PRODUCT MONOGRAPH

MIGRANAL®
(Dihydroergotamine Mesylate)

Nasal Spray
4 mg/mL

$5HT_1$ Receptor Agonist
Migraine Therapy

Sterimax Inc.
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March 01, 2004

Control # 089992

PRODUCT MONOGRAPH

NAME OF DRUG

PrMIGRANAL®

(Dihydroergotamine mesylate)

4 mg/mL

Nasal Spray

THERAPEUTIC CLASSIFICATION

Migraine Therapy

PHARMACOLOGICAL CLASSIFICATION

5-HT_1 Receptor Agonist

ACTIONS AND CLINICAL PHARMACOLOGY

MIGRANAL (dihydroergotamine mesylate) displays agonist activity at the 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors, which, by reducing 5-HT neuronal function and/or contracting elements of the cranial vasculature and/or suppressing neurogenic inflammation, is believed to underlie its anti-migraine efficacy. It also displays affinity for the 5-HT_{1A} and 5-HT_{1C} receptors and antagonistic activity at the 5-HT_2 subtype. Dihydroergotamine displays blocking actions at alpha adrenoreceptors, with a direct stimulating effect on the smooth muscle of peripheral blood vessels. Its tonic effect on capacitance vessels (veins) is particularly pronounced, compared to its effects on resistance vessels (arterioles). Dihydroergotamine differs from ergotamine by being more potent with respect to its adrenergic blocking actions and less potent with respect to its capacity to produce arterial vasoconstriction, but it maintains a marked venoconstrictor effect.

Dihydroergotamine reduces the incidence and degree of migraine-associated nausea, photophobia, and phonophobia.

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

Intranasally administered dihydroergotamine is rapidly absorbed in a dose-independent manner (t_{max} = approximately 45 minutes). Significant relief of migraine begins within approximately 30 minutes following nasal administration). Once pain is relieved, the incidence of return of pain within 24 hours is low. The bioavailability of dihydroergotamine administered intranasally is 43%.

Dihydroergotamine is 93% bound to plasma proteins and has a steady-state volume of distribution of about 800 L. The parent drug constitutes 70 to 80% of plasma concentrations of drug-related materials. The nasal spray form of dihydroergotamine, like most parenteral dose routes, is not subject to first-pass hepatic metabolism. The total body clearance is about 1.5 L/min., reflecting mainly a hepatic clearance. Plasma elimination of dihydroergotamine is biphasic with a mean terminal half-life of 10 hours. The major route of excretion is via the bile in the faeces. After intranasal administration, the urinary recovery of parent drug amounts to about 2% of the dose.

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 CLINICAL USE

MIGRANAL® (dihydroergotamine mesylate nasal spray) is indicated for the acute treatment of migraine headaches, with or without aura in adults.

MIGRANAL is not indicated for prophylactic therapy or for the management of hemiplegic, basilar or ophthalmoplegic migraine (see **CONTRAINDICATIONS**). Safety and efficacy have not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

MIGRANAL (dihydroergotamine mesylate nasal spray) is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias (especially tachycardias). In addition, patients with other significant underlying cardiovascular diseases (eg. atherosclerotic disease, congenital heart disease) should not receive MIGRANAL. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal's variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks (TIAs). Peripheral vascular disease includes, but is not limited to, ischemic bowel disease, or Raynaud's syndrome (see WARNINGS).

There have been a few reports of serious adverse events associated with the coadministration of dihydroergotamine and potent CYP 3A4 inhibitors, such as HIV protease or reverse transcriptase inhibitors, macrolide antibiotics and azole antifungals, 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).

Because MIGRANAL can give rise to increases in blood pressure, it is contraindicated in patients with uncontrolled or severe hypertension (see WARNINGS).

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because MIGRANAL may also cause coronary vasospasm and these effects may be additive, the use of MIGRANAL within 24 hours before or after treatment with other $5HT_1$ receptor agonists, or ergotamine-containing drugs or their derivatives (eg. methysergide) is contraindicated.

MIGRANAL is contraindicated in patients with hemiplegic, basilar, or ophthalmoplegic migraine.

MIGRANAL is contraindicated in patients with severe renal impairment (creatinine clearance <15 mL/min).

MIGRANAL is contraindicated in patients with severe hepatic impairment (Child-Pugh grade C)

MIGRANAL is contraindicated in patients with hypersensitivity to dihydroergotamine, ergot alkaloids or any component of the formulation.

In addition to those conditions mentioned above, MIGRANAL is also contraindicated in patients with known peripheral arterial disease, septic conditions, shock, obliterative vascular disease, temporal arteritis, and following vascular surgery.

Dihydroergotamine possesses oxytocic properties and, therefore, should not be administered during pregnancy. It is likely that dihydroergotamine is excreted in breast milk. MIGRANAL is therefore contraindicated for nursing mothers.

Dihydroergotamine mesylate should not be used with peripheral and central vasoconstrictors (other ergot alkaloids, sumatriptan and other 5-HT_1-receptor agonists) **because the combination may result in additive or synergistic elevation of blood pressure.**

WARNINGS

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)

MIGRANAL 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 HIV protease and reverse transcriptase inhibitors, azole antifungals 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.

