Dihydroergotamine Mesylate, USP Nasal Spray

The solution used in Dihydroergotamine Mesylate, USP Nasal Spray (4 mg/mL) is intended for intranasal use and must not be injected.

**Rx only**

**WARNING**
Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of DIHYDROERGOTAMINE with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of DIHYDROERGOTAMINE, the risk for vasoconstriction 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 section)

**DESCRIPTION**
Dihydroergotamine mesylate, USP is ergotamine hydrogenated in the 9,10 position as the mesylate salt. Dihydroergotamine mesylate, USP is known chemically as ergotamin-3', 6', 18-trione, 9,10-dihydro-12'-hydroxy-2'-methyl-5'- (phenylmethyl)-, (5'C)-, monomethanesulfonate. Its molecular weight is 679.80 and its empirical formula is C₃₁H₅₁NO₁₈CHO₃S. The chemical structure is:

Dihydroergotamine Mesylate, USP Nasal Spray is provided for intranasal administration as a clear, colorless to faintly yellow solution in an amber glass vial containing:
- Dihydroergotamine mesylate, USP ................................. 4.0 mg
- caffeine, anhydrous, USP ............................................. 10.0 mg
- dextrose, anhydrous, USP ............................. 50.0 mg
- carbon dioxide, USP .............................................................. qs
- purified water, USP ................................................ 1.0 mL

**CLINICAL PHARMACOLOGY**

**Mechanism of Action**
Dihydroergotamine binds with high affinity to 5-HT₂B, and 5-HT₁D receptors. It also binds with high affinity to serotonin 5-HT₁A, 5-HT₂A, and 5-HT₂C receptors, noradrenaline α₁, and 5-HT receptors, and dopamine D₃ and D₅ receptors. The therapeutic activity of dihydroergotamine in migraine is generally attributed to the agonist effect at 5-HT₁D receptors. Two current theories have been proposed to explain the efficacy of 5-HT₁D receptor agonists in migraine. One theory suggests that activation of 5-HT₁D 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-HT₁D 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**
Dihydroergotamine mesylate is poorly bioavailable following oral administration. Following intranasal administration, however, the mean bioavailability of dihydroergotamine mesylate is 32% relative to the injectable administration. Absorption is variable, probably reflecting both intersubject differences of absorption and the technique used for self-administration.

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

**Metabolism**
Four dihydroergotamine mesylate metabolites have been identified in human plasma following oral administration. The major metabolite, 8'-β-hydroxydihydroergotamine, exhibits affinity equivalent to its parent for adrenergic and 5-HT receptors and demonstrates equivalent potency in several vasoconstrictor activity models, in vivo and in vitro. The other metabolites, i.e., dihydroergosin acid, dihydroergosin 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. The systemic clearance of dihydroergotamine mesylate following I.V. and I.M. administration is 1.5 L/min. 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. After intranasal administration the urinary recovery of parent drug amounts to about 2% of the administered dose compared to 6% after I.M. administration. The total body clearance is 1.5 L/min which reflects mainly hepatic clearance. The renal clearance (0.1 L/min) is unaffected by the route of dihydroergotamine administration. The decline of plasma dihydroergotamine is biphasic with a terminal half-life of about 10 hours.

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

**Interactions**
The pharmacokinetics of dihydroergotamine did not appear to be significantly affected by the concomitant use of a local vasoconstrictor (e.g., fenoxazoline). Multiple oral doses of the β-adrenoceptor antagonist propranolol, used for migraine prophylaxis, had no significant influence on the Cmax, Tmax or AUC of dihydroergotamine doses up to 4 mg. Pharmacokinetic interactions have been reported in patients treated orally with other ergot alcohols (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.

