WARNING
Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of DIHYDROERGOTAMINE mesylate (Migranal® Nasal Spray) 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 meissel salt. Migranal® is known chemically as ergotaman-3', 6', 18-trione, 8,10-dihydro-12'-hydroxy-2'-methyl-5'- (phenylmethyl)- (5'-, mono)methanesulfonate. Its molecular weight is 679.80 and its empirical formula is C_{33}H_{33}N_{3}O_{9}S-CH_{3}O.

The chemical structure is:

\[
\text{Dihydroergotamine mesylate} \quad \text{C}_{33}\text{H}_{33}\text{N}_{3}\text{O}_{9}\text{S-CH}_{3}\text{O} \quad \text{Mol. wt. 679.80}
\]

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

dihydroergotamine mesylate, USP ........................................ 4.0 mg
caffeine, anhydrous, USP ............................................. 10.0 mg
dextrose, anhydrous, USP ........................................... 50.0 mg
carbon dioxide, USP ................................................ 80.0 liters
purified water, USP ................................................... qs 1.0 mL

CLINICAL PHARMACOLOGY
Mechanisms of Action
Dihydroergotamine binds with high affinity to 5-HT₂A and 5-HT₁D receptors. It also binds with high affinity to serotonin 5-HT₁D, 5-HT₁B, and 5-HT₁A receptors, noradrenaline (α₁A, α₁B, and α₁D), and dopamine D₃ and D₄ receptors. The therapeutic activity of dihydroergotamine in migraine is generally attributed to the agonist effect at 5-HT₁D receptors. Two current theories have been proposed to explain the efficacy of 5-HT₁D receptor agonists in migraine. One theory suggests that activation of 5-HT₁D receptors located on intracranial blood vessels, including those on sympathetic and parasympathetic neurons, leads to vasoconstriction, which correlates with the relief of migraine headache. The alternative hypothesis suggests that activation of 5-HT₁D receptors on sensory nerve endings of the trigeminal system results in the inhibition of pro-inflammatory neuropeptide release. In addition, dihydroergotamine possesses onxytocic properties. (See CONTRAINDICATIONS and WARNINGS)

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 the 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 metabolites, β- and δ-hydroxydihydroergotamine, exhibit affinity equivalent to its parent for 5-HT₂C/5-HT₆, and 5-HT₁A receptors and demonstrate equivalent potency in several vasoconstrictor activity models, in vivo and in vitro. The other metabolites, i.e., dihydrolysergic acid, dihydroxylysergic acid, 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 IV and IM 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 IM 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® (dihydroergotamine mesylate, USP) Nasal Spray was administered in patients with severely impaired hepatic or renal function. (See CONTRAINDICATIONS and WARNINGS)

Interactions
The pharmacokinetics of dihydroergotamine did not appear to be significantly affected by the concomitant use of a local vasoconstrictor (e.g., fenoxazoline).

Multiple oral doses of the β-adrenoceptor antagonist propranolol, used for migraine prophylaxis, had no significant influence on the Cmax, Tmax or AUC of dihydroergotamine doses up to 4 mg. Pharmacokinetic interactions have been reported in patients treated orally with other ergot alkaloids (e.g., increased levels of ergotamine) and macrolide antibiotics, principally troleandomycin, presumably due to inhibition of cytochrome P450 3A3 metabolism of the alkaloids by troleandomycin.

Dihydroergotamine has also been shown to be an inhibitor of cytochrome P450 3A4. CYP 3A4 and rare reports of ergotism have been obtained from patients treated with dihydroergotamine and macrolide antibiotics (e.g., troleandomycin) in combination, and in patients treated with dihydroergotamine and protease inhibitors (e.g., ritonavir), presumably due to inhibition of cytochrome P450 3A4 metabolism of ergotamine (See CONTRAINDICATIONS). No pharmacokinetic interactions involving other cytochrome P450 isozymes 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 conducted in the U.S. The patient population for the trials was predominately female (81%) and Caucasian (95%) with a mean age of 39 years (range 18 to 60 years). Patients treated at 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).

Chronic oral administration of diltiazem hydrochloride to patients in doses of up to 540 mg/day has resulted in small increases in PR interval, and on occasion produces abnormal prolongation (see WARNINGS).