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 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 has been associated with transient chest pain and tightness which may resemble angina pectoris. In rare cases, the symptoms have been identified as being the likely result of coronary vasospasm or myocardial ischemia. Rare cases of serious coronary events or arrhythmia have occurred following use of another 5-HT_1 agonist. MIGRANAL should not be given to patients who have documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS).

It is strongly recommended that MIGRANAL 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 should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD who are determined to have a satisfactory cardiovascular evaluation, the first dose of MIGRANAL should be administered in the setting of a physician's office or similar medically staffed and equipped facility. 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 , in these patients with risk factors. However, an absence of drug-induced cardiovascular effects on the occasion of the initial dose does not preclude the possibility of such effects occurring with subsequent administrations.

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

If symptoms consistent with angina occur after the use of MIGRANAL, ECG evaluation should be carried out to look for ischemic changes.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to MIGRANAL.

Cardiac Events and Fatalities associated with 5-HT_1 Agonists:

In special cardiovascular studies (see below), another 5-HT_1 agonist has been shown to cause coronary vasospasm. MIGRANAL has not been tested under similar conditions, however, owing to the common pharmacodynamic actions of 5-HT_1 agonists, the possibility of cardiovascular effects of the nature described below should be considered for all agents of this class. 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 and other 5-HT_1 agonists. Considering the extent of use of dihydroergotamine and other 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low.

Cerebrovascular Events and Fatalities associated with 5-HT_1 Agonists

Cerebral haemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with dihydroergotamine mesylate injection and other 5-HT_1 agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the dihydroergotamine mesylate 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, haemorrhage, transient ischemic attack).

Special Cardiovascular Pharmacology Studies with another 5-HT_1 Agonist:

In subjects (n=10) with suspected coronary artery disease undergoing angiography, a 5-HT_1 agonist at a subcutaneous dose of 1.5 mg produced an 8% increase in aortic blood pressure, an 18% increase in pulmonary artery blood pressure, and an 8% increase in systemic vascular resistance. In addition, mild chest pain or tightness was reported by four subjects. Clinically significant increases in blood pressure were experienced by three of the subjects (two of whom also had chest pain/discomfort). Diagnostic angiogram results revealed that 9 subjects had normal coronary arteries and 1 had insignificant coronary artery disease. In an additional study with this same drug, migraine patients, (n=35) free of cardiovascular disease were subjected to assessments of myocardial perfusion by positron emission tomography while receiving a subcutaneous 1.5 mg dose in the absence of a migraine attack. Reduced coronary vasodilatory reserve (~10%), increased coronary resistance (~20%), and decreased hyperaemic myocardial blood flow (~10%) were noted. The relevance of these findings to the use of the recommended oral dose of this 5-HT_1 agonist is not known.

Other Vasospasm Related Events

Dihydroergotamine and other 5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. This action appears to be dose-related. These reactions are manifested by intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia (e.g., muscle pains, numbness, coldness and pallor or cyanosis of the digits), angina or unusual syndromes, such as mesenteric ischemia. Consequently, MIGRANAL® (dihydroergotamine mesylate 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 and DHE (dihydroergotamine) injection. MIGRANAL is contraindicated in patients with uncontrolled or severe hypertension.

The solution used in MIGRANAL was developed especially for intranasal administration and **must not be injected**.

PRECAUTIONS

MIGRANAL is only indicated for the treatment of acute migraine attacks and not for prevention.

MIGRANAL should be used with caution in patients with rhinitis, nasal congestion and allergic rhinitis.

Patients with mild to moderate hepatic impairment, especially cholestatic patients should be appropriately monitored.

Cardiovascular: Chest tightness/pain has been reported after administration of MIGRANAL. Because $5HT_1$ agonists may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following MIGRANAL should be evaluated for the presence of CAD or a predisposition to variant angina before receiving additional doses, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following naratriptan administration should be evaluated for atherosclerosis or predisposition to vasospasm (see **CONTRAINDICATIONS** and **WARNINGS**).

Neurologic Conditions: Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine or who experience a headache that is atypical for them. There have been rare reports where patients received $5HT_1$ agonists for severe

headaches that were subsequently shown to have been secondary to an evolving neurologic lesion. For newly diagnosed patients or patients presenting with atypical symptoms, the diagnosis of migraine should be reconsidered if no response is seen after the first dose of MIGRANAL.

Drug Interactions:

Although formal studies have not been done, the concomitant use of oral contraceptives by female patients does not appear to influence the disposition of MIGRANAL® (dihydroergotamine mesylate nasal spray).

MIGRANAL should not be used with vasoconstrictors because the combination may cause a further elevation of blood pressure.

Concurrent use of vasoconstrictor agents including ergotamine or other ergot alkaloids, sumatriptan and other 5-HT_1-receptor agonists and nicotine may enhance the risk of vasoconstriction. Because there is a theoretical basis for these effects being additive, ergot-containing or ergot-type medications and nicotine are contraindicated within 24 hours of MIGRANAL administration (see CONTRAINDICATIONS).