**Clinical Trials**
The efficacy of Dihydroergotamine Mesylate, USP Nasal Spray for the acute treatment of migraine headaches was evaluated in four randomized, double blind, placebo controlled studies in the U.S. The patient population for the trials was predominantly female (67%) and Caucasian (95%) with a mean age of 39 years (range 18 to 65 years). Patients treated a single moderate to severe migraine headache with a single dose of study medication and assessed pain severity over the 24 hours following treatment. Headache response was determined 0.5, 1, 2, 3 and 4 hours after dosing and was defined as a reduction in headache severity to mild or no pain. In studies 1 and 2, a four-point pain intensity scale was utilized; in studies 3 and 4, a five-point scale was used that included both pain response and restoration of function for "severe" or "incapacitating" pain, a less clear endpoint. Although rescue medication was allowed in all four studies, patients were instructed not to use them during the four hour observation period. In studies 3 and 4, a total dose of 2 mg was compared to placebo. In studies 1 and 2, doses of 2 and 3 mg were evaluated, and showed no advantage of the higher dose for a single treatment. In all studies, patients received a regimen consisting of 0.5 mg in each nostril, repeated in 15 minutes (and again in another 15 minutes for the 3 mg dose in studies 1 and 2).

The percentage of patients achieving headache response 4 hours after treatment was significantly greater in patients receiving 2 mg doses of Dihydroergotamine Mesylate, USP Nasal Spray compared to those receiving placebo in 3 of the 4 studies (see Tables I & 2 and Figures 1 & 2).

**Table 1:** Studies 1 and 2: Percentage of patients with headache response* 2 and 4 hours following a single treatment of study medication

<table>
<thead>
<tr>
<th>Study</th>
<th>Dihydroergotamine Mesylate</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N 2 hours 4 hours</td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>105 61%** 70%**</td>
<td>98 23% 28%</td>
</tr>
<tr>
<td>Study 2</td>
<td>103 47% 56%</td>
<td>102 33% 35%</td>
</tr>
</tbody>
</table>

*Headache response was defined as a reduction in headache severity to mild or no pain. Headache response was based on pain intensity as interpreted by the patient using a four-point pain intensity scale.
**p value < 0.01
***p value < 0.001

**Table 2:** Studies 3 and 4: Percentage of patients with headache response* 2 and 4 hours following a single treatment of study medication

<table>
<thead>
<tr>
<th>Study</th>
<th>Dihydroergotamine Mesylate</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N 2 hours 4 hours</td>
<td></td>
</tr>
<tr>
<td>Study 3</td>
<td>50 32% 48%</td>
<td>50 20% 22%</td>
</tr>
<tr>
<td>Study 4</td>
<td>47 30% 47%</td>
<td>50 20% 30%</td>
</tr>
</tbody>
</table>

*Headache response was defined as a reduction in headache severity to mild or no pain. Headache response was evaluated on a five-point scale that included both pain response and restoration of function for "severe" or "incapacitating" pain.
**p value < 0.01

Comparisons of drug performance based upon results obtained in different clinical trials are never reliable. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment response and the timing of response may be expected to vary considerably from study to study.
The Kaplan-Meier plots below (Figures 1 & 2) provide an estimate of the probability that a patient will have responded to a single 2 mg dose of Dihydroergotamine Mesylate, USP Nasal Spray as a function of the time elapsed since initiation of treatment.

*The figure shows the probability over time of obtaining a response following treatment with Dihydroergotamine Mesylate, USP Nasal Spray. Headache response was based on pain intensity as interpreted by the patient using a four-point pain intensity scale. Patients not achieving response within 4 hours were censored to 4 hours.

For patients with migraine-associated nausea, photophobia, and phonophobia at baseline, there was a lower incidence of these symptoms at 2 and 4 hours following administration of Dihydroergotamine Mesylate, USP Nasal Spray compared to placebo.

Patients were not allowed to use additional treatments for eight hours prior to study medication dosing and during the four hour observation period following study treatment. Following the 4 hour observation period, patients were allowed to use additional treatments. For all studies, the estimated probability of patients using additional treatments for their migraines over the 24 hours following the single 2 mg dose of study treatment is summarized in Figure 3 below.