Hypertension. In a randomized, double-blind, parallel group, dose-response study involving 478 patients with essential hypertension, evening doses of CARIZEM LA 120, 240, 360, and 540 mg were compared to placebo and to 360 mg administered in the morning. The mean reductions in diastolic blood pressure by ABPM at roughly 24 hours after the morning (4 AM to 8 AM) evening (6 PM to 10 PM) administration (i.e., the time corresponding to expected trough serum concentration) are shown in the table below:

<table>
<thead>
<tr>
<th>Study</th>
<th>Migranal®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2 hours</td>
<td>4 hours</td>
</tr>
<tr>
<td>Study 1</td>
<td>105</td>
<td>61%</td>
</tr>
<tr>
<td>Placebo</td>
<td>98</td>
<td>23%</td>
</tr>
</tbody>
</table>

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

Table 1: Studies 1 and 2: Percentage of patients with headache response* 2 and 4 hours following a single treatment of study medication [Migranal® (dihydroergotamine mesylate, USP) Nasal Spray or Placebo]

<table>
<thead>
<tr>
<th>Study</th>
<th>Migranal®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2 hours</td>
<td>4 hours</td>
</tr>
<tr>
<td>Study 3</td>
<td>50</td>
<td>32%</td>
</tr>
<tr>
<td>Placebo</td>
<td>50</td>
<td>20%</td>
</tr>
</tbody>
</table>

| Study 4   | 47        | 30%     | 47%     |
| Placebo   | 50        | 20%     | 30%     |

*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.

Comparisons of drug performance based upon results obtained in different clinical trials are not 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.

Figure 1: Estimated Probability of a Patient Responding During the Four Hours Following a Single 2 mg Dose of Migranal® (dihydroergotamine mesylate, USP) Nasal Spray

- a function of the time elapsed since initiation of treatment

<table>
<thead>
<tr>
<th>Study 1 and 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Migranal® N = 209, Placebo N = 200)</td>
</tr>
</tbody>
</table>

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 period of organogenesis resulted in decreased fetal body weights and/or skeletal ossification at doses to a pregnant woman. Dihydroergotamine possesses oxytocic properties and, therefore, should not be used during pregnancy.

**INDICATIONS AND USAGE**

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

**CONTRAINDICATIONS**

There have been 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. Use of potent CYP 3A4 inhibitors (ritonavir, nefazodone, indinavir, erythromycin, clarithromycin, troleandomycin, ketoconazole, itraconazole) with dihydroergotamine is therefore contraindicated.

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 patients who have clinical symptoms or findings consistent with coronary artery vasospasm including Prinzmetal’s variant angina. (See WARNINGS)

**WARNINGS**

**CYP 3A4 Inhibitors**

Dihydroergotamine mesylate should not be used with peripheral and central vasoconstrictors because of the risk of vasospasm. Migranal® (dihydroergotamine mesylate, USP) Nasal Spray is contraindicated in patients who have complete heart block, sick sinus syndrome, or uncontrolled hypertension. Migranal® (dihydroergotamine mesylate, USP) Nasal Spray should be used with caution in patients with partial heart block, prolonged QT interval, or uncontrolled hypertension.

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

Migranal® (dihydroergotamine mesylate, USP) Nasal Spray should be given to patients with a history of coronary artery disease or who have 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., hypercholesterolemia, smoking, diabetes, hypertension, strong family history of CAD, female patients who are surgically or physiologically postmenopausal, or males aged over 40 years unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery disease). The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. (See DRUG-ASSOCIATED CEREBROVASCULAR EVENTS AND FATALITIES)

**Drug-Associated Cerebrovascular Events and Fatalities**

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with dihydroergotamine mesylate and/or associated vasospastic phenomena. (See WARNINGS) Because cerebrovascular events can occur in the absence of clinical symptoms, consideration should be given to obtaining an electrocardiogram (EKG) at the first occasion of use an electrocardiogram (ECG) during the interval immediately following 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 been observed for two hours after dosing with Migranal® (dihydroergotamine mesylate, USP) Nasal Spray. Consideration of the extent of use of dihydroergotamine mesylate in patients with migraine headache for the incidence of these events may be predictive of CAD, as described above, undergo periodic cardiovascular evaluation as they continue to use Migranal® (dihydroergotamine mesylate, USP) Nasal Spray.

**Local Irritation**

Local irritation at the site of administration has been reported in patients using Migranal® (dihydroergotamine mesylate, USP) Nasal Spray. Patients should be instructed to use the nasal spray with a clean, dry object such as a soft cotton tipped applicator or swab.
migraine headache and not reported at an equal incidence by placebo-treated patients were rhinitis, depression, elective surgery, somnolence, allergy, vomiting, hypotension, and paraesthesia.


**Incidence in Controlled Clinical Trials**

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 and WARNINGS).

**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 beta blockers, there have been reports that propranolol may potentiate the vasoconstrictive effect of ergotamine by blocking the vasodilating property of erginine.