Although there have been reports that propranolol may potentiate the vasoconstrictive action of ergotamine by synergism upon ß-blockade, the results of a limited clinical study (n=8) did not indicate a safety problem associated with the administration of MIGRANAL in subjects already receiving propranolol. Caution is required with the combination of a β-adrenergic blocking agent and dihydroergotamine in patients with impaired peripheral circulation.

CYP 3A4 Inhibitors (See also **CONTRAINDICATIONS and WARNINGS**)

The concomitant use of cytochrome P450 3A (CYP3A) inhibitors such as macrolide antibiotics (e.g. troleandomycin, erythromycin, clarithromycin), HIV protease or reverse transcriptase inhibitors (e.g.

ritonavir, indinavir, nelfinavir, delavirdine) or azole antifungals (e.g. ketoconazole, itraconazole, voriconazole) and MIGRANAL must be avoided (see CONTRAINDICATIONS), since this can result in an elevated exposure to dihydroergotamine and ergot toxicity(vasospasm and ischemia of the extremities and other tissues). Dihydroergotamine has also been shown to be an inhibitor of CYP3A. No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

Weakness, hyperreflexia and incoordination have been reported rarely when 5-HT_1 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 or DHE injection.

Fibrotic Complications:

Patients with a history of drug induced fibrotic disorders such as retroperitoneal and pleural fibrosis, should be monitored with caution (see also **WARNINGS**: Fibrotic Complications).

Pediatric Use:

Safety and effectiveness of MIGRANAL® (dihydroergotamine mesylate nasal spray) in children under 16 years of age have not been established.

Use in Elderly:

Experience with the use of MIGRANAL in patients aged over 65 years is limited.

Use in Pregnancy: Dihydroergotamine possesses oxytocic properties and, therefore, should not be administered during pregnancy. (See **CONTRAINDICATIONS**)

Nursing Mothers:

It is likely that dihydroergotamine is excreted in human milk, although it is not known at which concentration, while it is known that ergotamine is excreted in breast milk and may cause vomiting, diarrhea, weak pulse and unstable blood pressure in breastfed infants. Because of the potential for these serious adverse events in breastfed infants, nursing mothers should not use MIGRANAL® (dihydroergotamine mesylate nasal spray) (see **CONTRAINDICATIONS**).

Information for the Patient:

Currently available data have not demonstrated drug abuse and psychological dependence with MIGRANAL® (dihydroergotamine mesylate nasal spray). However, due to the chronicity of migraines, patients should be advised not to exceed recommended dosages.

Patients should be advised to report immediately to the physician 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.

Patients should be advised of the importance of priming the applicator (pump 4 times) prior to administration to ensure correct dosage. No more than four sprays (2 mg) of MIGRANAL should be administered for any single migraine headache attack. No more than eight sprays of MIGRANAL should be administered during any 24 hour period. The maximum weekly dosage is 24 sprays of MIGRANAL (12 mg) (See **DOSAGE AND ADMINISTRATION**.)

Administration of MIGRANAL should not exceed the dosing guidelines and should not be used for chronic daily administration (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The most commonly reported adverse events associated with the use of MIGRANAL® (dihydroergotamine mesylate nasal spray) in placebo-controlled, double-blind studies for the treatment of migraine headaches, and not reported at an equivalent incidence by placebo-treated patients, were rhinitis (which includes reports of all nasal-related adverse reactions), nausea, vomiting, taste disturbance, diarrhea, pharyngitis, dizziness and dose dependent application site reactions such as runny and stuffy nose, and flushing. Other adverse reactions include hypersensitivity reactions (such as skin rash, face oedema, urticaria and dyspnea). In clinical trials these events were transient and self-limiting, and generally did not result in patient drop-out. The following table lists the adverse events experienced at incidences greater than 1%.

Adverse Events Reported in Double-Blind Placebo Controlled Studies for the Treatment of Migraine Headaches (Reported at Incidences ≥ 1% and occurred more frequently than in the placebo group)

Adverse Reactions According to Body System	Rate of Occurrence (%) MIGRANAL (N=597)	Rate of Occurrence (%) Placebo (N=631)
Central Nervous System		
Dizziness	4	2
Somnolence	3	2
Paraesthesia	2	2
Fatigue	1	1
Asthenia	1	0
Gastrointestinal System		
Nausea	10	4
Taste disturbance	8	1
Vomiting	4	1
Diarrhea	2	<1
Respiratory System		
Rhinitis[1]	26	7
Application site reaction	6	2
Pharyngitis	3	1
Sinusitis	1	1
Musculo-Skeletal System		
Stiffness	1	<1
Autonomic Nervous System		
Hot Flushes	1	<1
Dry mouth	1	1

[1] Rhinitis includes reports of nasal/nose congestion, nose dryness, nose edema, rhinitis, rhinorrhea and excessive sneezing.

In a few patients who have taken oral dihydroergotamine continuously over years, development of fibrotic changes, in particular of the pleura and the retroperitoneum, has been observed. Fibrotic complications have been reported in association with long term use of injectable dihydroergotamine mesylate (see **WARNINGS**: Fibrotic Complications).

Chest tightness/pain was seen in earlier studies although the incidence was less than 1% and a causal relationship was not established.

