

N5-929 S-032 S-033
Package Insert
Page 1



T2001-89
89014801

D.H.E. 45[®]
(dihydroergotamine mesylate)
Injection, USP

Rx only

Prescribing Information

WARNING

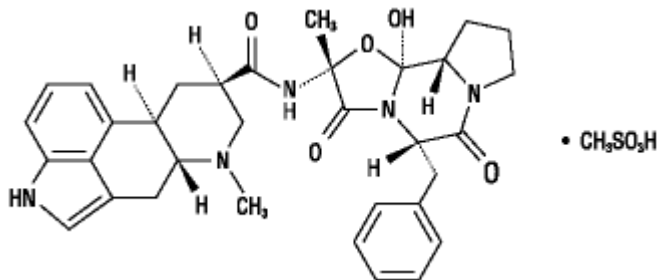
Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of DIHYDROERGOTAMINE with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of DIHYDROERGOTAMINE, the risk for vasospasm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

(See also **CONTRAINDICATIONS** and **WARNINGS** section)

DESCRIPTION

D.H.E. 45[®] is ergotamine hydrogenated in the 9, 10 position as the mesylate salt. D.H.E. 45[®] is known chemically as ergotaman-3',6',18-trione,9,10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-,(5' α)-, monomethanesulfonate. Its molecular weight is 679.80 and its empirical formula is C₃₃H₃₇N₅O₅·CH₄O₃S.

The chemical structure is



Dihydroergotamine mesylate

C₃₃H₃₇N₅O₅·CH₄O₃S

Mol. wt. 679.80

D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP is a clear, colorless solution supplied in sterile ampuls for I.V., I.M., or subcutaneous administration containing per mL:

dihydroergotamine mesylate, USP	1 mg
ethanol, 94% w/w.....	6.2% by vol.
glycerin.....	15% by wt.
water for injection, qs to	1 mL

N5-929 S-032 S-033

Package Insert

Page 2

CLINICAL PHARMACOLOGY

Mechanism of Action

Dihydroergotamine binds with high affinity to 5-HT_{1D α} and 5-HT_{1D β} receptors. It also binds with high affinity to serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors, noradrenaline α_{2A} , α_{2B} and α , receptors, and dopamine D_{2L} and D₃ receptors.

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

In addition, dihydroergotamine possesses oxytocic properties.
(See CONTRAINDICATIONS.)

Pharmacokinetics

Absorption

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

Distribution

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

Metabolism

Four dihydroergotamine mesylate metabolites have been identified in human plasma following oral administration. The major metabolite, 8'- β -hydroxydihydroergotamine, exhibits affinity equivalent to its parent for adrenergic and 5-HT receptors and demonstrates equivalent potency in several 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.

N5-929 S-032 S-033
Package Insert
Page 3

Subpopulations

No studies have been conducted on the effect of renal or hepatic impairment, gender, race, or ethnicity on dihydroergotamine pharmacokinetics. D.H.E. 45[®] (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

D.H.E. 45[®] (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).

D.H.E. 45[®] (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 D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP may increase blood pressure, it should not be given to patients with uncontrolled hypertension.

D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP, 5-HT₁ agonists (e.g., sumatriptan), ergotamine-containing or ergot-type medications or methysergide should not be used within 24 hours of each other.

D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP should not be administered to patients with hemiplegic or basilar migraine.

In addition to those conditions mentioned above, D.H.E. 45[®] (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.

N5-929 S-032 S-033

Package Insert

Page 4

D.H.E. 45[®] (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 uterine vessels and/or increased myometrial tone.

D.H.E. 45[®] (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

D.H.E. 45[®] (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 and/or and 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 CYP3A4 of other agents being considered for concomitant use with dihydroergotamine.

N5-929 S-032 S-033

Package Insert

Page 5

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 D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP, 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

D.H.E. 45[®] (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 D.H.E. 45[®] (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, D.H.E. 45[®] (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 D.H.E. 45[®] (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 D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP, in those patients with risk factors.