**Nicotine**

Nicotine may provoke vasospasm 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.

**SSRIs**

Some SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported to cause an increase in plasma levels of dihydroergotamine mesylate when used in combination with ergot derivatives (see WARNINGS).

**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**

Migranal (dihydroergotamine mesylate, USP) Nasal Spray is excreted in human milk, but there are no data on the concentration of dihydroergotamine in the milk of mothers who are breast feeding. Ergot alkaloids are known to inhibit prolactin. It is likely that Migranal (dihydroergotamine mesylate, USP) Nasal Spray may lower maternal prolactin levels, but the clinical significance of this is unknown. It is not known whether Migranal (dihydroergotamine mesylate, USP) Nasal Spray has the potential to cause fetal harm when administered to a pregnant woman. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**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 may lower maternal prolactin levels, but the clinical significance of this is unknown. It is not known whether Migranal (dihydroergotamine mesylate, USP) Nasal Spray has the potential to cause fetal harm when administered to a pregnant woman. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**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. Since patients over age 65 were excluded from the controlled clinical trials, it is not known whether they would respond differently than those patients receiving placebo.

**Adverse Reactions**

**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 observed for signs of CAD or frank myocardial infarction. Patients who present with or develop signs and symptoms suggestive of angina following an increase in the dose of Migranal (dihydroergotamine mesylate, USP) Nasal Spray, or with signs of arrhythmia should have their frequency of dosing reduced or Migranal (dihydroergotamine mesylate, USP) Nasal Spray discontinued immediately.

**Respiratory System**

Rhinitis: 26% 7%

Pharyngitis: 3% 1%

Sinusitis: 1% 1%

**Gastrointestinal System**

Nausea: 10% 4%

Vomiting: 4% 1%

Diarrhea: 2% 2%

**Special Senses, Other**

Application Site: Altered Sense of Taste

Application Site Reaction: Flushing, rash, pruritus, edema, cold clammy skin

**Body as a Whole, General**

Hot Flashes: 1% 1%

Fatigue: 1% 1%

Dizziness: 1% 1%

**Musculoskeletal System**

Mouth Dry: 1% 1%

**Skin and Appendages**

Infrequent: petechia, pruritus, rash, cold clammy skin; Rare: popular rash, urticaria, herpes simplex.

**Female Reproductive System**

Menstrual: Infrequent: cramps, myalgia, muscular weakness, dysmenorrhea; Rare: arthralgia, involuntary muscle contractions, rigidity.

**Central and Peripheral Nervous System**

Infrequent: confusion, tremor, hypertension, vertigo, Rare: speech disorder, hyperventilation, stupor, abnormal gait, aggravated migraine.

**Autonomic Nervous System**

Infrequent: increased sweating.

**Skin**

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, asthenia, 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, chills, pleural pain, epistaxis.

**Urine System**

Infrequent: increased frequency of micition, cystitis.

**Excessive Use**

Excessive use of Migranal (dihydroergotamine mesylate, USP) Nasal Spray may result in peripheral vasoconstriction, 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).

**Actions**

Migranal (dihydroergotamine mesylate, USP) Nasal Spray is an ergot alkaloid. This formulation is in the form of a 0.8 mg/ml solution of dihydroergotamine mesylate in water for injection. Migranal (dihydroergotamine mesylate, USP) Nasal Spray is to be avoided. Excessive doses of dihydroergotamine may result in peripheral signs and symptoms of ergotism.

**Pharmacology**

Excessive use of Migranal (dihydroergotamine mesylate, USP) Nasal Spray is associated with diminished or absent peripheral pulses; respiratory depression; an increase and/or decrease in blood pressure; confusion; headache; chest pain; abdominal pain; dyspepsia; dysphagia; hiccup; and vomiting; diarrhea; and increased salivation, esophagospasm.

**Pharmacokinetics**

The current available data have not demonstrated drug abuse or psychological dependence with Migranal (dihydroergotamine mesylate, USP) Nasal Spray.

**Drug Interactions**

Migranal (dihydroergotamine mesylate, USP) Nasal Spray contains dihydroergotamine mesylate in a nasal formulation. The current available data have not demonstrated drug abuse or psychological dependence with Migranal (dihydroergotamine mesylate, USP) Nasal Spray.

**Contraindications**

Migranal (dihydroergotamine mesylate, USP) Nasal Spray should not be used with peripheral vasoconstrictors because the combination may cause synergistic elevation of blood pressure.

**Adverse Events**

**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 the causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to denote adverse events, etc., limit the value of the quantitative frequency estimates provided.