In a few patients, paresthesia (e.g. numbness, tingling) in the fingers and toes, and symptoms of myocardial ischemia have been reported. In rare cases, vascular spasms may occur, particularly in the lower extremities. If signs of vascular spasms are observed, MIGRANAL should be discontinued and treatment with a peripheral vasodilator initiated (see SYMPTOMS AND TREATMENT OF OVERDOSAGE).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been no reports of acute overdosage with MIGRANAL® (dihydroergotamine mesylate nasal spray). The symptoms of an acute oral dihydroergotamine overdose are similar to those of an ergotamine overdose, although there is less pronounced nausea and vomiting with dihydroergotamine. These symptoms include the following: peripheral signs and symptoms of vasospasm (e.g. 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.

The treatment of an overdosage is symptomatic under close monitoring of the cardiovascular and respiratory systems. Treatment includes discontinuation of the drug, local application of warmth to the affected area and nursing care to prevent tissue damage; in case of severe vasospasms, vasodilators should be administered (e.g. Sodium nitroprusside, phentolamine or dihydralazine). In the case of coronary constriction, appropriate treatment such as nitroglycerin should be initiated.

DOSAGE AND ADMINISTRATION

MIGRANAL Nasal Spray is recommended only for the acute treatment of migraine attacks. MIGRANAL should not be used prophylactically.

The solution used in MIGRANAL Nasal Spray 4 mg/mL is intended for intranasal spray and must not be injected.

Prior to administration of MIGRANAL® (dihydroergotamine mesylate nasal spray) the sprayer must be primed (pumped 4 times in the air) (See PATIENT INFORMATION SECTION).

For best results, treatment should be initiated at the first symptom or sign of an attack. However, MIGRANAL can be used at any stage of a migraine attack. Each spray delivers 0.5 mg of MIGRANAL.

ADULTS:

The usual dosage required to obtain optimal efficacy and lasting relief is a total dosage of four sprays (corresponding to the use of one bottle) of MIGRANAL. At the first sign or symptoms of a migraine headache, or as early as possible after the onset of headache pain, one spray of MIGRANAL® (dihydroergotamine mesylate nasal spray) should be administered into each nostril (total of two sprays). If the condition has not sufficiently improved approximately fifteen minutes later, or to obtain optimal efficacy, an additional spray of MIGRANAL should be administered to each nostril (total of additional two sprays). **Once the sprayer has been prepared, it must be discarded with any remaining drug after 8 hours.**

In order to let the drug be absorbed through the skin in the nose, ***patients should not inhale deeply*** *through the nose while spraying or immediately after spraying.*

Significant relief of migraine begins within approximately 30 minutes following nasal administration of MIGRANAL.

No more than one bottle (four sprays) should be administered for any single migraine attack. An interval of at least 24 hours should be observed before treating another migraine attack with MIGRANAL or any drug containing dihydroergotamine or ergotamine. No more than two bottles (eight sprays) should be administered during any 24 hour period. The maximum weekly dosage is six bottles (24 sprays) of MIGRANAL. Once pain is relieved, the incidence of pain return within 24 hours (migraine recurrence) is low.

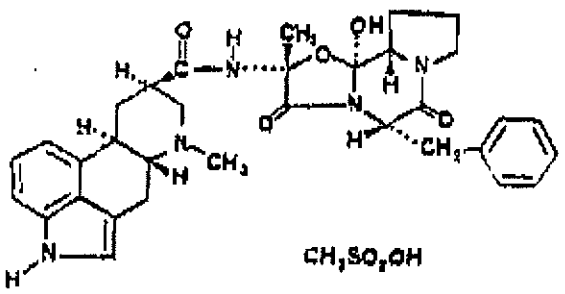
MIGRANAL does not need to be administered with an antiemetic, as is recommended with the parenteral form of dihydroergotamine mesylate, since the administration of the nasal spray form is not associated with nausea and vomiting to the same extent as the parenteral form.

PHARMACEUTICAL INFORMATION

Trade Name: MIGRANAL®

Common Name: 9-10-Dihydro-12'-hydroxy-2'-methyl-5'α (phenylmethyl) ergotaman -3', 6', 18-trione monomethanesulfonate

Structural Formula:



Molecular Formula: $C_{33}H_{37}N_5O_5 \cdot CH_4SO_3$

Molecular Weight: 679.8

Description: White or off-white, fine, crystalline, hygroscopic powder. Moderately soluble in water.

pK_a in ethanol-water (1:1): 6.35 ± 0.05

pH in solution: 4.4 - 5.4

Dihydroergotamine mesylate melts with strong decomposition between 220°C and 240°C.

Composition of MIGRANAL®:

Each bottle of MIGRANAL® contains 4.0 mg dihydroergotamine mesylate USP as well as the following non-medicinal ingredients: anhydrous caffeine, carbon dioxide, anhydrous dextrose, and purified water.

Storage Requirements:

MIGRANAL should be stored at room temperature (15-25 °C).

AVAILABILITY OF DOSAGE FORM

MIGRANAL® (dihydroergotamine mesylate nasal spray) is available as a clear, colourless to faintly yellow solution, in an amber glass bottle. MIGRANAL is provided as a package of three units, each unit consisting of one bottle and one sprayer.

