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
_____	II	_____	_____	1	Not Adequate	08-24-2002	_____
_____	III	_____	_____	4			

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

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

**APPEARS THIS WAY  
ON ORIGINAL**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending for review		
EES	Pending		
Methods Validation	Not Required		M. Selvam (USP proucts)
Labeling	Not Approved		A.Vezza, 08/19/2002
Bioequivalence	Approved		Lin-Whei Chuang, 08/05/2002
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

**APPEARS THIS WAY  
ON ORIGINAL**



### **III. Administrative**

#### **A. Reviewer's Signature**

#### **B. Endorsement Block**

Mouna P. Selvam/09/13/2002

U.V. Venkataram/9.5.02

S.Shepperson/9/18/02

#### **C. CC Block**

cc: ANDA: 40-475

ANDA DUP

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**APPEARS THIS WAY  
ON ORIGINAL**

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**Page(s) of trade**

**secret and /or**

**confidential**

**commercial**

**information**

**ANDA 40-475**

**Drug Name**

Dihydroergotamine Mesylate Injection USP, 1.0 mg/mL.

**Firm Name**

**PADDOCK LABORATORIES, INC.**

**Chemistry Reviewer's Name**

**Mouna P. Selvam, Ph.D.,**

**Chemistry Division Name**

**Division of Chemistry II**

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# Chemistry Review Data Sheet

1. ANDA # 40-475
2. REVIEW #: 2
3. REVIEW DATE: 27-NOV-2002
4. REVIEWER: Mouna P. Selvam, Ph.D.,
5. PREVIOUS DOCUMENTS:

## Previous Documents

## Document Date

### **Firm:**

Original Submission.	28-FEB-2002
Original Amendment	19-JUL-2002
Minor Amendment	04-OCT-2002

### **FDA:**

Refuse to receive	08-APR-2002
Acceptable for Filing	30-APR-2002
Acknowledgement.	03-MAY-2002
Bio-Review	05-AUG-2002
Labeling Review	19-AUG-2002

6. SUBMISSION(S) BEING REVIEWED:

## Submission(s) Reviewed

## Document Date

Original Submission	28-FEB-2002
---------------------	-------------

7. NAME & ADDRESS OF APPLICANT:

Name: Paddock Laboratories.

Address: 3940 Quebec Ave North  
Minneapolis, MN 55427

Representative: Marilyn A. Friedly  
PharmaForce

Telephone: 614-486-7360

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A  
b) Non-Proprietary Name (USAN): Dihydroergotamine Mesylate Injection

## 9. LEGAL BASIS FOR 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 or Exclusivity in effect.

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

## 10. PHARMACOL. CATEGORY:

Antimigraine

## 11. DOSAGE FORM:

Injection

## 12. STRENGTH/POTENCY:

1.0 mg/mL

## 13. ROUTE OF ADMINISTRATION:

IM, IV

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note23]:

SPOTS product – Form Completed

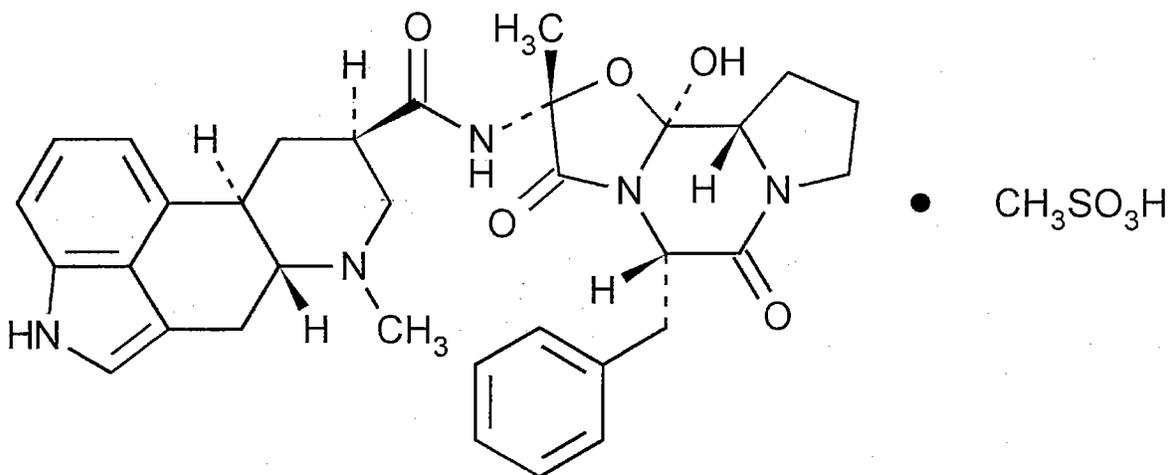
Not a SPOTS product

**APPEARS THIS WAY  
ON ORIGINAL**

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

Generic name: Dihydroergotamine Mesylate

Chemical name: Ergotaman-3 $\phi$ ,6 $\phi$ ,18-trione, 9,10-dihydro-12 $\phi$ -hydroxy-2 $\phi$ -methyl-5 $\phi$ -(phenylmethyl)-, (5 $\phi$ a)-, monomethanesulfonate (salt).



C<sub>33</sub>H<sub>37</sub>N<sub>5</sub>O<sub>5</sub>·CH<sub>4</sub>O<sub>3</sub>S; Mol. Wt. 679.78

Dihydroergotamine monomethanesulfonate [6190-39-2].

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
—	II	—	—	1	Not Adequate	11-27-2002	—
—	III	—	—	4			

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

1 – DMF Reviewed.