It is recommended that patients who are intermittent long-term users of D.H.E. 45[®] (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 D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP.

The systematic approach described above is currently recommended as a method to identify patients in whom D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP may be used to treat migraine headaches with an acceptable margin of cardiovascular safety.

N5-929 S-032 S-033

Package Insert

Page 6

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 D.H.E. 45[®] (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 D.H.E. 45[®] (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

D.H.E. 45[®] (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 D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP.

D.H.E. 45[®] (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. D.H.E. 45[®] (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. D.H.E. 45[®] (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-HT₁ agonist in a study evaluating subjects undergoing cardiac catheterization.

PRECAUTIONS

General

D.H.E. 45[®] (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 agonist are candidates for further evaluation. (See WARNINGS.)

Fibrotic Complications: see WARNINGS: Fibrotic Complications

N5-929 S-032 S-033
Package Insert
Page 7

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 D.H.E. 45[®] (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 D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP, should not exceed the dosing guidelines and should not be used for chronic daily administration (see DOSAGE AND ADMINISTRATION).

Drug Interactions

Vasoconstrictors

D.H.E. 45[®] (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 D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP. Sumatriptan and D.H.E. 45[®] (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 D.H.E. 45[®] (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.

N5-929 S-032 S-033
Package Insert
Page 8

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-HT₁ agonists have been co-administered with SSRI's (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline). There have been no reported cases from spontaneous reports of drug interaction between SSRI's and D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP.

Oral Contraceptives

The effect of oral contraceptives on the pharmacokinetics of D.H.E. 45[®] (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 D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP. There was no evidence of impairment of fertility in rats given intranasal doses of Migranal[®] Nasal Spray up to 1.6 mg/day (associated with mean plasma dihydroergotamine mesylate exposures [AUC] approximately 9 to 11 times those in humans receiving the MRDD of 4 mg).

Pregnancy

Pregnancy Category X. See CONTRAINDICATIONS.

Nursing Mothers

Ergot drugs are known to inhibit prolactin. It is likely that D.H.E. 45[®] (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 D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP,

N5-929 S-032 S-033

Package Insert

Page 9

nursing should not be undertaken with the use of D.H.E. 45[®] (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 D.H.E. 45[®] (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 D.H.E. 45[®] (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.

D.H.E. 45[®] (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 D.H.E. 45[®] (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 D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP overdose are similar to those of an ergotamine overdose, although there is less pronounced nausea and vomiting with D.H.E. 45[®] (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.

N5-929 S-032 S-033
Package Insert
Page 10

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 Physician's Desk Reference® (PDR).*

DOSAGE AND ADMINISTRATION

D.H.E. 45® (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. D.H.E. 45® (dihydroergotamine mesylate) Injection, USP, should not be used for chronic daily administration.

HOW SUPPLIED

D.H.E. 45® (dihydroergotamine mesylate) Injection, USP

Available as a clear, colorless, sterile solution in single 1 mL sterile ampuls containing 1 mg of dihydroergotamine mesylate per mL, in packages of 10 (NDC 0078-0041-01).

Store below 25°C (77°F), in light-resistant containers. Do not refrigerate or freeze.

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

INSTRUCTION FOR PATIENTS ON SUBCUTANEOUS SELF-INJECTION

Information for the Patient

D.H.E. 45® (dihydroergotamine mesylate) Injection, USP

Before self-injecting D.H.E. 45® (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 D.H.E. 45® (dihydroergotamine mesylate) Injection, USP. Your pharmacist and/or health care provider can provide more detailed information.

Purpose of your Medication

D.H.E. 45® (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 D.H.E. 45® (dihydroergotamine mesylate) Injection, USP, 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 D.H.E. 45® dihydroergotamine mesylate Injection, USP 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.

N5-929 S-032 S-033

Package Insert

Page 11

Do not use D.H.E. 45[®] (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 toleandomycin, clarithromycin or erythromycin.

Important questions to consider before using D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP

Please answer the following questions before you use your D.H.E. 45[®] (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 D.H.E. 45[®] (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 D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP 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 D.H.E. 45 and protease inhibitors or macrolide antibiotics.