INFORMATION FOR THE PATIENT

Keep this information handy. Read this now, but prepare the sprayer only when you have a migraine attack. Contains medication to treat one migraine. (4 sprays as instructed ensures optimal efficacy and lasting relief). Before using MIGRANAL® (dihydroergotamine mesylate nasal spray) for the first time, please read this information carefully.

Information About Your Medicine:

The name of your medicine is MIGRANAL nasal spray. It can be obtained only by prescription from your doctor. The decision to use MIGRANAL is one that you and your doctor should make jointly, taking into account your individual preferences and medical circumstances. The majority of patients who have taken MIGRANAL have not experienced any significant side effects. However, drugs like MIGRANAL have

caused serious side effects in some patients, especially people with heart or blood vessel disease. If 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), you should tell your doctor, who should evaluate you for heart disease, in order to determine if MIGRANAL is appropriate for you.

Purpose of your medication:

MIGRANAL® (dihydroergotamine mesylate nasal spray) is indicated for the treatment of the acute attack of migraine headaches. **As with other acute migraine medications, MIGRANAL should not be used on a daily basis, as an attempt to prevent or to reduce the number of attacks you experience.** MIGRANAL should not be used to relieve pain other than that associated with migraine headache.

Do not use MIGRANAL if you:

* are pregnant or breastfeeding
* have any disease affecting your heart, arteries or circulation

Important questions to consider before using MIGRANAL:

Please answer the following questions before you use MIGRANAL. **If you answer YES to any of these questions, or are unsure of the answer, you should talk to your doctor before using MIGRANAL.**

* 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 a sexually active female and not using birth control? Are you breastfeeding?
* 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 containing sumatriptan or ergotamine, erythromycin or other macrolide antibiotics, or medications for blood pressure prescribed by your doctor, or any 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?

REMEMBER TO TELL YOUR DOCTOR IF YOU HAVE ANSWERED YES TO ANY OF THESE QUESTIONS.

How to get your MIGRANAL ready for use:

It is best to use MIGRANAL at the beginning of a migraine attack. However, it may be used at any stage of an attack.

Your MIGRANAL package contains: (A) a bottle containing medication to treat one migraine, (B) the sprayer, (C) a blue plastic protective cap, and (D) a transparent plastic protective cover.(ILLUSTRATION 1)

Only start to prepare the sprayer when you have a migraine attack. Slowly lift and bend back the lip of the blue seal to show the rubber stopper. Try not to break the blue seal. (ILLUSTRATION 2)

Completely remove the seal and metal collar in one piece, if possible. If the two should break apart, carefully continue removing the metal collar. **The edge of the collar is sharp - please handle with care.**(ILLUSTRATION 3)

Gently pull the rubber stopper out of the bottle being careful not to spill the contents. (ILLUSTRATION 4)

Gently remove the transparent plastic protective cover from the bottom of the sprayer. Insert the sprayer into the bottle and tighten firmly onto the bottle in a clockwise direction. (ILLUSTRATION 5)

Holding the bottle upright, gently remove the blue plastic protective cap from the top of the sprayer.(ILLUSTRATION 6)

Holding the bottle upright, pump firmly 4 times (not in your nostrils). Some medication will spray out; this is normal and prepares the sprayer for accurate delivery of the medication. (ILLUSTRATION 7)

Hold your head straight.

- Insert the sprayer into one of your nostrils and pump the sprayer once to release the medication.

- Repeat in the other nostril (a total of 2 sprays).
- Don't blow your nose.
- Wait about 15 minutes. If you have not already experienced sufficient relief, or to obtain optimal and long lasting relief, repeat spraying once in each nostril. (ILLUSTRATION 8)

Spraying 4 times as shown (step 8) ensures optimal efficacy and lasting relief. Discard the bottle and sprayer after use.

One complete dose of MIGRANAL is one bottle, which is 4 sprays (2 mg), after priming.

* Do not use more than 2 bottles of MIGRANAL (8 sprays) in a 24 hour period.
* Do not use more than 6 bottles (24 sprays) in one week.
* An interval of 6-8 hours should pass before treating another migraine attack with MIGRANAL

Important notes:

* The chance of pain returning within 24 hours (migraine recurrence) following the administration of one bottle of MIGRANAL is low.
* Throw away the sprayer and bottle after use **or within 8 hours of preparation of the sprayer.**

Side Effects to Watch Out for:

In clinical trials, most migraine patients have used MIGRANAL without serious side effects. You may experience nasal irritation, nasal congestion, excessive sneezing, runny nose, taste disturbance, application site reactions, nausea and vomiting after using MIGRANAL. These side effects are temporary and usually do not require you to stop using MIGRANAL. 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

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 centre immediately.

Storing MIGRANAL:

Keep medication in a safe place away from children.

Keep MIGRANAL away from heat.

- Store MIGRANAL at room temperature (15- 25°C).
- Never freeze MIGRANAL.

Do not keep an opened MIGRANAL bottle for more than 8 hours.

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

Answers to patients' questions about MIGRANAL:

How quickly does MIGRANAL work?

You should start to feel relief in less than 30 minutes and your migraine and associated symptoms should continue to improve.

Can I prepare the sprayer so it is ready before I need to use it?

No. The bottle containing your medication must remain sealed until you are ready to use it.

Why do I have to prime the sprayer before using? Am I wasting the medication?

You have to prime the sprayer (pump 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 bottle to allow you to prepare your applicator properly and still receive a full dose of MIGRANAL (4 sprays).

Can I reuse my MIGRANAL Sprayer?

No. After completing the full dose (4 sprays), you must throw the sprayer and bottle out.

Can I use MIGRANAL if I have a stuffy nose, cold or allergies?

Yes. You can use MIGRANAL 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 or pharmacist before using MIGRANAL.

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

No, you should not sniff, because MIGRANAL is absorbed through the lining of the nose.

What does MIGRANAL contain?

Each MIGRANAL bottle contains a solution containing dihydroergotamine mesylate. It also contains caffeine, dextrose, carbon dioxide and water.

What if I need help in using MIGRANAL?

If you have any questions or if you need help in preparing, or using MIGRANAL, speak to your doctor or pharmacist.

This medicine is prescribed for your specific medical problem and for your own use only. Do not give to other people.

Keep all medicines out of the reach of children.

This leaflet does not contain all the information on MIGRANAL. If you need any further information, ask your doctor or pharmacist.

PHARMACOLOGY

Human Pharmacodynamics

Studies in humans with dihydroergotamine mesylate nasal spray indicated that the vascular changes observed after nasal administration of dihydroergotamine mesylate involved the venous capacitance, and only slightly, arterial resistance. The pharmacodynamic effects observed did not have any clinical relevance regarding the tolerability of dihydroergotamine mesylate nasal spray in migraine patients. The magnitude of the pharmacodynamic responses obtained after the doses of 1 or 2 mg was lower than that obtained with 1 mg dihydroergotamine mesylate i.m.

The hemodynamic effects induced by dihydroergotamine mesylate nasal spray, whether administered alone or in association with propranolol, remained minimal after a dose of 2 mg of dihydroergotamine and became evident, although moderate, only after a cumulative dose of 4 mg of dihydroergotamine. This hemodynamic study revealed no additive or potentiating effect of the association of a β-blocker and dihydroergotamine mesylate nasal spray at a dose equivalent to double the maximum permitted dosage.

1 mg dose of dihydroergotamine did not produce any significant variation of air flow resistance.

Human Pharmacokinetics

Several studies were conducted to determine the pharmacokinetics of dihydroergotamine in humans. Overall, the following results were obtained:

Absorption: Nasally administered dihydroergotamine was rapidly absorbed, the time to reach peak plasma concentration (t_{max}) being 45 minutes. The absolute bioavailability was 43%, whereas the relative bioavailability compared to i.m. injection is approximately 32%. The dose-bioavailability relationship of dihydroergotamine mesylate nasal spray based on C_{max} and AUC values of plasma dihydroergotamine was shown to be linear in the 0-4 mg range. Peak plasma concentrations were reached within 1 hour regardless of the dose, and the mean peak level was 0.6 ng/mL per mg dosed.

Distribution: Plasma and urine data were in excellent agreement. Dihydroergotamine has a steady state volume of distribution of 796 L. From human in vivo and in vitro binding studies, the distribution of dihydroergotamine in blood was found to be 2/3 plasma and 1/3 blood cells. In both the in-vivo and -in-vitro studies, the binding of dihydroergotamine to plasma proteins was 93%.

Metabolism: Dihydroergotamine is partially metabolized in man prior to excretion. A major metabolite, 8'OH-Dihydroergotamine mesylate, has a similar venoconstriction effect as the parent drug. The nasal spray form of dihydroergotamine mesylate, like most parenteral dose routes, is not subject to first-pass hepatic metabolism.

Excretion: The predominant excretory route of dihydroergotamine is via the bile in the feces. Following nasal administration, the urinary recovery of parent drug amounted to only 1.4-

2.2 % of the dose, compared with 5.9-6.9% after i.m. doses. The decline of plasma dihydroergotamine is biphasic with a mean terminal half-life of 10 hours.

Additional pharmacokinetic studies in humans found the following results:

- no statistically significant difference in C_{max}, t_{max} or AUC and a relative bioavailability of the nasal spray of 124% during a migraine attack versus the migraine free period
- a clinically irrelevant drug interaction between MIGRANAL and fenoxazoline chlorhydrate
- the caffeine in the nasal spray does not affect its bioavailability

Animal Pharmacodynamics

Dihydroergotamine was shown to have 5-HT antagonistic properties in addition to its alpha adrenergic blocking activity when it was studied in various animal models. Effects of dihydroergotamine included: small increases in resistance of resistance vessels; dose dependent constriction of capacitance vessels; increases in blood pressure on its own, but a depressor response following an increase in blood pressure elicited by epinephrine, and dose dependent changes in cardiovascular parameters.