*Kaplan-Meier plot based on data obtained from all studies with patients not using additional treatments censored to 24 hours. All patients received a single treatment of study medication for their migraine attack. The plot also includes patients who had no response to the initial dose.

Neither age nor sex appear to affect the patient’s response to Dihydroergotamine Mesylate, USP Nasal Spray. While patients with menstrual migraine, migraine with aura, and migraine without aura by medical history were included in the clinical evaluation of Dihydroergotamine Mesylate, USP Nasal Spray, patients were not required to report the specific type of migraine treated with study medication. Thus, neither the effect of menses on migraine nor the presence or the absence of aura were assessed. The racial distribution of patients was insufficient to determine the effect of race on the efficacy of Dihydroergotamine Mesylate, USP Nasal Spray.

INDICATIONS AND USAGE
Dihydroergotamine Mesylate, USP Nasal Spray is indicated for the acute treatment of migraine headaches with or without aura. Dihydroergotamine Mesylate, USP Nasal Spray is not intended for the prophylactic therapy of migraine or for the management of hemiplegic or basilar migraine.

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, neflavinav, indinavir, erythromycin, clarithromycin, troleandomycin, ketoconazole, itraconzole) with dihydroergotamine is, therefore contraindicated (See WARNINGS: CYP 3A4 Inhibitors).

Dihydroergotamine Mesylate, USP Nasal Spray 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, USP Nasal Spray may increase blood pressure, it should not be given to patients with uncontrolled hypertension.

Dihydroergotamine Mesylate, USP Nasal Spray, 5-HT1 agonists (e.g., sumatriptan), ergotamine-containing or ergot-type medications or methysergide should not be used within 24 hours of each other.

Dihydroergotamine Mesylate, USP Nasal Spray should not be administered to patients with hemiplegic or basilar migraine.

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

Dihydroergotamine Mesylate, USP Nasal Spray 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 embryofetal development studies of Dihydroergotamine Mesylate, USP 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) following administration of dihydroergotamine mesylate. USP Nasal Spray was administered intranasally to female rats during pregnancy and lactation, decreased body weights and impaired reproductive function (decreased mating indices) were observed in the offspring at doses of 0.16 mg/day or greater. A no effect level was not established. Effects on development occurred at doses below those that produced evidence of significant maternal toxicity in these studies. Dihydroergotamine-induced intrauterine growth retardation has been attributed to reduced uteroplacental blood flow resulting from prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone.

Dihydroergotamine Mesylate, USP Nasal Spray 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.

WARNING

Dihydroergotamine Mesylate, USP Nasal Spray 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 vasoospasm that led to cerebral ischemia and/or ischemia of the extremities. The use of potent CYP 3A4 inhibitors with dihydroergotamine should therefore be avoided. (See CONTRAINDICATIONS). Examples of some of the more potent CYP 3A4 inhibitors include: alfentanil, ketocazole 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, fluoxetine, flufenoxime, 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 alkaloids 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, USP Nasal Spray, 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, USP Nasal Spray should not be used by patients with documented ischemic or vasospastic coronary artery disease. (See CONTRAINDICATIONS) It is strongly recommended that Dihydroergotamine Mesylate, USP Nasal Spray 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 has been performed. (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, USP Nasal Spray take place in the setting of a physician's office and who 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, USP Nasal Spray, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of Dihydroergotamine Mesylate, USP Nasal Spray who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use Dihydroergotamine Mesylate, USP Nasal Spray.

The systematic approach described above is currently recommended as a method to identify patients in whom Dihydroergotamine Mesylate, USP Nasal Spray may be used to treat migraine headaches with an acceptable margin of cardiovascular safety.