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

2 –Type 1 DMF

- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

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

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

**APPEARS THIS WAY  
ON ORIGINAL**

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending for review		
EES	Acceptable	10-28-02	
Methods Validation	Not Required		M. Selvam (USP products)
Labeling	Not Satisfactory	08-19-02	A. Vezza, 08/19/2002
Bioequivalence	Approved	08-05-02	Lin-Whei Chuang, 08/05/2002
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

**APPEARS THIS WAY  
ON ORIGINAL**



### III. Administrative

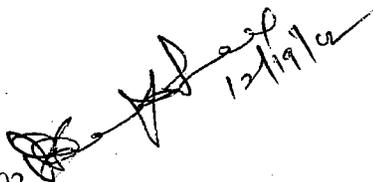
#### A. Reviewer's Signature

#### B. Endorsement Block

Mouna P. Selvam/27-NOV-2002

U.V. Venkataram/12.2.02; 12.13.02 (revised)

S.Shepperson/12-16-02

Handwritten signature and date: 12/19/02

#### C. CC Block

cc: ANDA: 40-475

ANDA DUP

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APPEARS THIS WAY  
ON ORIGINAL

**Redacted** 23

**Page(s) of trade**

**secret and /or**

**confidential**

**commercial**

**information**

**✓ ANDA 40-475**

**Drug Name**

Dihydroergotamine Mesylate Injection USP, 1.0 mg/mL.

**Firm Name**

**PADDOCK LABORATORIES, INC.**

**Chemistry Reviewer's Name**

**Mouna P. Selvam, Ph.D.,**

**Chemistry Division Name**

**Division of Chemistry II**

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DRUG PRODUCT [Name, Dosage form] .....	
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A. Labeling & Package Insert .....	
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**APPEARS THIS WAY  
ON ORIGINAL**

# Chemistry Review Data Sheet

1. ANDA # 40-475
2. REVIEW #: 3
3. REVIEW DATE: 02-APR-2003
4. REVIEWER: Mouna P. Selvam, Ph.D.,
5. PREVIOUS DOCUMENTS:

## Previous Documents

## Document Date

### **Firm:**

Original Submission.	28-FEB-2002
Original Amendment	19-JUL-2002
Minor Amendment	04-OCT-2002
Labeling Amendment	16-DEC-2002
Minor Amendment	30-DEC-2002
Micro Amendment	13-JAN-2003
Tel Amendment	14-MAR-2003
Labeling amendments:	17-MAR-2003,
	09-APR-2003
	16-APR-2003

### **FDA:**

Refuse to receive	08-APR-2002
Acceptable for Filing	30-APR-2002
Acknowledgement.	03-MAY-2002
Bio-Review	05-AUG-2002
Minor deficiency letter	19-AUG-2002
Minor deficiency letter	01-OCT-2002
Labeling Review	23-DEC-2002
Micro Review	02-JAN-2003
Micro Review	10-FEB-2003
Labeling Review	03-MAR-2003
Telecon	03-MAR-2003
Labeling Review	28-MAR-2003

6. SUBMISSION(S) BEING REVIEWED:

## Submission(s) Reviewed

## Document Date

**Firm:**

Original Submission.	28-FEB-2002
Original Amendment	19-JUL-2002
Minor Amendment	04-OCT-2002
Labeling Amendment	16-DEC-2002
Minor Amendment	30-DEC-2002
Micro Amendment	13-JAN-2003
Tel Amendment	14-MAR-2003

**7. NAME & ADDRESS OF APPLICANT:**

Name: Paddock Laboratories.  
Address: 3940 Quebec Ave North  
Minneapolis, MN 55427  
Representative: Marilyn A. Friedly  
PharmaForce  
Telephone: 614-486-7360

**8. DRUG PRODUCT NAME/CODE/TYPE:**

- a) Proprietary Name: N/A  
b) Non-Proprietary Name (USAN): Dihydroergotamine Mesylate Injection

**9. LEGAL BASIS FOR 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 or Exclusivity in effect.

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

**10. PHARMACOL. CATEGORY:**

Antimigraine

**11. DOSAGE FORM:**

Injection

**12. STRENGTH/POTENCY:**

1.0 mg/mL

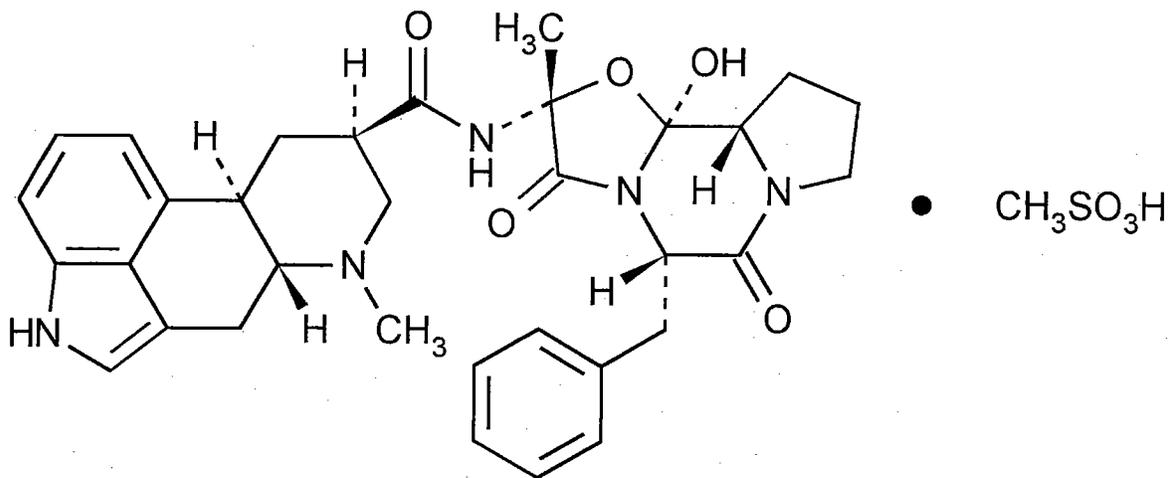
**13. ROUTE OF ADMINISTRATION:**

IM, IV

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note20]: SPOTS product – Form Completed Not a SPOTS product

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

Generic name: Dihydroergotamine Mesylate

Chemical name: Ergotaman-3 $\phi$ ,6 $\phi$ ,18-trione, 9,10-dihydro-12 $\phi$ -hydroxy-2 $\phi$ -methyl-5 $\phi$ -(phenylmethyl)-, (5 $\phi$ a)-, monomethanesulfonate (salt). $C_{33}H_{37}N_5O_5 \cdot CH_4O_3S$ ; Mol. Wt. 679.78

Dihydroergotamine monomethanesulfonate [6190-39-2].