Animal Pharmacokinetics

The pharmacokinetics of dihydroergotamine were studied in a 17-day and 13-week toxicology/PK study in cynomolgus monkeys and in an ADME study in dogs where tritiated dihydroergotamine was given orally. In the two monkey studies, plasma and urine were examined to investigate the pharmacokinetics of dihydroergotamine (oral and/or nasal route). The nasal absorption was relatively rapid and linear over the tested dose range with a t_{max} of 1-2 hours. Relative bioavailability of the parent drug for the nasal route compared to the oral route in the preliminary study was 850% and 710%, based on plasma and urinary data, respectively. For AUC of plasma, the ratio of parent drug to parent plus metabolites was

approximately 65% for the nasal route, but only about 20% for the oral route. In the urine, the ratio of parent drug to parent plus metabolites was about 56% for the nasal route, but only 13% for the oral route. These differences are due to the absence of a first pass hepatic metabolism with the nasal route.

In the dog radioactivity study, at four hours post dosing, the tissues with the highest radioactivity content were the pancreas, liver, kidneys, lymph nodes, and bile. At the 4 hour mark, 101% of the radioactivity in the dose given was found in the G.I. tract. Excretion mostly took place via the feces, where, at 120 hours post dosing, 83.7% of the radioactivity was found, with 18.3 % in the urine.

TOXICOLOGY

ACUTE TOXICOLOGY

Acute Toxicology in Mice, Rats and Rabbits

The acute toxicity of dihydroergotamine was ascertained by intravenous, oral and subcutaneous administration of a single dose in mice, rats and rabbits as well as by intraperitoneal administration of a single dose in mice.

Animals were observed following administration until death occurred or for a period of seven days. The following signs were observed after administration: forced breathing; periodic recurrence of motor excitation; periods of drowsiness and disturbed equilibrium; piloerection; rhythmic jerking of the whole body; skin necrosis at the injection site following subcutaneous administration.

Dihydroergotamine LD_{50} (mg/kg Body Weight)

Species	**i.v.**	**oral**	**s.c.**	**i.p.**
Mouse	117 ± 7.7	> 2000 (0/10)	> 625 (0/10)	212 ± 25
Rat	130 ± 8.0	> 2000 (0/10)	> 500 (0/10)	-
Rabbit	37 ± 6.1	> 1000 (0/6)	c. 95*	-

*extrapolated

Acute Toxicity in Rats and Mice:

The acute toxicity of dihydroergotamine mesylate nasal spray, 4 mg/mL was assessed by oral and intravenous administration of a single dose in rats and mice.

Animals were observed for 14 days after administration.

Dihydroergotamine mesylate nasal spray LD50 (mg/kg Body Weight)

Species	Sex	i.v.	oral
Rat	Male	> 40	> 40
Rat	Female	> 40	> 40
Mouse	Male	44	> 100
Mouse	Female	49	> 100

Signs observed included ptosis and/or clonic then tonic convulsions which usually disappeared the day after dosing. For male mice dosed with 48 mg/kg dihydroergotamine i.v., ptosis remained throughout the 14-day observation period. Macroscopic examinations of the principal organs of the animals sacrificed at the end of the observation period did not reveal any apparent abnormalities.

LONG TERM TOXICOLOGY

4-Week Intranasal Dose Range Finding Study in Mice

Dihydroergotamine mesylate nasal spray was administered intranasally to CD-1 mice at doses of 0.04, 0.08, and 0.12 mg/day. Treatment for 28 days produced reduced body weight gain and food consumption and minor hematological changes when compared to untreated controls. These changes were not observed when the drug treated animals were compared to the vehicle control. There were no treatment related effects in clinical chemistry, organ weights, or macroscopic findings. Microscopic findings were restricted to the nasal cavity and were consistent with mild nasal irritation. No neoplasia or pre-neoplasia was seen. Eosinophilic inclusions in the nasal epithelium and minimal to slight goblet cell hyperplasia were seen in some animals that had mild rhinitis.

3-Month Intranasal Toxicity Study in Mice

This was a maximum-tolerated dose study in CD-1 mice where dihydroergotamine was intranasally instilled daily for three months at doses of 0, 0.04, 0.12, 0.16, and 0.20 mg/day. Body weight and food consumption changes were sporadic. Organ weight findings included increased heart and liver weights and decreased thyroid weights. Microscopically, mild rhinitis, eosinophilic inclusions and very mild goblet cell proliferation were observed in several treated animals.

4-Week Intranasal Study in Rats

Doses of 0, 0.4, 0.8, or 1.2 mg/day of dihydroergotamine mesylate nasal spray) were intranasally instilled to Fischer F344 rats. Immediately following dosing, transient clinical signs of piloerection, subdued behaviour, laboured breathing and nasal foam were seen. Body weight gains and food consumption were

decreased in the treated groups. Microscopic findings included rhinitis observed in most treated animals, goblet cell proliferation, focal erosion and luminal inflammatory exudate in some mid and/or high dose animals.

3-Month Intranasal Study in Rats

This intranasal study was conducted at doses of 0, 0.08, 0.32 (this dose was escalated to 1.6 mg/day in week 8), 0.72, and 1.2 mg/day. Body weight gains were significantly decreased in males in the high dose (1.6 mg/day) group. There were no treatment related effects on hematology, clinical chemistry, urinalysis, ophthalmoscopy or organ weights. Microscopic changes restricted to the nasal cavity and consistent with mild nasal irritation included rhinitis characterized by goblet cell proliferation, and non-neoplastic focal hyperplasia and eosinophilic inclusions were observed in a few animals.

In a subsequent study, following a 13-week recovery period, all nasal histological changes reversed, except for the very mild to mild eosinophilic inclusions in the respiratory and olfactory epithelium. Although the significance of the eosinophilic inclusions in not known, they can be seen as a spontaneous change in aged rodents.

26-Week Oral Toxicity Study in Rats:

Dihydroergotamine was administered to rats in their feed at 3 dosage levels: 0.004%, 0.02% and 0.1% (equivalent to 2, 11 and 53 mg/kg/day, respectively) for 26 weeks.

Dosage mg/kg/day	Observation
2	– Slightly decreased food intake
11	– Slight diarrhea in weeks 11–17 – Slightly decreased food intake in females
53	– Diarrhea in weeks 5–26 – Blue–red discoloration of tail-tip in week 5–10 – Decreased food intake – Slight weight loss (females) – Increased SGPT at week 26

The non-toxic effect level was set at 11 mg/kg/day.

26-Week Oral Toxicity Study in Dogs:

Dihydroergotamine was administered to beagle dogs in gelatin capsules at 3 dosage levels: 0.5, 1.5 and 5.0 mg/kg/day 7 days a week for 26 weeks.

Dosage mg/kg/day	Observation
0.5 1.5 and 5.0	– Miosis, prolapsed nictitating membrane – Slight slowing of heart rate with prolonged PQ interval
1.5 5.0	– Sedation, occasional vomiting – Induration and crusting of dependent ear margins – Decreased spleen weight
5.0	– Slightly impaired weight gain – Increased hepatocyte eosinophilic inclusions – Decreased splenic reaction centers

The non-toxic effect level was set at 1.5 mg/kg/day

17-day Intranasal and Oral Toxicity Study in the Cynomolgus Monkey

In a study performed to evaluate the toxicity of dihydroergotamine administered either orally (9 mg tablets) or intranasally (0.46 mg dihydroergotamine mesylate per pulse) 2 male cynomolgus monkeys were dosed for 17 days (9mg oral on day one, then nasal administration for the remainder of the study, up to 6 mg per day). One of the two animals was found dead the morning after the final dose. The cause of death was of uncertain toxicological significance as the cause of death was not established. The surviving animal had a slight anemia. The other findings reported for the two animals were: loss of a small amount of body weight, marked and progressive consumption of food intake and pallor of heart and liver.

13-Week Intranasal Toxicity Study in the Cynomolgus Monkey

Doses of 0.46, 1.38 and 3.68 mg/day of dihydroergotamine mesylate nasal spray was administered by nasal spray. One monkey died from intractable diarrhea but there was no treatment-related mortality. Clinical examination of the nostrils at 4 and 8 weeks revealed superficial mucosal ulceration with haemorrhage or scabbing in treated animals. This lesion regressed during the course of the test and at week 13 the incidence in control and treated animals was similar with most treated animals appearing normal. Treatment related microscopic findings were present only in the nasal cavities and were characteristic of minor intranasal irritation. There was no evidence of systemic toxicity at any dose level.

SPECIAL TOXICITY STUDIES

Determination of the ocular irritation index in the rabbit of dihydroergotamine solution administered by nasal spray.

An aqueous solution of dihydroergotamine for nasal spray produced an ocular irritation index of 4.17 on day 1. The ocular lesions observed regressed rapidly from day 2 onwards (index=0) and no abnormality of the eye was observed during the reminder of the study. These results indicate that dihydroergotamine nasal spray has a weak irritant potential.

TERATOLOGICAL AND REPRODUCTIVE STUDIES

Oral or intranasal administration of dihydroergotamine to pregnant rats, rabbits and/or monkeys did not suggest any greater evidence of embryo/fetal than maternal susceptibility or teratogenic potential at the dose levels studied. There were no compound related fetal malformations. Minimal maternal toxicity was observed at 1.2 mg/day and 3.6 mg/day in the rat and rabbit, respectively. A slight delay in fetal skeletal development was observed at 1.44 mg/day in the rat or 3.6 mg/day in the rabbit, and was associated with maternal toxicity.

MUTAGENICITY

Four studies conducted in vitro (Ames test using Salmonella typhimurium cells; HGPRT test with V79 Chinese hamster cells; Induction of Chromosome Aberrations in Cultured Human Peripheral Blood Lymphocytes; and DNA repair synthesis in rat hepatocyte primary cultures), gave no evidence of mutagenic potential for dihydroergotamine. A fifth study, a chromosomal aberration test in V79 Chinese hamster cells resulted in a slight but statistically significant enhancement of the number of cells with

aberrations at only one time point and with only the highest dose. This finding was, however, not considered toxicologically relevant.

In in-vivo mutagenicity studies (a micronucleus test using adult CD-1 mice, a mouse bone marrow micronucleus test by the oral route, and a micronucleus test and chromosome assay using adult Chinese hamsters), dihydroergotamine was not found to be mutagenic.

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