Cardiac Events and Fatalities

No deaths have been reported in patients using Dihydroergotamine Mesylate, USP Nasal Spray. However, 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 (e.g., D.H.E. 45® 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 D.H.E. 45® injection; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the D.H.E. 45® injection having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

Increase in Blood Pressure

Significant elevation in blood pressure has been reported on rare occasions in patients with migraine who have not had a history of hypertension treated with Dihydroergotamine Mesylate, USP Nasal Spray and dihydroergotamine mesylate injection. Dihydroergotamine Mesylate, USP Nasal Spray is contraindicated in patients with uncontrolled hypertension. (See CONTRAINDICATIONS)

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5HT1 agonist in a study evaluating subjects undergoing cardiac catheterization.

Local Irritation

Approximately 30% of patients using Dihydroergotamine Mesylate, USP Nasal Spray (compared to 9% of placebo patients) have reported irritation in the nose, throat, and/or disturbances in taste. Irritative symptoms include congestion, burning sensation, dryness, paraesthesia, discharge, epistaxis, pain, or soreness. The symptoms were predominantly mild to moderate in severity and transient. In approximately 70% of the above mentioned cases, the symptoms resolved within four hours after dosing with Dihydroergotamine Mesylate, USP Nasal Spray. Examination of the nose and throat in a double-blind, placebo-controlled study (N = 66) of study participants treated for up to 36 months (range 1-36 months) did not reveal any clinically noticeable injury. Other than this limited number of patients, the consequences of extended and repeated use of Dihydroergotamine Mesylate, USP Nasal Spray on the nasal and/or respiratory mucosa have not been systematically evaluated in patients.

Nasal tissue in animals treated with dihydroergotamine mesylate daily at nasal cavity surface area exposures (in mg/mm2) that were equal to or less than those achieved in human subjects did not reveal any clinically noticeable injury. Other than this limited number of patients, the consequences of extended and repeated use of Dihydroergotamine Mesylate, USP Nasal Spray on the nasal and/or respiratory mucosa have not been systematically evaluated in patients.

PRECAUTIONS

General

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

Fibrotic Complications: see WARNINGS: Fibrotic Complications Information for Patients

The text of a patient information sheet is printed at the end of this insert. To assure safe and effective use of Dihydroergotamine Mesylate, USP Nasal Spray, the information and instructions provided in the patient information sheet should be discussed with patients. Once the nasal spray applicator has been prepared, it should be discarded (with any remaining drug) after 8 hours.

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, USP Nasal Spray, should not exceed the dosing guidelines and should not be used for chronic daily administration (see DOSAGE AND ADMINISTRATION).

Drug Interactions

Vasoconstrictors

Dihydroergotamine Mesylate, USP Nasal Spray 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, USP nasal spray. Sumatriptan and Dihydroergotamine Mesylate, USP Nasal Spray 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, USP Nasal Spray 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 5HT1 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, USP Nasal Spray or D.H.E. 45®.

Oral Contraceptives

The effect of oral contraceptives on the pharmacokinetics of Dihydroergotamine Mesylate, USP Nasal Spray 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

There was no evidence of impairment of fertility in rats given intranasal doses of Dihydroergotamine Mesylate, USP 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, USP Nasal Spray 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, USP Nasal Spray, nursing should not be undertaken with the use of Dihydroergotamine Mesylate, USP Nasal Spray. (See CONTRAINDICATIONS)

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in the Elderly

There is no information about the safety and effectiveness of Dihydroergotamine Mesylate, USP Nasal Spray in this population because patients over age 65 were excluded from the controlled clinical trials.

ADVERSE REACTIONS

During clinical studies and the foreign postmarketing experience with Dihydroergotamine Mesylate, USP Nasal Spray there have been no fatalities due to cardiac events.