17. RELATED/SUPPORTING DOCUMENTS:

**APPEARS THIS WAY  
ON ORIGINAL**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	04-02-2003	
	III			4			

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

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

**APPEARS THIS WAY  
ON ORIGINAL**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	02-10-2003	N. Nath
EES	Acceptable	10-28-2002	
Methods Validation	Not Required -USP products)		M. Selvam
Labeling	Satisfactory	03-28-2003	A. Vezza
Bioequivalence	Approved	08-05-2002	Lin-Whei Chuang
EA	N/A		
Radiopharmaceutical	N/A		

**APPEARS THIS WAY  
ON ORIGINAL**

**19. ORDER OF REVIEW**

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

**APPEARS THIS WAY  
ON ORIGINAL**



### **III. Administrative**

#### **A. Reviewer's Signature**

#### **B. Endorsement Block**

Mouna P. Selvam/04/02/2003

U.V. Venkataram/4.3.03

S.Shepperson/

Labeling/

Micro/

#### **C. CC Block**

cc: ANDA: 40-475

ANDA DUP

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**APPEARS THIS WAY  
ON ORIGINAL**

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**confidential**

**commercial**

**information**

**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**40-475**

**MICROBIOLOGY REVIEW**

# Product Quality Microbiology Review Review for HFD-640

2 January 2003

ANDA: 40-475

**Drug Product Name**

**Proprietary:** N/A

**Non-proprietary:** Dihydroergotamine Mesylate Injection USP

**Drug Product Classification:** Treatment of migraine headaches

**Review Number:** #1

**Subject of this Review**

**Submission Date:** February 28, 2002 (refuse to receive)

Amendment April 30, 2002 (May 1, 2002; Accepted for filling)

Gratuitous Amendment July 19, 2002

**Consult Date:** N/A

**Date Assigned for Review:** November 12, 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:** Paddock Laboratories, Inc.

**Address:** 3940 Quebecc Avenue North, Minneapolis, MN 55427

**Representative:** Marilyn A. Friendly

**Telephone:** 614-486-7360

**Name of Reviewer:** Nrapendra Nath

**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:** Draxis Pharma Inc.  
16751 Trans-Canada Road  
Kirkland, Quebec H9H4J4, Canada
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 1mg/mL; 1mL/ampoule; I/V, S/C I/M
  5. **METHOD(S) OF STERILIZATION:** filtration.
  6. **PHARMACOLOGICAL CATEGORY:** For treatment of migraine headaches.
- B. **SUPPORTING/RELATED DOCUMENTS:** None
- C. **REMARKS:** Draxis Pharma Inc. manufactures the subject drug product for the applicant in their facility in Quebec, Canada. The Type V DMF # (Draxis Pharma) has been reviewed and found deficient for sterility assurance.

The applicant provided additional information about sterility assurance in gratuitous amendment dated July 19, 2002. The information provided was incorporated in the subject review.

**APPEARS THIS WAY  
ON ORIGINAL**

**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 manufactured using \_\_\_\_\_
- B. Brief Description of Microbiology Deficiencies -**  
DMF \_\_\_\_\_ is deficient. The applicant should clarify which activities were performed by them and list those by the DMF Holder.
- C. Assessment of Risk Due to Microbiology Deficiencies -**  
Low.

**III. Administrative**

- A. Reviewer's Signature** Nrapendra Nath 1/6/03
- B. Endorsement Block**  
Microbiologist / Nrapendra Nath  
Microbiology Team Leader/Neal J. Sweeney Neal J. Sweeney 1/6/03
- C. CC Block**  
cc:  
Original ANDA  
HFD- 600/Division File/ANDA 40-475  
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**filename:** V:\Microrev\40-475.doc

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**Page(s) of trade**

**secret and /or**

**confidential**

**commercial**

**information**

# Product Quality Microbiology Review

## Review for HFD-640

10 February 2003

ANDA: 40-475

### Drug Product Name

**Proprietary:** N/A

**Non-proprietary:** Dihydroergotamine Mesylate Injection USP

**Drug Product Classification:** Treatment of migraine headaches

**Review Number:** #2

### Subject of this Review

**Submission Date:** January 13, 2003

**Consult Date:** N/A

**Date Assigned for Review:** January 24, 2003

### Submission History (for amendments only)

**Date(s) of Previous Submission(s):** Amendment April 30, 2002  
(May 1, 2002; Accepted for filling); Gratuitous Amendment July 19,  
2002

**Date(s) of Previous Micro Review(s):** January 2, 2003

### Applicant/Sponsor

**Name:** Paddock Laboratories, Inc.

**Address:** 3940 Quebecc Avenue North, Minneapolis, MN 55427

**Representative:** Marilyn A. Friendly

**Telephone:** 614-486-7360

**Name of Reviewer:** Nrapendra Nath

**Conclusion:** The submission is **recommended** for approval on the basis of sterility assurance.



**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 manufactured using \_\_\_\_\_
- B. Brief Description of Microbiology Deficiencies -**  
None.
- C. Assessment of Risk Due to Microbiology Deficiencies -**  
N/A

**III. Administrative**

- A. Reviewer's Signature** Nrapendra NR 2/10/03
- B. Endorsement Block** Neal J. Sweeney 2/12/03  
Microbiologist / Nrapendra Nath  
Microbiology Team Leader/Neal J. Sweeney
- C. CC Block**  
cc:  
Original ANDA  
HFD- 600/Division File  
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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**40-475**

**BIOEQUIVALENCE  
REVIEW(S)**

AUG 30 2002

Dihydroergotamine Mesylate Injection USP  
1 mg/mL, 1 mL ampoules  
ANDA # 40-475  
Reviewer: Lin-Whei Chuang  
V:\FIRMSNZ\PADDOCK\LTRS&REV\40475W0402.doc

Paddock Labs., Inc.  
Minneapolis, MN  
Submission Date:  
April 30, 2002  
(Date acceptable for Filing)

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 ampoules, in accordance with 21 CFR 320.22 (b) (1). The application is based on D.H.E. 45® (dihydroergotamine mesylate) injection, USP manufactured by Novartis Pharmaceuticals Corp. which was approved on 4/12/1946 through NDA #005929.