N5-929 S-032 S-033
Package Insert
Page 12

REMEMBER TO TELL YOUR DOCTOR IF YOU HAVE ANSWERED YES TO ANY OF THESE QUESTIONS BEFORE YOU USE D.H.E. 45[®] (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 D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP unless at least 6 hours have elapsed since your last injection. No more than 6 mL of D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP should be injected during a one-week period. D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP 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 D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP

1. Use available training materials.
 - Read and follow the instructions in the patient instruction booklet which is provided with the D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP package before attempting to use the product.
 - If there are any questions concerning the use of your D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP, ask your Doctor or pharmacist.
2. Preparing for the Injection
 - Carefully examine the ampul (glass vial) of D.H.E. 45[®] (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 ampul, make certain it is intact, and return the defective ampul to your doctor or pharmacy. Once you open an ampul, if it is not used within an hour, it should be thrown away.

N5-929 S-032 S-033
Package Insert
Page 13

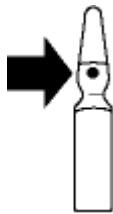
3. Locating an Injection Site

- 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 ampul. If there is, gently flick the ampul with your finger to get all the liquid into the bottom portion of the ampul.
- Hold the bottom of the ampul in one hand. To break, place the thumb of the other hand on the dot as shown and snap off backwards.

Instructions for Use



One-point-cut ampul with cut below colored dot.



To break, place thumb on the dot and snap back.

- Tilt the ampul down at a 45° angle. Insert the needle into the solution in the ampul.
 - 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.

N5-929 S-032 S-033

Package Insert

Page 14

- 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 ampul containing medication. If the expiration date has passed, do not use it.

Answers to patients' questions about D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP

What if I need help in using my D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP?

If you have any questions or if you need help in opening, putting together, or using D.H.E. 45[®] (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 D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP unless at least 6 hours have elapsed since your last injection. No more than 6 mL of D.H.E. 45[®] (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. D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP is not intended for chronic daily use.

If you have any other unanswered question about D.H.E. 45[®] (dihydroergotamine mesylate) Injection, USP, consult your doctor or pharmacist.

*Trademark of Medical Economics Company, Inc.



Manufactured by:
Novartis Pharma AG
Basle, Switzerland

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

N 20-148/ S-007 S-008
Package Insert
Page 1



T2000-79
89011901

Migranal[®]
(dihydroergotamine mesylate, USP)
Nasal Spray

The solution used in Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray (4 mg/mL) is intended for intranasal use and must not be injected.

Rx Only

WARNING

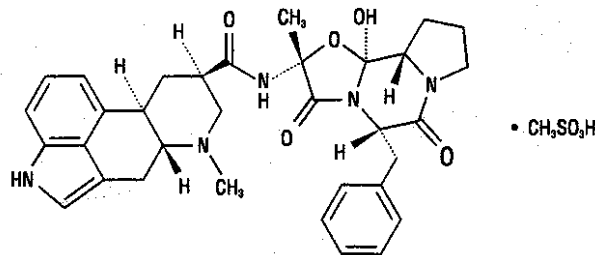
Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of DIHYDROERGOTAMINE with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of DIHYDROERGOTAMINE, the risk for vasospasm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

DESCRIPTION

Migranal[®] is ergotamine hydrogenated in the 9,10 position as the mesylate salt. Migranal[®] is known chemically as ergotaman-3',6',18-trione,9,10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-,(5'α)-,monomethanesulfonate. Its molecular weight is 679.80 and its empirical formula is C₃₃H₃₇N₅O₅•CH₄O₃S.