Serious cardiac events, including some that have been fatal, have occurred following use of the parenteral form of dihydroergotamine mesylate (D.H.E. 45® injection), but are extremely rare. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

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

Incidence in Controlled Clinical Trials

Of the 1,796 patients and subjects treated with Dihydroergotamine Mesylate, USP Nasal Spray doses 2 mg or less in U.S. and foreign clinical studies, 26 (1.4%) discontinued because of adverse events. The adverse events associated with discontinuation were, in decreasing order of frequency: rhinitis 13, dizziness 2, facial edema 2, and one each due to cold sweats, accidental trauma, depression, elective surgery, somnolence, anxiety, vomiting, hypotension, and paraesthesia.

The most commonly reported adverse events associated with the use of Dihydroergotamine Mesylate, USP Nasal Spray during placebo-controlled, double-blind studies for the treatment of migraine headache and not reported at an equal incidence by placebo-treated patients were rhinitis, altered sense of taste, application site reactions, dizziness, nausea, and vomiting. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Dihydroergotamine Mesylate, USP Nasal Spray was generally well tolerated. In most instances these events were transient and self-limited and did not result in patient discontinuation from a study. The following table summarizes the incidence rates of adverse events reported by at least 1% of patients who received Dihydroergotamine Mesylate, USP Nasal Spray for the treatment of migraine headaches during placebo-controlled, double-blind clinical studies and were more frequent than in those patients receiving placebo.

| Table 3: Adverse events reported by at least 1% of the Dihydroergotamine Mesylate, USP Nasal Spray treated patients and occurred more frequently than in the placebo-group in the migraine placebo-controlled trials |
|-------------------------------------------------|----------------|----------------|
| Dihydroergotamine Mesylate | Placebo |
| Respiratory System |  |  |
| Rhinitis | 26% | 7% |
| Pharyngitis | 3% | 1% |
| Sinusitis | 1% | 1% |
| Gastrointestinal System |  |  |
| Nausea | 10% | 4% |
| Vomiting | 4% | 1% |
| Diarrhea | 2% | <1% |
| Special Senses, Other |  |  |
| Altered Sense of Taste | 8% | 1% |
| Application Site |  |  |
| Application Site Reaction | 6% | 2% |
| Central and Peripheral Nervous System |  |  |
| Dizziness | 4% | 2% |
| Somnolence | 3% | 2% |
| Parasthesia | 2% | 2% |
| Body as a Whole, General |  |  |
| Hot Flashes | 1% | <1% |
| Fatigue | 1% | 1% |
| Asthenia | 1% | 0% |
| Autonomic Nervous System |  |  |
| Mouth Dry | 1% | 1% |
| Musculoskeletal System |  |  |
| Stiffness | 1% | <1% |

Other Adverse Events During Clinical Trials

In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of Dihydroergotamine Mesylate, USP Nasal Spray in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used Dihydroergotamine Mesylate, USP Nasal Spray in placebo-controlled trials and reported an event divided by the total number of patients (n=1796) exposed to Dihydroergotamine Mesylate, USP Nasal Spray. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within
Dihydroergotamine Mesylate, USP Nasal Spray (4 mg/mL) is indicated for the acute treatment of migraine headache. Administration of Dihydroergotamine Mesylate, USP Nasal Spray is intended to treat an active migraine headache. It is not intended for intranasal use and must not be injected.

Information for the Patient

Please read this information carefully before using your Dihydroergotamine Mesylate, USP Nasal Spray. Your pharmacist and/or health care provider can provide you with more detailed information.

Do not use dihydroergotamine mesylate, USP nasal spray 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, USP Nasal Spray

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

- Are you pregnant or nursing?
- Have you any disease affecting your heart, arteries, or circulation?
- 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 postmenopausal or a male over 40?
- Are you diabetic (or have you had diabetes in the past)?
- Are you pregnant? Do you think you might be pregnant? Are you trying to become pregnant? Have you ever had to stop taking this or any other medication because of an allergy or bad reaction?
- Are you diabetic (or have you had diabetes in the past)?
- 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?

DOSAGE AND ADMINISTRATION

The solution used in Dihydroergotamine Mesylate, USP Nasal Spray (4 mg/mL) is intended for intranasal use and must not be injected.

