WHEN MIGRAINE THERAPY REACHES AN IMPASSE
Triptans — Not for Everyone
- Triptans only exert agonist effects on 5-HT<sub>1</sub> receptors, with the greatest affinity on 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub>.
- Current therapies do not always provide complete headache relief.<sup>24</sup>
- In clinical practice, approximately 30% of patients do not get satisfactory results from oral sumatriptan.<sup>3</sup>

MIGRANAL Nasal Spray — Broader Appeal
- MIGRANAL Nasal Spray works in a similar way to triptans and has a comparable safety profile, but with a broader receptor profile.<sup>6</sup>
- MIGRANAL Nasal Spray is an α-adrenergic as well as a 5-HT agonist while triptans act specifically on 5-HT receptors only.<sup>7,12</sup>
- MIGRANAL Nasal Spray has a greater affinity for some serotonergic, adrenergic, and dopaminergic receptors.<sup>7,12</sup>

Interactions of Neurotransmitter Receptor Sites<sup>7,14</sup>

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Dihydroergotamine</th>
<th>Triptan Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonergic</td>
<td><img src="image" alt="Interaction Icons" /></td>
<td><img src="image" alt="Interaction Icons" /></td>
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<tr>
<td>5-HT&lt;sub&gt;1B&lt;/sub&gt;</td>
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<tr>
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<td><img src="image" alt="Interaction Icons" /></td>
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<tr>
<td>Adrenergic</td>
<td><img src="image" alt="Interaction Icons" /></td>
<td><img src="image" alt="Interaction Icons" /></td>
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<tr>
<td>α&lt;sub&gt;1&lt;/sub&gt;</td>
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<tr>
<td>β&lt;sub&gt;1&lt;/sub&gt;</td>
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<tr>
<td>Dopaminergic</td>
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<tr>
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<td>D&lt;sub&gt;2&lt;/sub&gt;</td>
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</tr>
</tbody>
</table>

MIGRANAL Nasal Spray is indicated for the acute treatment of migraine with or without aura. Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of dihydroergotamine with potent CYP3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP3A4 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 in full Prescribing Information.) MIGRANAL 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. MIGRANAL Nasal Spray is also contraindicated in patients with known peripheral arterial disease, sepsis, following vascular surgery, and severely impaired hepatic or renal function. MIGRANAL Nasal Spray should not be administered during pregnancy.
MIGRANAL Nasal Spray — Clinically Proven Efficacy

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.

- 70% of patients treated with MIGRANAL Nasal Spray reported resolution of their migraine at 4 hours ($P<0.001$); 61% at 2 hours ($P<0.001$).
- In all clinical trials, there was a reduction in migraine-associated nausea, photophobia, and phonophobia at 2 and 4 hours following administration of MIGRANAL Nasal Spray compared to placebo.

MIGRANAL Nasal Spray — Rapid Onset of Action
As Soon As 30 Minutes

(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.)

- MIGRANAL Nasal Spray has a plasma half-life of 10 hours.

MIGRANAL Nasal Spray — Safe and Well-Tolerated Migraine Relief

- Of the 1,796 patients treated with MIGRANAL Nasal Spray 2 mg or less in US and foreign clinical studies, only 1.4% discontinued due to adverse events.
- MIGRANAL Nasal Spray is the nasal formulation of DHE 45°, a safe and effective migraine treatment used for over 50 years.
When Triptan Therapy Fails...

MIGRANAL® NASAL SPRAY — A TRUE ALTERNATIVE FOR MIGRAINE RELIEF

- A unique mechanism of action
  → Broader receptor profile than the triptans
- Efficacy proven in clinical trials
  → 70% of patients had headache response at 4 hours
- Well-documented tolerability
  → In clinical trials of 1,796 patients, only 1.4% discontinuation rate

MIGRANAL Nasal Spray — Easy Dosing

- One spray (0.5 mg) of MIGRANAL Nasal Spray should be administered in each nostril
- Fifteen minutes later, an additional spray (0.5 mg) of MIGRANAL Nasal Spray should be administered in each nostril, for a total dosage of four sprays (2.0 mg) of MIGRANAL Nasal Spray

Please visit www.migranal.com
Please see your sales representative for full Prescribing Information.

DHE 45®——
ESTABLISHED EFFICACY IN MIGRAINE THERAPY

Not Just Another Ergotamine®

<table>
<thead>
<tr>
<th>Drug Properties</th>
<th>DHE</th>
<th>Ergotamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial Vasoconstriction</td>
<td>minimal</td>
<td>marked</td>
</tr>
<tr>
<td>Drug Dependence</td>
<td>none</td>
<td>possible</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>minimal</td>
<td>marked</td>
</tr>
<tr>
<td>Safety</td>
<td>serious adverse effects are rare</td>
<td>potential for ergotism; contraindicated in those with prolonged aura due to potential for frank migrainous infarction</td>
</tr>
</tbody>
</table>

Dosing

- DHE 45 Injection, USP should be administered in a dose of 1 mL intravenously, intramuscularly, or subcutaneously.
- The dose can be repeated, as needed, at 1 to 2 hour intervals for a total dose of 3 mL for intramuscular or subcutaneous delivery or 2 mL for intravenous delivery (IV) in a 24 hour period.
- The total weekly dosage should not exceed 6 mL.

DHE 45 is indicated for the treatment of acute migraine headaches with or without aura. Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of DHIHYDROERGOTAMINE with potent CYP3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP3A4 inhibition elevates the serum levels of DHIHYDROERGOTAMINE, 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 in full Prescribing Information.) DHE 45 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.
DHE 45® (dihydroergotamine mesylate) Injection, USP —
ESTABLISHED EFFICACY IN MIGRAINE THERAPY

A History of Effective Treatment
- Dihydroergotamine (DHE) was developed as a safer alternative to ergotamine.
- DHE has been used in the treatment of migraine for more than 50 years.

Proven in the Toughest Cases
- DHE has been established as a standard treatment for status migrainosus or intractable migraine.
- DHE has provided up to 90% relief in these patients.
- Peak plasma levels of DHE are achieved within 1 to 2 minutes of IV injection, providing a rapid onset of migraine relief.

The Quality Standards Subcommittee of the American Academy of Neurology recommends triptans and DHE as first-line therapy for the treatment of acute, moderate-to-severe migraine.

Migraine Treatment With Flexibility
- IV, IM, or subcutaneous delivery for acute migraine.
- IV for management of refractory, intractable migraine.

References: