



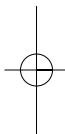
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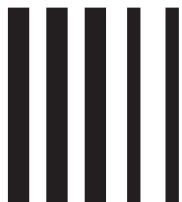
Revisione	Off. di Produzione		Lingua		Distribuzione		Controlli	
	MILANO		USA		VENDITA		USA/93/1366	
Classe	Colore 5		Colore 4		Colore 3		Colore 2	
	FRONTE		NERO		1		476,35 x 297,4	

VIETATA LA MANOMISSIONE - RENDERE DOPO LA STAMPA

05-07-07



## Migranal<sup>®</sup> (dihydroergotamine mesylate, USP) Nasal Spray



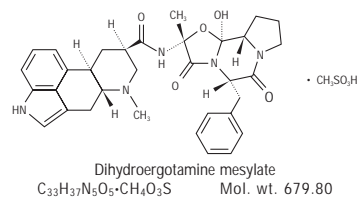
### Migranal<sup>®</sup> (dihydroergotamine mesylate, USP) Nasal Spray

The solution used in Migranal<sup>®</sup> (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<sup>®</sup> is ergotamine hydrogenated in the 9,10 position as the mesylate salt. Migranal<sup>®</sup> is known chemically as ergotaman-3', 6', 18-trione, 9,10-dihydro-12'-hydroxy-2'-methyl-5'- (phenylmethyl)-, (5'a)-, monomethane-sulfonate. Its molecular weight is 679.80 and its empirical formula is C<sub>33</sub>H<sub>33</sub>N<sub>5</sub>O<sub>5</sub>·CH<sub>3</sub>O<sub>2</sub>S. The chemical structure is:



Migranal<sup>®</sup> (dihydroergotamine mesylate, USP) Nasal Spray is provided for intranasal administration as a clear, colorless to faintly yellow solution in an amber glass vial containing:

dihydroergotamine mesylate, USP	4.0 mg
caffeine, anhydrous, USP	10.0 mg
dextrose, anhydrous, USP	50.0 mg
carbon dioxide, USP	qs
purified water, USP	qs 1.0 mL

#### CLINICAL PHARMACOLOGY

##### Mechanism of Action

Dihydroergotamine binds with high affinity to 5-HT<sub>1A</sub> and 5-HT<sub>1D</sub> receptors. It also binds with high affinity to serotonin 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, and 5-HT<sub>2C</sub> receptors, noradrenergic α<sub>2A</sub>, α<sub>2B</sub> and α<sub>1</sub> receptors, and dopamine D<sub>2</sub> and D<sub>3</sub> receptors.

The therapeutic activity of dihydroergotamine in migraine is generally attributed to the agonist effect at 5-HT<sub>1D</sub> receptors. Two current theories have been proposed to explain the efficacy of 5-HT<sub>1D</sub> receptor agonists in migraine. One theory suggests that activation of 5-HT<sub>1D</sub> receptors located on intracranial blood vessels, including those on arterio-venous anastomoses, leads to vasoconstriction, which correlates with the relief of migraine headache. The alternative hypothesis suggests that activation of 5-HT<sub>1D</sub> receptors on sensory nerve endings of the trigeminal system results in the inhibition of pro-inflammatory neuropeptide release. In addition, dihydroergotamine possesses oxytocic properties. (See **CONTRAINDICATIONS**)

##### Pharmacokinetics

##### Absorption

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., dihydroergic 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 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<sup>®</sup> (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<sub>max</sub>, T<sub>max</sub> 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<sup>®</sup> (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<sup>®</sup> (dihydroergotamine mesylate, USP) Nasal Spray compared to those receiving placebo in 3 of the 4 studies (see Tables 1 & 2 and Figures 1 & 2).

Study	Treatment	N	2 hours		4 hours	
			No.	%	No.	%
Study 1	Migranal <sup>®</sup>	105	61%**	70%**		
	Placebo	98	23%	28%		
Study 2	Migranal <sup>®</sup>	103	47%	56%*		
	Placebo	102	33%	35%		

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

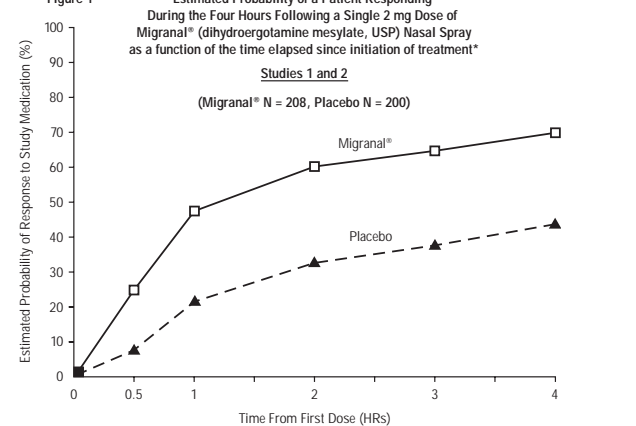
Study	Treatment	N	2 hours		4 hours	
			No.	%	No.	%
Study 3	Migranal <sup>®</sup>	50	32%	48%*		
	Placebo	50	20%	22%		
Study 4	Migranal <sup>®</sup>	47	30%	47%		
	Placebo	50	20%	30%		

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

Comparisons of drug performance based upon results obtained in different clinical trials are never reliable. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment response and the timing of response may be expected to vary considerably from study to study.

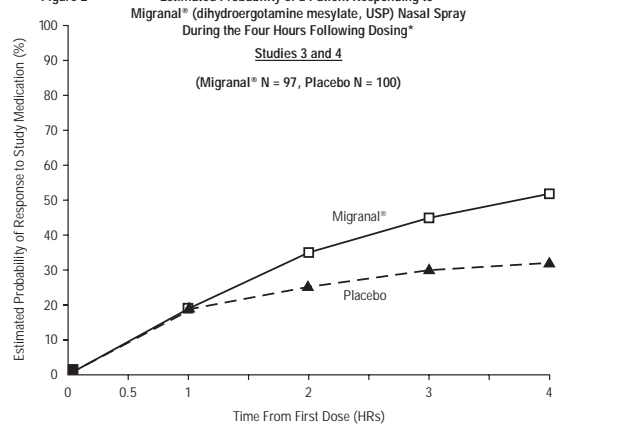
The Kaplan-Meier plots below (Figures 1 & 2) provides an estimate of the probability that a patient will have responded to a single 2 mg dose of Migranal<sup>®</sup> (dihydroergotamine mesylate, USP) Nasal Spray as a function of the time elapsed since initiation of treatment.

Figure 1



\*The figure shows the probability over time of obtaining a response following treatment with Migranal<sup>®</sup> (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.

Figure 2



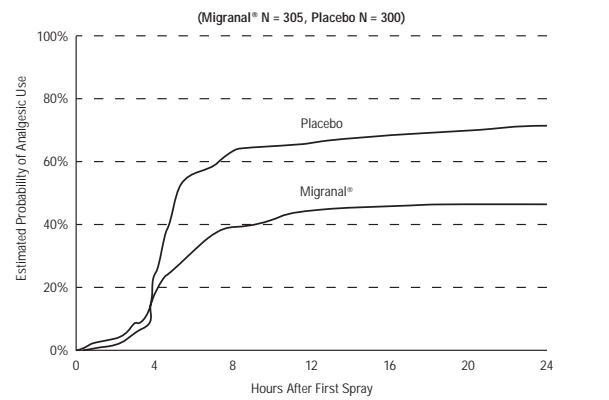
\*The figure shows the probability over time of obtaining a response following treatment with Migranal<sup>®</sup> (dihydroergotamine mesylate, USP) Nasal Spray. Headache response was evaluated on a five-point scale that confounded pain response and restoration of function for "severe" or "incapacitating"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

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<sup>®</sup> (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.

Figure 3  
Estimated Probability of Patients Using Additional Treatments for Migraine Over the 24 Hours Following Either Migranal<sup>®</sup> (dihydroergotamine mesylate, USP) Nasal Spray 2 mg (or placebo)\* (Migranal<sup>®</sup> N = 305, Placebo N = 300)



\*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<sup>®</sup> (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<sup>®</sup> (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<sup>®</sup> (dihydroergotamine mesylate, USP) Nasal Spray.

##### INDICATIONS AND USAGE

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

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

##### CONTRAINDICATIONS

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

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

Migranal<sup>®</sup> (dihydroergotamine mesylate, USP) Nasal Spray, 5-HT<sub>1</sub> agonists (e.g., sumatriptan), ergotamine-containing or ergot-type medications or methysergide should not be used within 24 hours of each other.

Migranal<sup>®</sup> (dihydroergotamine mesylate, USP) Nasal Spray should not be administered to patients with hemiplegic or basilar migraine.

In addition to those conditions mentioned above, Migranal<sup>®</sup> (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<sup>®</sup> (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.

Migranal<sup>®</sup> (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<sup>®</sup> (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: antifungals ketocazole and itraconazole, of 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, fluozazole, 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<sup>®</sup> (dihydroergotamine mesylate, USP) Nasal Spray, should not exceed the dosing guidelines and should not be used for chronic daily administration (see **DOSE AND ADMINISTRATION**).

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

Migranal<sup>®</sup> (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<sup>®</sup> (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 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<sup>®</sup> (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<sup>®</sup> (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<sup>®</sup> (dihydroergotamine mesylate, USP) Nasal Spray, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of Migranal<sup>®</sup> (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<sup>®</sup> (dihydroergotamine mesylate, USP) Nasal Spray.

The systematic approach described above is currently recommended as a method to identify patients in whom Migranal<sup>®</sup> (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<sup>®</sup> (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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> Injection having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

##### Other Vasospasm Related Events

Migranal<sup>®</sup> (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<sup>®</sup> (dihydroergotamine mesylate, USP) Nasal Spray. Migranal<sup>®</sup> (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<sup>®</sup> (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<sup>®</sup> (dihydroergotamine mesylate, USP) Nasal Spray and dihydroergotamine mesylate injection. Migranal<sup>®</sup> (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 5HT<sub>1</sub> agonist in a study evaluating subjects undergoing cardiac catheterization.

##### Local Irritation

Approximately 30% of patients using Migranal<sup>®</sup> (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<sup>®</sup> (dihydroergotamine mesylate, USP) Nasal Spray. Examinations of the nose and throat in a small subset (N = 64) 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<sup>®</sup> (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/m<sup>2</sup>) 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<sup>®</sup> (dihydroergotamine mesylate, USP) Nasal Spray may cause coronary artery vasospasm; patients who experience signs