The chemical structure is:



Dihydroergotamine mesylate

C₃₃H₃₇N₅O₅•CH₄O₃S Mol. wt. 679.80

Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray is provided for intranasal administration as a clear, colorless to faintly yellow solution in an amber glass ampul containing:

dihydroergotamine mesylate, USP	4.0 mg
caffeine, anhydrous, USP	10.0 mg
dextrose, anhydrous, USP	50.0 mg

N 20-148/ S-007 S-008

Package Insert

Page 2

carbon dioxide..... qs

water for injection, USP..... qs 1.0 mL

CLINICAL PHARMACOLOGY

Mechanism of Action

Dihydroergotamine binds with high affinity to 5-HT_{1Dα} and 5-HT_{1Dβ} receptors. It also binds with high affinity to serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors, noradrenaline α_{2A}, α_{2B} and α₁ receptors, and dopamine D_{2L} and D₃ receptors.

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

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

Pharmacokinetics

Absorption

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., 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. 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

N 20-148/ S-007 S-008

Package Insert

Page 3

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. Migranal[®] (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 C_{max} , T_{max} or AUC of dihydroergotamine doses up to 4 mg.

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.

Clinical Trials

The efficacy of Migranal[®] (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 (87%) 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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray compared to those receiving placebo in 3 of the 4 studies (see Tables 1 & 2 and Figures 1 & 2).

Table 1: Studies 1 and 2: Percentage of patients with headache response^a

N 20-148/ S-007 S-008
Package Insert
Page 4

**2 and 4 hours following a single treatment of study medication
[Migranal® (dihydroergotamine mesylate, USP) Nasal Spray or Placebo]**

		N	2 hours	4 hours
Study 1	Migranal®	105	61%**	70%**
	Placebo	98	23%	28%
Study 2	Migranal®	103	47%	56%*
	Placebo	102	33%	35%

^aHeadache 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^a
2 and 4 hours following a single treatment of study medication
[Migranal® (dihydroergotamine mesylate, USP) Nasal Spray or Placebo]**

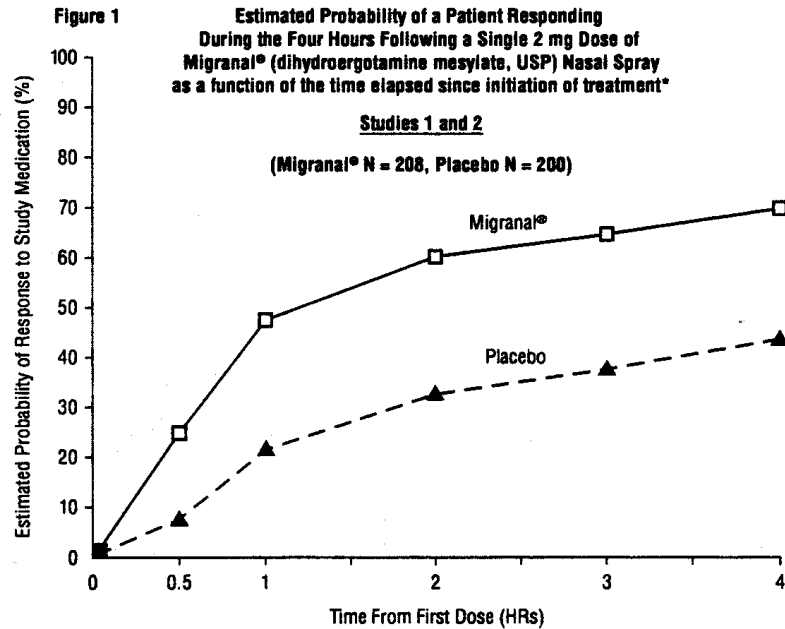
		N	2 hours	4 hours
Study 3	Migranal®	50	32%	48%*
	Placebo	50	20%	22%
Study 4	Migranal®	47	30%	47%
	Placebo	50	20%	30%

^aHeadache 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.