**Frequency of Adverse Events**

The incidence of adverse events was determined 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 meaningful, or 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 events are defined as those occurring in 1/10 to 1/100 patients; infrequent 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. The following table lists adverse events reported in association with the use of Migranal (dihydroergotamine mesylate, USP) Nasal Spray.
DOSE AND ADMINISTRATION
The solution used in Migranal® (dihydroergotamine mesylate, USP) Nasal Spray is available as a clear, colorless to faintly yellow solution. Each mL contains 5.0 mg (0.5 mL amber color container glass vial), USP Migranal® (dihydroergotamine mesylate, USP) Nasal Spray is provided as a package of 8 units, administration instruction sheet, and one package insert. Each unit consists of one vial and one sprayer.

HOW SUPPLIED
Migranal® (dihydroergotamine mesylate, USP) Nasal Spray is available in a 4 mg/mL formulation, for intranasal use and must not be injected. It must be swallowed whole and not chewed or crushed. 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 administration instructions) Once the nasal spray applicator has been prepared, it should be discarded (with any remaining drug in opened vial) after 6 hours.

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

Once the nasal spray applicator has been prepared, it should be discarded (with any remaining drug in opened vial) after 6 hours.

The safety of doses greater than 3.0 mg in a 24 hour 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, call your doctor, hospital, emergency department, or nearest poison control center immediately.

To use the Migranal® (dihydroergotamine mesylate, USP) Nasal Spray
1. Use available training materials. 
2. Read and follow the instructions in the administration instructions which are provided with the Migranal® (dihydroergotamine mesylate, USP) Nasal Spray package before attempting to use the product.
3. 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.
4. Using the sprayer:
   - Remove cap from spray unit. Holding the vial upright, point nasal sprayer away from face and pump 4 times before using. DO NOT PUMP MORE THAN 4 TIMES. (Although some medication will spray out, there is enough medication in each vial to allow you to prepare your nasal spray pump properly and still receive a full treatment of Migranal®.)
   - Spray into each nostril. Repeat, if necessary, until symptoms improve.
   - After completing these instructions: Carefully dispose of the nasal spray pump with the vial.

Important Notes:
• Once a Migranal® (dihydroergotamine mesylate, USP) Nasal Spray vial has been opened, it must be thrown away.
• Storing Migranal® (dihydroergotamine mesylate, USP) Nasal Spray:
  - Store in a cool, dry place. Keep the Migranal® (dihydroergotamine mesylate, USP) Nasal Spray away from heat and light.
  - Do not expose Migranal® (dihydroergotamine mesylate, USP) Nasal Spray to temperatures over 100°F (38°C).
  - Never refrigerate or freeze Migranal® (dihydroergotamine mesylate, USP) Nasal Spray.
  - Do not keep an opened Migranal® (dihydroergotamine mesylate, USP) Nasal Spray vial for more than 8 hours.

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

Answers to patients’ questions about 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) or visit www.migranal.com.

How much medication should I use and how often?
Each vial 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 4 sprays in 1 hour. You may need to add a second sprayer.

Can I reuse my Migranal® (dihydroergotamine mesylate, USP) Nasal Spray?
No. The Migranal® (dihydroergotamine mesylate, USP) Nasal Spray, should not be reused or refilled. Each vial contains one complete dose of Migranal® (dihydroergotamine mesylate, USP) Nasal Spray.

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.

Do I need to store the medication in my medicine cabinet?
No. You should not store Migranal® (dihydroergotamine mesylate, USP) Nasal Spray at temperatures over 100°F (38°C).

To REMEMBER YOUR DOCTOR IF YOU HAVE ANSWERED YES TO ANY OF THESE QUESTIONS BEFORE USING MIGRAL® (DIHYDROERGOTAMINE MESYLATE, USP) NASAL SPRAY
Side Effects To Watch Out For
In clinical trials, most patients who have used Migranal® (dihydroergotamine mesylate, USP) Nasal Spray without serious side effects. You may experience some nasal congestion or irritation, altered taste/smell, sore throat, nasal and nasal cavity discomfort, headache, dizziness, or flushing. 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 valve fibrosis.

Important questions to consider before using Migranal® (dihydroergotamine mesylate, USP) Nasal Spray
• Are you pregnant or nursing?
• Have any disease affecting your heart, arteries, or circulation?
• Are you taking protease inhibitors or macrolide antibiotics.
• Are you smoking?
• Have you ever had to stop taking this or any other medication because of an allergy or bad reaction?
• Are you sexually active and not using birth control? Are you breast feeding?
• 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?
• Have you had 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 are you 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? You may have:
• 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
• 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.

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