In clinical trials, Dihydroergotamine Mesylate, USP Nasal Spray has been effective for the acute treatment of migraine headaches with or without aura. One spray (0.5 mg) of Dihydroergotamine Mesylate, USP Nasal Spray should be administered in each nostril. Fifteen minutes later, an additional one spray (0.5 mg) of Dihydroergotamine Mesylate, USP Nasal Spray should be administered in each nostril, for a total dosage of four sprays (2.0 mg) of Dihydroergotamine Mesylate, USP Nasal Spray. Studies have shown no additional benefit from acute doses greater than 2.0 mg for a single migraine administration. The safety of doses greater than 3.0 mg in a 24 hour period and 4.0 mg in a 7 day period has not been established.

Dihydroergotamine Mesylate, USP Nasal Spray, should not be used for chronic daily administration.

Prior to administration, the pump must be primed (i.e., squeeze 4 times) before use. (See administration instructions).

Once the nasal spray applicator has been prepared, it should be discarded (with any remaining drug in opened vial) after 8 hours.

HOW SUPPLIED

Dihydroergotamine Mesylate, USP Nasal Spray is available (as a clear, colorless to faintly yellow solution) in 3.5 mL amber glass vials containing 4 mg of dihydroergotamine mesylate. USP Dihydroergotamine Mesylate, USP Nasal Spray is provided as a package of 8 units, administration instruction sheet, and one package insert. Each unit consists of one vial and one sprayer. (NDC 66862-357-10)

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

Patient Information

Information for the Patient

Dihydroergotamine Mesylate, USP Nasal Spray. The solution used in Dihydroergotamine Mesylate, USP Nasal Spray (4 mg/mL) is intended for intranasal use and must not be injected.

Please read this information carefully before using your Dihydroergotamine Mesylate, USP Nasal Spray for the first time. Keep this information handy for future reference. This leaflet does not contain all of the information on Dihydroergotamine Mesylate, USP Nasal Spray. Your pharmacist and/or health care provider can provide more detailed information.

Dihydroergotamine Mesylate, USP Nasal Spray has been evaluated in a limited number of patients long term (e.g., 1 year or longer).

Purpose of your Medication

Dihydroergotamine Mesylate, USP Nasal Spray is intended to treat an active migraine headache. Do not use it to treat 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, USP Nasal Spray, should not exceed the dosing guidelines and should not be used for chronic daily administration. There have been reports of stiffness (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, USP Nasal Spray 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, USP nasal spray 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.

Body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; and rare adverse events are those occurring in fewer than 1/1,000 patients.

Skin and Appendages: Infrequent: petechia, pruritus, rash, cold clammy skin; Rare: papular rash, urticaria, herpes simplex.

Musculoskeletal: Infrequent: cramps, myalgia, muscular weakness, dystonia; Rare: arthralgia, involuntary muscle contractions, rigidity.

Central and Peripheral Nervous System: Infrequent: confusion, tremor, hypoesthesia, vertigo; Rare: speech disorder, hyperkinesia, stupor, abnormal gait, aggravated migraine.

Autonomic Nervous System: Infrequent: increased sweating.

Special Senses: Infrequent: sense of smell altered, photophobia, conjunctivitis, abnormal lacrimation, abnormal vision, tinnitus, earache; Rare: eye pain.

Psychiatric: Infrequent: nervousness, euphoria, insomnia, concentration impaired; Rare: anxiety, anorexia, depression.

Gastrointestinal: Infrequent: abdominal pain, dyspepsia, dysphagia, hiccup; Rare: increased salivation, esophagospasm.

Cardiovascular: Infrequent: edema, palpitation, tachycardia; Rare: hypotension, peripheral ischemia, angina.

Respiratory System: Infrequent: dyspnea, upper respiratory tract infections; Rare: bronchospasm, bronchitis, pleural pain, epistaxis.