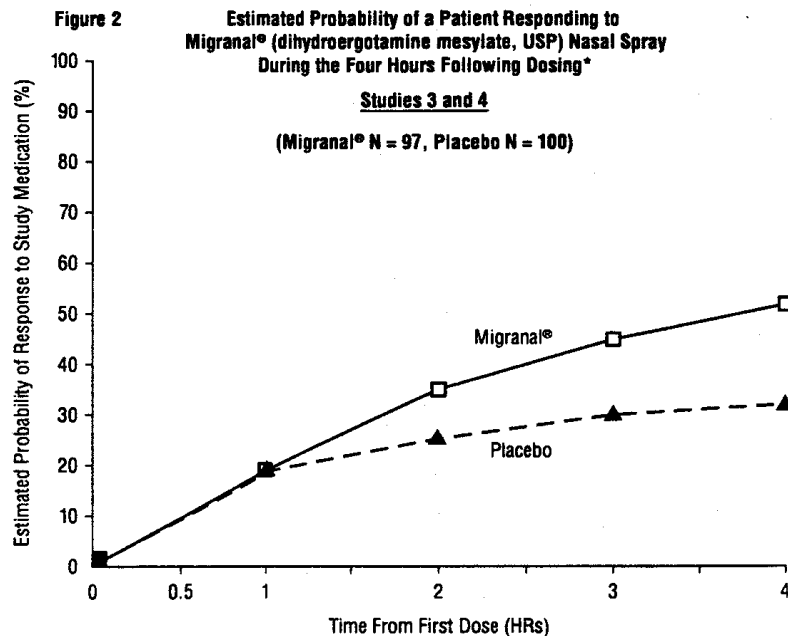
*p value < 0.01

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) provides an estimate of the probability that a patient will have responded to a single 2 mg dose of Migranal® (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 Migranal® (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.

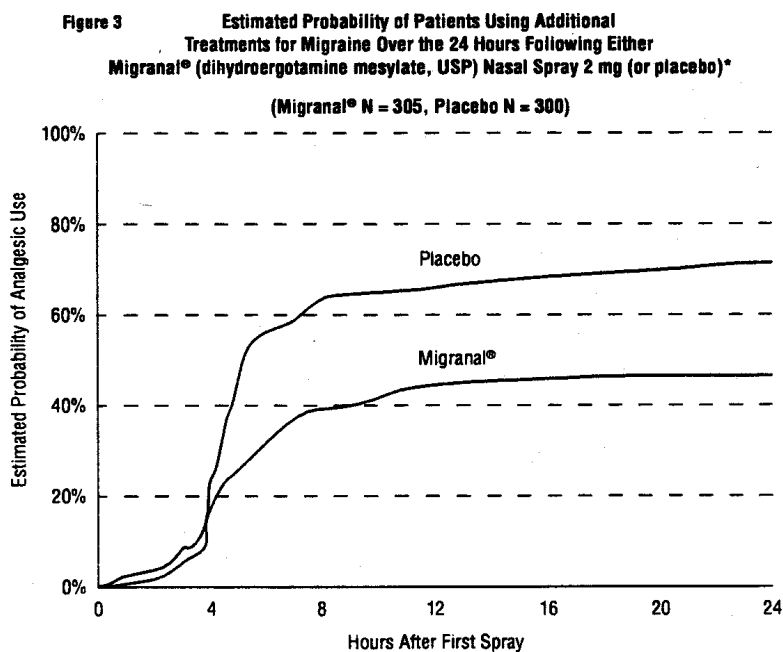


*The figure shows the probability over time of obtaining a response following treatment with Migranal® (dihydroergotamine mesylate, USP) Nasal Spray. Headache response was evaluated on a five-point scale that confounded pain response and restoration of function for “severe” or “incapacitating” pain. Patients not achieving response within 4 hours were censored to 4 hours.

N 20-148/ S-007 S-008
Package Insert
Page 6

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 Migranal[®] (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 effect the patient's response to Migranal[®] (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 Migranal[®] (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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray.

INDICATIONS AND USAGE

Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray is indicated for the acute treatment of migraine headaches with or without aura.

Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray is not intended for the prophylactic therapy of migraine or for the management of hemiplegic or basilar migraine.

N 20-148/ S-007 S-008
Package Insert
Page 7

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*).

Migranal[®] (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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray may increase blood pressure, it should not be given to patients with uncontrolled hypertension.

Migranal[®] (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.

Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray should not be administered to patients with hemiplegic or basilar migraine.

In addition to those conditions mentioned above, Migranal[®] (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.

Migranal[®] (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 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 uterine vessels and/or increased myometrial tone.

N 20-148/ S-007 S-008

Package Insert

Page 8

Migranal[®] (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.

WARNINGS

Migranal[®] (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 vasospasm that led to cerebral ischemia and/or ischemia of the extremities. The use of potent CYP 3A4 inhibitors with dihydroergotamine should therefore be avoided (*see CONTRAINDICATIONS*). Examples of some of the more potent CYP 3A4 inhibitors include: anti-fungals ketoconazole and itraconazole, the protease inhibitors ritonavir, nelfinavir, and indinavir, and macrolide antibiotics erythromycin, clarithromycin, and troleandomycin. Other less potent CYP 3A4 inhibitors should be administered with caution. Less potent inhibitors include saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton, and clotrimazole. These lists are not exhaustive, and the prescriber should consider the effects on CYP3A4 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 Migranal[®] (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:

Migranal[®] (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 Migranal[®] (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 provides satisfactory clinical evidence that the patient is

N 20-148/ S-007 S-008

Package Insert

Page 9

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, Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray 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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray 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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray.

The systematic approach described above is currently recommended as a method to identify patients in whom Migranal[®] (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 Migranal[®] (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).

N 20-148/ S-007 S-008

Package Insert

Page 10

Other Vasospasm Related Events

Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray, like other ergot alkaloids, may cause vasospastic reactions other than coronary artery vasospasm. Myocardial and peripheral vascular ischemia have been reported with Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray.

Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray 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, Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray 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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray and dihydroergotamine mesylate injection. Migranal[®] (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 Migranal[®] (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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray. Examinations of the nose and throat in a small subset (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 Migranal[®] (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 humans receiving the maximum recommended daily dose of 0.08 mg/kg/day showed mild mucosal irritation characterized by mucous cell and transitional cell hyperplasia and squamous cell metaplasia. Changes in rat nasal mucosa at 64 weeks were less severe than at 13 weeks. Local effects on respiratory tissue after chronic intranasal dosing in animals have not been evaluated.

PRECAUTIONS

General

Migranal[®] (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.

N 20-148/ S-007 S-008
Package Insert
Page 11

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 Migranal[®] (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 Migranal[®] (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

Migranal[®] (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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray. Sumatriptan and Migranal[®] (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 Migranal[®] (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.

N 20-148/ S-007 S-008
Package Insert
Page 12

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 co-administered with SSRI's (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline). There have been no reported cases from spontaneous reports of drug interaction between SSRI's and Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray or D.H.E. 45[®].

Oral Contraceptives

The effect of oral contraceptives on the pharmacokinetics of Migranal[®] (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 Migranal[®] (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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray is excreted in human milk, but there are no data on the concentration of dihydroergotamine in

N 20-148/ S-007 S-008

Package Insert

Page 13

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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray, nursing should not be undertaken with the use of Migranal[®] (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 Migranal[®] (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 Migranal[®] (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 Migranal[®] (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, allergy, vomiting, hypotension, and paraesthesia.

The most commonly reported adverse events associated with the use of Migranal[®] (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.

Migranal[®] (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 Migranal[®] (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.

N 20-148/ S-007 S-008
Package Insert
Page 14

Table 3: Adverse events reported by at least 1% of the Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray treated patients and occurred more frequently than in the placebo-group in the migraine placebo-controlled trials

	Migranal [®] N=597	Placebo N=631
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%
Paraesthesia	2%	2%
Body as a Whole, General		
Hot Flushes	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 Migranal[®] (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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray in placebo-controlled trials and reported an event divided by the total number of patients (n=1796) exposed to Migranal[®] (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 body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as 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.