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:

<u>Ingredients</u>	<u>Test Formulation</u> (per mL)	<u>D.H.E. 45® Formulation</u> (per mL)
Dihydroergotamine Mesylate	1 mg	1 mg
Alcohol	6.1 v/v	6.1% v/v
Glycerin	15% w/v	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.

3. It should be noted by the Chemistry Division that the labeling of RLD states a pH range of 3.6 + 0.4 while the proposed labeling of the test drug states a pH range of 3.4-4.9.

Recommendations:

The Division of Bioequivalence agrees that the information submitted by Paddock Laboratories, Inc. demonstrates that its Dihydroergotamine Mesylate Injection USP, 1 mg/mL in 1 mL ampoules, 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 Mesylate Injection USP, 1 mg/mL in 1 mL ampoules, is deemed bioequivalent to the currently approved D.H.E. 45®

Injection, 1 mg/mL, manufactured by Novartis.

*Lin-Whei Chuang* 8/5/02

Lin-Whei Chuang  
Division of Bioequivalence  
Review Branch I

RD INITIALED YHUANG  
FT INITIALED YHUANG

*[Signature]* 8/12/2002

Concur: *[Signature]* Date: 8/30/2002

*fr* Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence

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APPEARS THIS WAY  
ON ORIGINAL

BIOEQUIVALENCY COMMENTS

ANDA: 40-475

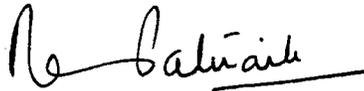
APPLICANT: Paddock Laboratories, Inc.

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

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,



fr

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 40-475  
ANDA DUPLICATE  
DIVISION FILE  
HFD-652/ Bio Secretary - Bio Drug File  
HFD-652/ LChuang

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Endorsements: (Final with Dates)  
HFD-652/ L. Chuang *LWC 8/5/02*  
HFD-652/ Y. Huang *YH 8/12/02*  
HFD-617/ K. Scardina *KS 8/12/02*  
HFD-650/ D. Conner *DC 8/30/2002*

BIOEQUIVALENCY - ACCEPTABLE Submission Date: 4/30/02

WAIVER (WAI) *o/c*

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 # : 40-475                      SPONSOR : Paddock Laboratories, Inc.  
DRUG AND DOSAGE FORM : Dihydroergotamine Mesylate Injection USP  
STRENGTH(S) : 1 mg/mL (in 1 mL ampoules)  
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:	Inspection status:	Inspection results:
NO		
First Generic <u>No</u>	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Lin-Whei Chuang      BRANCH : I  
INITIAL : LWC                              DATE : 8/5/02

TEAM LEADER : Yih-Chain Huang      BRANCH : I  
INITIAL : [Signature]                      DATE : 8/12/2002

*for* DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.  
INITIAL : [Signature]                      DATE : 8/30/2002

APPEARS THIS WAY  
ON ORIGINAL

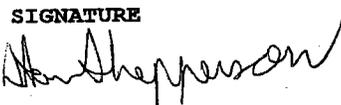
**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**40-475**

**ADMINISTRATIVE  
DOCUMENTS**

RECORD OF TELEPHONE CONVERSATION

<p>A call was placed to M.Friedly of Pharmaforce to discuss their December 30, 2002 amendment. The Agency called to request:</p> <ol style="list-style-type: none"><li>1. A revised protocol with 18-month expiration dating and</li><li>2. A revised specification for DHER and total known impurity degradedants.</li></ol> <p>The firm will make the revisions and send these in as a Telephone Amendment.</p> <p>FDA Participants: Dr. Ubrani Venkataram, Ph.D. Team leader Dr. Mouna Selvam, Ph.D., review chemist</p> <p><b>APPEARS THIS WAY ON ORIGINAL</b></p>	<b>DATE: 13-March-2003</b>
	<b>APPLICATION NUMBER</b>  40-475
	<b>TELECON</b>
	<b>INITIATED BY AGENT FOR SPONSOR</b>
	<b>PRODUCT NAME</b> D.H.E. USP 1 mg/mL, 1 mL ampules
	<b>Firm Name:</b> Paddock Laboratories, Inc. (Pharmaforce US Agent)
	<b>NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD</b> Marilyn Friedly
	<b>TELEPHONE NUMBER</b> 614-486-7360
<b>SIGNATURE</b> 	

Orig: ANDA 40-475  
Cc: Division File  
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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**40-475**

**CORRESPONDENCE**

# PharmaForce, Inc.

April 16, 2003

Office of Generic Drugs, CDER, FDA  
Gary J. Buehler, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

## LABELING AMENDMENT

ORIG AMENDMENT  
N/A

RE: DIHYDROERGOTAMINE MESYLATE INJECTION USP,  
1 MG/ML, 1 ML AMPOULES  
ANDA 40-475  
RESPONSE TO TELEPHONE REQUEST OF APRIL 15, 2003

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above and to an April 15 2003 telephone discussion with the Agency's Ms. Lillie Golson. Paddock Laboratories, Inc. wishes to amend this application in response to the Agency's request of April 15<sup>th</sup>.

During the April 15<sup>th</sup> discussion, Ms. Golson requested that the storage condition stated on the labeling be revised to address current nomenclature regarding USP Controlled Room Temperature. For example:

"Store at 20 to 25°C (68 to 77°F). Excursions permitted to 15 to 30°C (59 to 86°F).  
[See USP Controlled Room Temperature]."