Urinary System: Infrequent: increased frequency of micturition, cystitis.

Reproductive, Female: Rare: pelvic inflammation, vaginitis.

Body as a Whole - General: Infrequent: feeling cold, malaise, rigors, fever, periorbital edema; Rare: flu-like symptoms, shock, loss of voice, yawning.

Application Site: Infrequent: local anesthesia.

Post-introduction Reports

Voluntary reports of adverse events temporally associated with dihydroergotamine products used in the management of migraine that have been received since the introduction of the injectable formulation are included in this section save for those already listed above. Because of their source (open and uncontrolled clinical use), whether or not events reported in association with the use of dihydroergotamine are causally related to it cannot be determined.

There have been reports of peripheral and retroperitoneal fibrosis in patients following prolonged daily use of injectable dihydroergotamine mesylate. Dihydroergotamine Mesylate, USP Nasal Spray is not recommended for prolonged daily use. (See DOSAGE AND ADMINISTRATION).

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC, at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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, USP Nasal Spray 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, USP Nasal Spray overdose are similar to those of an ergotamine overdose, although there is less 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 overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the Physicians’ Desk Reference (PDR).

DOSAGE AND ADMINISTRATION

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Dihydroergotamine Mesylate, USP Nasal Spray, should not be used for chronic daily administration.

Prior to administration, the pump must be primed (i.e., squeeze 4 times) before use. (See administration instructions).

Once the nasal spray applicator has been prepared, it should be discarded (with any remaining drug in opened vial) after 8 hours.
Answer to patients' questions about Dihydroergotamine Mesylate, USP Nasal Spray

What if I need help in using my Dihydroergotamine Mesylate, USP Nasal Spray?
If you have any questions or if you need help in opening, putting together, or using Dihydroergotamine Mesylate, USP Nasal Spray, speak to your doctor or pharmacist, or contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576.

How much medication should I use and how often?
Each vial contains one complete dose of Dihydroergotamine Mesylate, USP Nasal Spray, which is 1 spray in each nostril, followed by an additional spray in each nostril 15 minutes later for a total of 4 sprays. Do not use more than this amount unless instructed to do so by your doctor. Dihydroergotamine Mesylate, USP Nasal Spray is not intended for chronic daily use.

Am I wasting the medication?
You have to prime the Nasal Sprayer 4 times to make sure that you get the proper amount of medication when you use it. Although you will see some medication spray out, there is enough medication in each sprayer to allow you to prepare your sprayer properly and still receive a full dose of Dihydroergotamine Mesylate, USP Nasal Spray.

Can I assemble the medication vial and the Nasal Sprayer so it is ready before I need to use it?
No. The brown (amber) glass vial containing your medication must remain unopened until you are ready to use it. It may not be fully effective if opened and not used within 8 hours.

Can I reuse my dihydroergotamine mesylate, USP nasal spray?
No. After completing the full dose, you must carefully dispose of your Dihydroergotamine Mesylate, USP Nasal Spray and the opened vial. You should use a new unit for your next migraine attack. Each Unit contains a new Nasal Sprayer, and a vial of Dihydroergotamine Mesylate, USP Nasal Spray medication.

Can I use dihydroergotamine mesylate, USP nasal spray if I have a stuffy nose, cold, or allergies?
Yes. Dihydroergotamine Mesylate, USP Nasal Spray can be used if you have a stuffy nose, cold, or allergies. However, if you are taking any medications for your cold, or allergies, even those you can buy without a doctor's prescription, speak with your doctor before using Dihydroergotamine Mesylate, USP Nasal Spray.

Do I need to sniff the medication when I spray it in my nostril?
No. You should not sniff because Dihydroergotamine Mesylate, USP Nasal Spray should remain in the nose so that it can be absorbed into the bloodstream through the lining of the nose.

If you have any other unanswered questions about Dihydroergotamine Mesylate, USP Nasal Spray, consult your doctor or pharmacist.