N 20-148/ S-007 S-008

Package Insert

Page 15

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 pleural and retroperitoneal fibrosis in patients following prolonged daily use of injectable dihydroergotamine mesylate. Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray 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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray is to be avoided. Excessive doses of dihydroergotamine may result in peripheral signs and symptoms of

N 20-148/ S-007 S-008
Package Insert
Page 16

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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray overdose are similar to those of an ergotamine overdose, although there is less pronounced nausea and vomiting with Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray. 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 Physicians' Desk Reference[®] (PDR).*

DOSAGE AND ADMINISTRATION

The solution used in Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray (4 mg/mL) is intended for intranasal use and must not be injected.

In clinical trials, Migranal[®] (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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray should be administered in each nostril. Fifteen minutes later, an additional one spray (0.5 mg) of Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray should be administered in each nostril, for a total dosage of four sprays (2.0 mg) of Migranal[®] (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.

Migranal[®] (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 Patient Information Sheet or Patient Instruction Booklet)

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

HOW SUPPLIED

Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray is available (as a clear, colorless to faintly yellow solution) in 1 mL amber glass ampuls containing 4 mg of dihydroergotamine mesylate, USP (NDC 0078-0245-98).

Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray is provided in individual kits. The kits consist of four unit dose trays, a patient instruction booklet, one assembly case, and one patient information sheet packed in a carton. Each unit dose tray contains one ampul, a nasal spray applicator, and a breaker cap on the ampul.

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

N 20-148/ S-007 S-008
Package Insert
Page 17

Patient Information

Information for the Patient

Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray.

The solution used in Migranal[®] (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 Migranal[®] (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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray. Your pharmacist and/or health care provider can provide more detailed information.

Migranal[®] (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

Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray 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 Migranal[®] (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 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 Migranal[®] (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 Migranal[®] (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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray

Please answer the following questions before you use your Migranal[®] (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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray.

- 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?

N 20-148/ S-007 S-008

Package Insert

Page 18

- 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 Migranal[®] (dihydroergotamine mesylate, USP) 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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray and protease inhibitors or macrolide antibiotics.

REMEMBER TO TELL YOUR DOCTOR IF YOU HAVE ANSWERED YES TO ANY OF THESE QUESTIONS BEFORE YOU USE MIGRANAL[®] (dihydroergotamine mesylate, USP) NASAL SPRAY.

Side Effects To Watch Out For

In clinical trials, most migraine patients have used Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray without serious side effects. You may experience some nasal congestion or irritation, altered sense of taste, sore throat, nausea, vomiting, dizziness, and fatigue after using Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray. These side effects are temporary and usually do not require you to stop using Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray. 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

N 20-148/ S-007 S-008
Package Insert
Page 19

Dosing Information

- Each ampul contains one complete dose of Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray, which is 1 spray in each nostril followed in 15 minutes by an additional spray in each nostril, for a total of 4 sprays.
- Studies have shown no benefit from acute doses greater than 2.0 mg (4 sprays) for a single administration. The safety of doses greater than 3.0 mg in a 24 hour period has not been established.
- The safety of doses greater than 4.0 mg in a 7-day period has not been established.
- Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray, should not be used for chronic daily administration.

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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray

1. Use available training materials.
 - Read and follow the instructions in the patient instruction booklet which is provided with the Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray package before attempting to use the product.
 - If there are any questions concerning the use of your Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray, ask your doctor or pharmacist, or call the Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray Information Line at 1-888-MY-RELIEF (1-888-697-3543) for training in the use of the spray.
2. Check the contents of the package.
 - Assembly Case
 - Well (which is part of the Assembly Case)
 - Unit Dose Tray
 - Brown (amber) glass ampul with yellow breaker cap
 - Nasal Sprayer with cover
3. Assemble the sprayer.

Assemble your Nasal Sprayer only when you are ready to use it.

 - Tap top of ampul until all medication is in the bottom.
 - Place ampul upright and straight in well of the Assembly Case with breaker cap pointing up.
 - Push down the Assembly Case lid slowly but firmly, until you hear ampul snap open.
 - Without removing ampul from well, push Nasal Sprayer onto ampul until it clicks. (To ensure that the ampul fits properly into the Nasal Sprayer, first look at the tube through the bottom of sprayer to make sure it is straight. If it is curved, straighten it with your finger.)