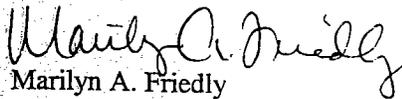
As acknowledged by Ms. Golson, the storage statement of the Reference Listed Drug, D.H.E. 45® (dihydroergotamine mesylate) Injection USP, does not include the current nomenclature.

Ms. Golson indicated that Paddock may commit to revise the storage statement at the next printing of the labeling. Paddock acknowledges the Agency's request and commits to revise the storage statement at the time of next printing.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted, has been forwarded to the FDA's Minneapolis District Office.

This correspondence is submitted in duplicate. All communication regarding this application should be directed to the attention of the undersigned at PharmaForce, Inc., 1507 Chambers Road, Columbus, Ohio, 43212. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (614) 486-7360 and/or facsimile number (614) 486-9029.

Sincerely,



Marilyn A. Friedly  
PharmaForce, Inc.

Authorized Agent for Paddock Laboratories, Inc.

RECEIVED

APR 17 2003

OGD / CDER

1507 Chambers Road • Columbus, Ohio, USA 43212  
Phone: 614-486-7360 Fax: 614-486-9029



# PharmaForce, Inc.

April 9, 2003

ORIG AMENDMENT

M/AF

Office of Generic Drugs, CDER, FDA  
Gary J. Buehler, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

LABELING AMENDMENT,

(LABELING INFORMATION  
ENCLOSED)

RE: DIHYDROERGOTAMINE MESYLATE INJECTION USP,  
1 MG/ML, 1 ML AMPOULES  
ANDA 40-475  
RESPONSE TO TELEPHONE DEFICIENCIES OF APRIL 4, 2003

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above and to an April 4, 2003 telephone discussion with Agency representatives. Paddock Laboratories, Inc. wishes to amend this application in response to the Agency's requests of April 4<sup>th</sup>.

During the April 4<sup>th</sup> discussion, the Agency requested that a revision date be included on the package insert. As requested, the labeling has been revised accordingly. Revised final printed labeling is provided as an attachment to this correspondence.

The Agency also asked that a separate patient booklet or perforated insert be included as part of the product labeling. As discussed with the Agency, the Reference Listed Drug (RLD) product, D.H.E. 45® (dihydroergotamine mesylate) Injection USP, does not include either a patient booklet or a perforated insert as part of marketed labeling, the most current version having been approved on July 31, 2002. It was agreed that this would not be required of Paddock as it has not been required for the RLD.

Attachment B contains twelve (12) copies of the final printed package insert for Dihydroergotamine Mesylate Injection USP, 1 mg/mL. In order to facilitate the review of the labeling, Attachment A contains a side-by-side comparison of the final printed labeling to that previously submitted. It is noted that, prior to approval, the Agency may request further changes to the labeling. Paddock may further revise the labeling pursuant to approved changes for the referenced listed drug. Paddock will monitor FDA's website for any approved labeling changes.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted, has been forwarded to the FDA's Minneapolis District Office.

RECEIVED

APR 10 2003

1507 Chambers Road • Columbus, Ohio, USA 43212  
Phone: 614-486-7360 Fax: 614-486-9029

OGD / CDER

Gary J. Buehler  
Page 2 of 2

This correspondence is submitted in duplicate. All communication regarding this application should be directed to the attention of the undersigned at PharmaForce, Inc., 1507 Chambers Road, Columbus, Ohio, 43212. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (614) 486-7360 and/or facsimile number (614) 486-9029.

Sincerely,



Marilyn A. Friedly

PharmaForce, Inc.

Authorized Agent for Paddock Laboratories, Inc.

Enclosures

APPEARS THIS WAY  
ON ORIGINAL



# PharmaForce, Inc.

March 14, 2003

ORIG AMENDMENT

*N/A*

Office of Generic Drugs, CDER, FDA  
Gary J. Buehler, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

**TELEPHONE AMENDMENT**

(CMC INFORMATION ENCLOSED)

RE: DIHYDROERGOTAMINE MESYLATE INJECTION USP, 1 MG/ML,  
1 ML AMPOULES  
ANDA 40-475  
RESPONSE TO TELEPHONE DEFICIENCIES OF MARCH 13, 2003

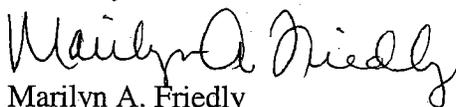
Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above and to a March 13, 2003 telephone discussion with Agency representatives. Paddock Laboratories, Inc. wishes to amend this application in response to the Agency's request of March 13<sup>th</sup>. That request, along with a response applicable to filing, is attached to this correspondence.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Minneapolis District Office.

This correspondence is submitted in duplicate. All communication regarding this application should be directed to the attention of the undersigned at PharmaForce, Inc., 1507 Chambers Road, Columbus, Ohio, 43212. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (614) 486-7360 and/or facsimile number (614) 486-9029.

Sincerely,



Marilyn A. Friedly  
PharmaForce, Inc.  
Authorized Agent for Paddock Laboratories, Inc.

**RECEIVED**

**MAR 17 2003**

**OGD / CDER**

Enclosures



# PharmaForce, Inc.

January 13, 2003

CONFIDENTIAL  
N/A

Office of Generic Drugs, CDER, FDA  
Gary J. Buehler, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

**RESPONSE TO  
MICROBIOLOGY  
DEFICIENCIES**  
(STERILITY ASSURANCE INFORMATION  
ENCLOSED)

RE: DIHYDROERGOTAMINE MESYLATE INJECTION USP, 1 MG/ML,  
1 ML AMPOULES  
ANDA 40-475  
RESPONSE TO AGENCY CORRESPONDENCE DATED  
JANUARY 7, 2003

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above and to the Agency's correspondence dated January 7, 2003 (provided on page 03). In response to the Agency's comments of January 7<sup>th</sup> Paddock Laboratories wishes to amend this application as follows.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Minneapolis District Office.

This correspondence is submitted in duplicate. All communication regarding this application should be directed to the attention of the undersigned at PharmaForce, Inc., 1507 Chambers Road, Columbus, Ohio, 43212. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (614) 486-7360 and/or facsimile number (614) 486-9029.

Sincerely,

Marilyn A. Friedly  
PharmaForce, Inc.  
Authorized Agent for Paddock Laboratories, Inc.

Enclosures

RECEIVED

JAN 14 2003

OGD / CDER



# PharmaForce, Inc.

December 30, 2002

**ORIG AMENDMENT**

*N/AAM*

Office of Generic Drugs, CDER, FDA  
Gary J. Buehler, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

**MINOR AMENDMENT**

**(CMC INFORMATION ENCLOSED)**

RE: DIHYDROERGOTAMINE MESYLATE INJECTION USP, 1 MG/ML,  
1 ML AMPOULES  
ANDA 40-475  
RESPONSE TO AGENCY CORRESPONDENCE DATED  
DECEMBER 23, 2002

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above and to the Agency's correspondence dated December 23, 2002 (provided on page 03). In response to the Agency's comments of December 23<sup>rd</sup>, Paddock Laboratories wishes to amend this application as follows.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Minneapolis District Office.

This correspondence is submitted in duplicate. All communication regarding this application should be directed to the attention of the undersigned at PharmaForce, Inc., 1507 Chambers Road, Columbus, Ohio, 43212. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (614) 486-7360 and/or facsimile number (614) 486-9029.

Sincerely,

Marilyn A. Friedly  
PharmaForce, Inc.  
Authorized Agent for Paddock Laboratories, Inc.

**RECEIVED**

**DEC 31 2002**

**OGD / CDER**

Enclosures

*MFL*  
*1-7-03*



# PharmaForce, Inc.

December 16, 2002

Office of Generic Drugs, CDER, FDA  
Gary J. Buehler, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

*Labeling review  
drafted 1/17/03  
A. Vezza*

**LABELING AMENDMENT**

**(LABELING INFORMATION  
ENCLOSED)**

RE: DIHYDROERGOTAMINE MESYLATE INJECTION USP,  
1 MG/ML, 1 ML AMPOULES  
ANDA 40-475  
RESPONSE TO AGENCY CORRESPONDENCE DATED  
SEPTEMBER 13, 2002

**ORIGINAL AMENDMENT**

**N/A**

**FPL**

Dear Mr. Buehler:

Reference is made to the Agency's correspondence dated September 13, 2002 (provided in Attachment A) regarding the Abbreviated New Drug Application (ANDA) identified above, and to a September 20, 2002 conversation with Mr. Adolph Veza of your Office. Mr. Veza confirmed that the September 13<sup>th</sup> comments pertaining to the 10 x 1 mL carton should also apply to the 5 x 1 mL carton. In response to the Agency's comments of September 13<sup>th</sup>, Paddock Laboratories wishes to amend this application as follows.

Attachment C contains twelve (12) copies of the final printed container label, cartons and package insert for Dihydroergotamine Mesylate Injection USP, 1 mg/mL. In order to facilitate the review of the labeling, Attachment B contains a side-by-side comparison of the final printed labeling to those previously submitted. It is noted that, prior to approval, the Agency may request further changes to the labeling. Paddock may further revise the labeling pursuant to approved changes for the referenced listed drug. Paddock will monitor FDA's website for any approved labeling changes.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted, has been forwarded to the FDA's Minneapolis District Office.

This correspondence is submitted in duplicate. All communication regarding this application should be directed to the attention of the undersigned at PharmaForce, Inc., 1507 Chambers Road, Columbus, Ohio, 43212. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (614) 486-7360 and/or facsimile number (614) 486-9029.

Sincerely,

Marilyn A. Friedly  
PharmaForce, Inc.  
Authorized Agent for Paddock Laboratories, Inc.

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# PharmaForce, Inc.

October 3, 2002

**ORIG AMENDMENT**

N/Am

Office of Generic Drugs, CDER, FDA  
Gary J. Buehler, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

**MINOR AMENDMENT**

**(CMC INFORMATION ENCLOSED)**

RE: DIHYDROERGOTAMINE MESYLATE INJECTION USP, 1 MG/ML,  
1 ML AMPOULES  
ANDA 40-475  
RESPONSE TO AGENCY CORRESPONDENCE DATED  
OCTOBER 1, 2002

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above and to the Agency's correspondence dated October 1, 2002 (provided on page 03). In response to the Agency's comments of October 1<sup>st</sup>, Paddock Laboratories wishes to amend this application as follows.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Minneapolis District Office.

This correspondence is submitted in duplicate. All communication regarding this application should be directed to the attention of the undersigned at PharmaForce, Inc., 1507 Chambers Road, Columbus, Ohio, 43212. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (614) 486-7360 and/or facsimile number (614) 486-9029.

Sincerely,

Marilyn A. Friedly  
PharmaForce, Inc.  
Authorized Agent for Paddock Laboratories, Inc.

Enclosures

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7/6/02  
10/7/02



# PharmaForce, Inc.

3.1

July 19, 2002

ORIG AMENDMENT

N/AA

Office of Generic Drugs, CDER, FDA  
Gary J. Buehler, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

GRATUITOUS AMENDMENT

(CMC INFORMATION ENCLOSED)

RE: DIHYDROERGOTAMINE MESYLATE INJECTION USP,  
1 MG/ML, 1 ML AMPOULES  
ANDA 40-475

Dear Mr. Buehler:

The purpose of this correspondence is to amend the above referenced Abbreviated New Drug Application. Specifically, we wish to provide the following additional information, which may aid in the review process. In cases where documentation revisions have occurred, the revised documents included in this amendment serve as replacements for those in the original application.

**Chemistry**

**1. Revised Drug Substance Specifications and Corresponding Documentation**

The drug substance specifications and corresponding documentation for Dihydroergotamine Mesylate, USP have been revised to include method references for the residual solvents, ethanol and acetone. These revised drug substance specifications will be applied to all subsequent lots of Dihydroergotamine Mesylate, USP. The revised specifications, corresponding test summary sheet and general drug substance testing method are provided under Attachment 1.a. Analytical procedures for the analysis of \_\_\_\_\_ and their corresponding method validations are provided under Attachment 1.b.

**2. Revised Master Batch Record Documentation**

Minor revisions to the master batch record were made subsequent to the submission of the original ANDA. The compounding pH range (listed on pages 0343 and 0392 of the original application) has been revised from \_\_\_\_\_ to reflect a more appropriate range for the drug product. The in-process pH result of the exhibit batch meets the revised specification. Copies of the revised compounding portions of the Master Batch Records for the \_\_\_\_\_ batch sizes are provided in Attachment 2.a and \_\_\_\_\_ respectively.

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In addition, the bills of materials (found on pages 0329 and 0378 of the initial submission) for the \_\_\_\_\_ batch records were revised to correctly reflect the \_\_\_\_\_ the \_\_\_\_\_ used in exhibit batch manufacture. The

\_\_\_\_\_ respectively.

**3. *Corrected In-Process Specification and Method of Analysis (MOA)***

The In-Process specification document, provided on page 0431 of the original application, has been revised to state the in-process assay criteria as \_\_\_\_\_ to correspond with the Master Batch Records (\_\_\_\_\_) found on pages 0362 and 0411 of the original application. The revised limit reflects the \_\_\_\_\_ active ingredient \_\_\_\_\_ from the drug product formulation (as discussed on page 0326 of the initial submission). The format of the specification document and corresponding "Method of Analysis" document have also been revised to include reference to the commercial batch code number for the drug product. The revised In-Process Specifications document and corresponding Method of Analysis (MOA) are provided in this amendment under Attachment 3.

**4. *USP<661> Type I Glass Testing***

Draxis Pharma, the contracted drug product manufacturer, approves ampoules for use following performance of dimensional checks and a satisfactory review of certificates of compliance from qualified ampoule suppliers. For the exhibit batch, the ampoules (Code No. 230310) were \_\_\_\_\_

Paddock Laboratories elected to perform full USP <661> testing on samples of ampoule Code No. 230310 (\_\_\_\_\_) providing independent assurance that Code No. 230310 meets established USP criteria. An alternate lot of the same glass ampoules used in the exhibit batch (Code No. 230310) was evaluated. Established criteria were met in all cases. Results are provided under Attachment 4.a.

Additionally, a quality certificate from the component supplier and in-house documentation are included in this correspondence, under Attachment 4.b, providing assurance that tested components conform to the same specifications as those utilized in the exhibit batch. Satisfactory results from USP <661> Chemical Resistance – Glass Containers USP, in addition to periodic vendor auditing and ongoing dimensional evaluation, provide evidence of material safety and quality.

**5. *Revised Finished Product Release and Stability Documentation***

The Agency has requested, as part of its recent review of other ANDAs, that revisions be made to Finished Product Release and Stability documentation. Those requests have been applied to this application. Accordingly, the following information is provided:

- For the Finished Product Test Summary Sheet (found on page 0451 of the original application), the letters “B” and “E” have been defined on page 3 of the document as “beginning” and “end” of fill, respectively.
- For the Finished Product Test Summary Sheet, In-house Tabular Summary, PharmaForce SOP CHM-104, and Pre-Marketed and Marketed Stability Protocols, the visual test for ‘particulate matter’ has been changed to ‘foreign matter,’ consistent with the descriptive found within USP <1>.

Documentation can be found in the application as follows:

Document	Location
Finished Product Test Summary	Page 0451 of the original application
In-house Tabular Summary	Page 1141 of the original application
PharmaForce SOP CHM-104	Page 1374 of the original application
Pre-Marketed Stability Protocols	Page 114 of June 7, 2002 amendment
Marketed Stability Protocols	Page 124 of June 7, 2002 amendment

- For the Finished Product Test Summary Sheet, In-house Tabular Summary, PharmaForce SOP CHM-104, and Pre-Marketed and Marketed Stability Protocols, a specification for “Other Requirements” as listed in USP<1> has been added. Nomenclature and Definitions, Ingredients, Labels and Labeling are evaluated as part of the Agency’s labeling and CMC (Chemistry, Manufacturing and Controls) review. Once approved, these USP <1> requirements will be routinely met throughout the use of the approved methods, controls, labeling, etc. and adequate quality assurance review.

Revised Finished Product Release documentation (Finished Product Test Summary Sheet, In-house Tabular Summary and PharmaForce SOP CHM-104) is provided under Attachment 5.a. Revised Pre-Marketed and Marketed Stability Protocols are provided under Attachment 5.b. All results remain within established specifications.

**6. Alcohol (Ethanol) Content in the Finished Product**

Paddock Laboratories has chosen to include the evaluation of alcohol content in Dihydroergotamine Mesylate Injection at time of release (see page 0453 of the original submission). The most current version of the PharmaForce procedure, CHM-109, and corresponding method validation are provided in this amendment under Attachment 6.

**7. SOP Revisions (PharmaForce) QC-016: Operation, Performance Verification and**

The Standard Operating Procedure referenced above has been revised subsequent to the initial submission. The update addresses test conditions not related to this drug product. A copy of the most current document revision is provided under Attachment 7.

Gary J. Buehler  
Page 4 of 4

As required by 21 CFR 314.96(b), we certify that a true copy of the technical sections of this correspondence, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Minneapolis District Office.

This correspondence is submitted in duplicate. All communication regarding this application should be directed to the attention of the undersigned at PharmaForce, Inc., 1507 Chambers Road, Columbus, Ohio, 43212. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (614) 486-7360 and/or facsimile number (614) 486-9029.

Sincerely,



Marilyn A. Friedly  
PharmaForce, Inc.  
Authorized Agent for Paddock Laboratories, Inc.

Enclosures

APPEARS THIS WAY  
ON ORIGINAL



# PharmaForce, Inc.

June 7, 2002

*Labeling review  
drafted 8-2-02  
A. Vega*

Office of Generic Drugs, CDER, FDA  
Gary J. Buehler, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

**ORIG AMENDMENT**  
**.N/AF**

RE: DIHYDROERGOTAMINE MESYLATE INJECTION USP,  
1 MG/ML, 1 ML AMPOULES  
ANDA 40-475  
GRATUITOUS AMENDMENT

Dear Mr. Buehler:

The purpose of this correspondence is to amend the above referenced Abbreviated New Drug Application. Specifically, we wish to revise the labeled storage condition of the proposed drug product from the originally submitted refrigerated conditions (2 - 8°C) to storage at room temperature conditions [Store below 25° (77°F)]. Documentation provided in support of this revision is as follows.

- A side-by-side comparison of the proposed draft labeling reflecting the revised storage condition and the reference listed drug product is provided under Attachment A. These pages serve as a replacement for pages 0038 - 0069 in the original application (Section IV).
- Four (4) copies of draft labeling for Dihydroergotamine Mesylate Injection, USP reflecting the revised storage condition and a side-by-side comparison of the proposed draft labeling and the reference listed drug product are provided under Attachment B. These pages serve as a replacement for pages 0071 - 0150 in the original application (Section V).
- The Sampling Instructions document has been revised to remove reference to the 5°C stability samples and is provided under Attachment C. This page serves a replacement for page 0450 in the original application (Section XI).
- Revised pre- and post-approval stability protocols reflecting the revised storage condition are provided under Attachment D. These pages serve as a replacement for pages 1545 - 1555 in the original application (Section XVI).

**RECEIVED**  
**JUN 11 2002**  
**OGD / CDER**

Gary J. Buehler

Page 2 of 2

- A revised stability summary report including data for samples stored at the following conditions are provided under Attachment E in support of the revised labeled storage:

$40^{\circ} \pm 2C/75\% \text{ RH} \pm 5\%$

$30^{\circ} \pm 2C/60\% \text{ RH} \pm 5\%$

$25^{\circ} \pm 2C/60\% \text{ RH} \pm 5\%$

These pages serve as a replacement for pages 1556 - 1574 in the original application (Section XVI).

- A revised Proposed Expiration Date document reflecting the revised storage condition is provided under Attachment F. This page serves as a replacement for page 1576 in the original application (Section XVI).

As required by 21 CFR 314.96(b), we certify that a true copy of the technical sections of this correspondence, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Minneapolis District Office.

This correspondence is submitted in duplicate. All communication regarding this application should be directed to the attention of the undersigned at PharmaForce, Inc., 1507 Chambers Road, Columbus, Ohio, 43212. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (614) 486-7360 and/or facsimile number (614) 486-9029.

Sincerely,



Marilyn A. Friedly

PharmaForce, Inc.

Authorized Agent for Paddock Laboratories, Inc.

ANDA 40-475

MAY - 3 2002

PharmaForce, Inc.  
U.S. Agent for: Paddock Laboratories, Inc.  
Attention: Marilyn A. Friedly  
1507 Chambers Road  
Columbus, OH 43212

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 our "Refuse to Receive" letter dated April 8, 2002 and to your correspondence dated April 30, 2002.

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

DATE OF APPLICATION: February 28, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: April 30, 2002

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:

Stanley Shepperson  
Project Manager  
(301) 827-5849

Sincerely yours,



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





# PharmaForce, Inc.

February 28, 2002

Office of Generic Drugs, CDER, FDA  
Gary J. Buehler, Acting Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

*Refuse to receive!*  
*08-APR-2002*  
*Judy S. Davis*

RE: DIHYDROERGOTAMINE MESYLATE INJECTION USP, 1 MG/ML  
INITIAL ANDA SUBMISSION

Dear Mr. Buehler:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.92 and 314.94, we submit the enclosed abbreviated new drug application for Dihydroergotamine Mesylate Injection USP, 1 mg/mL.

This application consists of a total of **10** volumes.

Archival Copy - **4** volumes.

Chemistry Copy - **4** volumes.

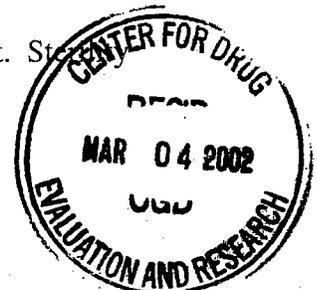
Analytical Methods - **2** extra copies; 1 volume each.

This application is being filed by PharmaForce Inc., the Authorized Agent for Paddock Laboratories, Inc. A Letter of Authorization is provided in the appropriate section of the application. The subject drug product is manufactured at Draxis Pharma Inc., Kirkland, Quebec, Canada. Information regarding the sterile manufacturing facility and processes are included in Draxis Pharma's Type V Drug Master File. A Letter of Access is provided in the appropriate section of the application.

It should be noted that this Abbreviated New Drug Application has been organized according to the Agency's February 1999 Guidance for Industry - 'Organization of an ANDA'. Pursuant to this guidance, Paddock Laboratories commits to resolve any issues identified in the methods validation process after approval.

As required by 21 CFR 314.94(d)(5), we certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Minneapolis District Office. The Table of Contents details the documentation submitted in support of this application.

Dihydroergotamine Mesylate Injection USP, 1 mg/mL is a sterile drug product. Sterility assurance data is provided for review under Section XXII of this submission.



Gary J. Buehler  
Page 2 of 2

Standard Operating Procedures (SOPs) are provided throughout this application as an aid in the review process. Revisions may be made to these SOPs after appropriate in-house review and approval. Changes which may influence the manufacture of Dihydroergotamine Mesylate Injection USP, 1 mg/mL will be reported to the Agency per the current established criteria.

All correspondence regarding this application should be directed to the attention of the undersigned at PharmaForce, Inc., 1507 Chambers Road, Columbus, Ohio, 43212. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (614) 486-7360 and/or facsimile number (614) 486-9029.

Sincerely,



Marilyn A. Friedly  
PharmaForce, Inc.  
Authorized Agent for Paddock Laboratories, Inc.