N 20-148/ S-007 S-008
Package Insert
Page 20

4. Using the sprayer:
 - Remove cover from the Nasal Sprayer.
 - Pump the Nasal Sprayer 4 times before using. (Point the Nasal Sprayer up and away from your face when pumping.) *Do not* prime the Nasal Sprayer more than 4 times. Although some medication will spray out, there is enough medication in each ampul to allow you to prepare your sprayer properly and still receive a full dose of Migranal® (dihydroergotamine mesylate, USP) Nasal Spray.
 - Spray once in each nostril. You should not tilt head back or inhale through your nose while spraying.
 - Wait 15 minutes, then spray once in each nostril again.
5. After completing these instructions:
 - Carefully dispose of the Nasal Sprayer containing the ampul and the breaker cap containing the top of the ampul.
 - Load a new Unit Dose Tray into your Assembly Case.
 - Keep the Assembly Case for a maximum of 4 treatments, then discard it along with the Unit Dose Tray.

Important Notes:

- Once a Migranal® (dihydroergotamine mesylate, USP) Nasal Spray ampul has been opened, it must be thrown away after 8 hours.
- You should not sniff or tilt your head back when using Migranal® (dihydroergotamine mesylate, USP) Nasal Spray.

Storing Migranal® (dihydroergotamine mesylate, USP) Nasal Spray

- Keep medication in a safe place away from children.
- Keep Migranal® (dihydroergotamine mesylate, USP) Nasal Spray away from heat and light.
 - Do not expose Migranal® (dihydroergotamine mesylate, USP) Nasal Spray to temperatures over 77°F.
 - Never refrigerate or freeze Migranal® (dihydroergotamine mesylate, USP) Nasal Spray.
- Keep Migranal® (dihydroergotamine mesylate, USP) Nasal Spray components in the Unit Dose Tray.
- Keep the Unit Dose Tray loaded in the Assembly Case.
- Do not keep an opened Migranal® (dihydroergotamine mesylate, USP) Nasal Spray ampul for more than 8 hours.

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

N 20-148/ S-007 S-008
Package Insert
Page 21

Answers to patients' questions about Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray

What if I need help in using my Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray?

If you have any questions or if you need help in opening, putting together, or using Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray, speak to your doctor or pharmacist, or call the Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray Information Line at 1-888-MY-RELIEF (1-888-697-3543).

How much medication should I use and how often?

Each ampul contains one complete dose of Migranal[®] (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.

Why do I have to prime or pump the Nasal Sprayer 4 times before using? 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 still enough medication in each ampul to allow you to prepare your sprayer properly and still receive a full dose of Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray.

Can I load the medication ampul into the Nasal Sprayer so it is ready before I need to use it?

No. The brown (amber) glass ampul 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. However, after each migraine attack, you should load a new plastic Unit Dose Tray containing an unopened Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray ampul and Nasal Sprayer into the Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray Assembly Case, so you will be prepared for your next migraine attack.

Can I reuse my Migranal[®] (dihydroergotamine mesylate, USP) Nasal Sprayer?

No. After completing the full dose, you must carefully dispose of your Migranal[®] (dihydroergotamine mesylate, USP) Nasal Sprayer containing the opened ampul. Each Unit Dose Tray contains a new Nasal Sprayer, an ampul of Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray medication, and a breaker cap on the ampul. But you should keep your Assembly Case and load it with a new Unit Dose Tray after each migraine so you are ready to treat your next migraine attack.

Can I use Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray if I have a stuffy nose, cold, or allergies?

Yes. Migranal[®] (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 Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray.

N 20-148/ S-007 S-008

Package Insert

Page 22

Do I need to sniff the medication when I spray it in my nostril?

No, you should not sniff because Migranal[®] (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 question about Migranal[®] (dihydroergotamine mesylate, USP) Nasal Spray, consult your doctor or pharmacist.

*Trademark of Medical Economics Company, Inc.

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

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

/s/

Russell Katz
7/31/02 09:15:34 AM