IMITREX® TABLETS FORMULATED WITH RT TECHNOLOGY™

IMITREX (sumatriptan succinate) was the first triptan medication to target the nerves and blood vessels believed to trigger a total migraine (including throbbing pain, nausea, and sensitivity to light and sound, with or without aura). The first triptan to receive Food and Drug Administration (FDA) approval for the acute treatment of migraines in adults, IMITREX has treated more than 750 million migraines in the past decade.

IMITREX Tablets formulated with RT Technology offer significantly faster dissolution and absorption after swallowing in the crucial first two hours after the onset of migraine symptoms compared with conventional IMITREX Tablets. Just as with conventional IMITREX Tablets, IMITREX Tablets with RT Technology can be swallowed whole at the first sign of headache pain for effective migraine relief without drowsiness. Introduced in 2004, IMITREX Tablets with RT Technology are bioequivalent to conventional IMITREX Tablets as measured by AUC0 to 24 and Cmax.

INSIDE
- What are migraine headaches?
- Causes of migraine
- Migraine prevalence
- Pharmacotherapy

A FASTER-DISSOLVING IMITREX TABLET
Pharmaceutical manufacturer GlaxoSmithKline conducted a gastric scintigraphy study to demonstrate the effectiveness of RT Technology in sumatriptan tablet disintegration and absorption in subjects who were actually in the midst of having a migraine attack. In the study, five subjects with International Headache Society-defined migraine ingested the tablets, swallowed with radioactively labeled water. The four-way crossover design enabled the subjects to take conventional IMITREX Tablets at some times and IMITREX Tablets formulated with RT Technology at others. The dissolution of both tablet formulations and other endpoints were also evaluated when the subjects were not having a migraine attack. End points were the rate of tablet disintegration, the rate of gastric emptying, and the rate of absorption as measured by plasma levels.

The results were notable. RT Technology helps oral tablets dissolve and disperse more efficiently—even in the presence of gastric stasis.*

*Rapid dispersion in the gut is confirmed by scintigraphy results†

Scintigraphy at 9 minutes during a migraine

Radiolabeled images of IMITREX emptying from the stomach into the small intestine (n=1). Images are from a single patient and are for illustrative purposes only.

*Based on in vitro dissolution; †Scintigraphy: Conventional and current IMITREX 100-mg Tablets were radiolabeled with indium-111 and administered to 5 migraine subjects between migraine attacks. Images of radiolabeled tablets were obtained at various intervals with a scintillation camera as they dissolved in the GI tract.


"In my experience, many migraineurs prefer oral therapy to treat their migraines. However, gastric stasis, a common occurrence in migraine patients, has the potential to limit efficacy of medicine that is swallowed. Therefore, research to identify innovative ways to deliver migraine medication is crucial."

Sheena Aurora, MD
Director, Swedish Headache Center
Seattle, Washington

IMITREX Tablets formulated with RT Technology are bioequivalent to conventional IMITREX Tablets as measured by AUC0 to 24 and Cmax.
Technology allowed the IMITREX tablets to dissolve up to four times faster than conventional sumatriptan tablets. IMITREX Tablets formulated with RT Technology dissolved in 9.5 minutes. Conventional sumatriptan tablets took 33 minutes to dissolve (Figure 1). In addition to IMITREX formulated with RT Technology dissolving into a particulate suspension more rapidly, the movement of particles into a liquid suspension was also accelerated. Once IMITREX formulated with RT Technology was in liquid form, the drug passed swiftly through the stomach into the small intestine and to absorption. With a liquid, gastric emptying was made easier. The speed of gastric emptying was dramatically increased with RT Technology. IMITREX Tablets formulated with RT Technology resulted in gastric emptying of the tablets more than three times faster than conventional sumatriptan tablets without RT Technology.2,3

MIGRAINE: A NATIONAL HEADACHE

More than 36 million Americans suffer from migraine headaches, characterized by painful, disabling, and recurring symptoms. Migraine is three times more common in women than in men. An attack may be preceded or accompanied by a sensory warning sign (aura), such as flashes of light, blind spots, or tingling in an arm or leg. Other signs and symptoms include nausea, vomiting, and extreme sensitivity to light and sound. Migraineurs tend to have recurring attacks triggered by a lack of food or sleep, exposure to light, allergies, or, in the case of women, hormonal irregularities. Anxiety, stress, or relaxation after stress can also be triggers.4,5

CAUSES OF MIGRAINE

Four common explanations of migraine pathogenesis are advanced:

The vascular theory6 posits that the major pathophysiologic events that initiate a migraine attack occur in the nerves that surround the major cerebral vessels in the brain. Most of the brain is insensitive to pain, but meningeal blood vessels show a high level of innervation (Figure 2). For example, the trigeminal sensory nerve, which envelopes the meningeal blood vessels, releases vasoactive neuropeptides that cause vasodilation and resultant pain.

The cortical spreading depression theory6 holds that a wave of depolarization spreads across the surface of the brain, beginning with a brief surge of excitation, followed by a prolonged period of neuronal depression. The abnormal firing of brain neurons is associated with disturbances in nerve cell metabolism and regional reductions in blood flow.

The neurovascular hypothesis6 conceptualizes migraine as a state of central neuronal hyperexcitability. Fibers from the trigeminal nerve contain nociceptors, which innervate blood vessels in the meninges and extracranial arteries by releasing certain neuropeptides. These drench regional blood vessels, resulting in vasodilation and inflammation in the area around the innervated vasculature.

The serotonergic abnormalities hypothesis proposes a derangement of the metabolism of the neurotransmitter serotonin (5-hydroxytryptamine, or 5-HT).7 When platelets are activated by inflammatory factors, such as prostaglandins, their serotonin reserves are expelled into the plasma, leaving serotonin levels depressed in the brain and setting the stage for a migraine attack.

While migraine pathogenesis is currently uncertain, it is possible that all these pathways may play a role in creating a migraine-inducing environment.6

MIGRAINE PREVALENCE

There are two types of headaches: primary and secondary. Secondary headaches are the result of an assault on or injury to the brain. Primary headaches
can be tension type, migraine, or cluster (Table 1), and they can manifest individually or in combination.

While tension headache remains the most prevalent primary headache, among patients who present to a clinician with primary headache, the diagnosis is most likely to be migraine. To improve the recognition of migraine by clinicians, patients with a stable pattern of episodic, disabling headache and a normal physical exam (eg, no history of trauma, laboratory values within normal limits) should be considered migraineurs in the absence of contradictory evidence. Based on that principle, the Landmark Study, a prospective multinational trial, analyzed 1,217 patients who visited their primary-care physician with a headache complaint. Published in 2004, the results showed that 94% of subjects received a diagnosis of migraine or migrainous headache and 3% a diagnosis of episodic tension-type headache; 3% were unclassifiable.

Migraine headaches are more prevalent in younger adults; incidence decreases with age. When the diagnosis is in doubt, the patient’s use of a headache diary that records specific symptoms can add further precision to the final diagnosis. A patient can download a headache diary at: http://www.migrainehelp.com/pdf/MigraineDiary.pdf

Table 1. Characteristics of Primary Headaches As Defined by the International Headache Society

<table>
<thead>
<tr>
<th>Primary headache</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine without aura</td>
<td>Recurrent; lasts 4-72 hours; unilateral, pulsating, moderate or severe intensity; aggravated by physical activity; associated with nausea and/or phonophobia/photophobia</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>Recurrent; reversible focal neurological symptoms; develops gradually over 5-20 minutes and lasts for &lt;60 minutes; headache with features of migraine without auras usually follows aura symptoms but no headache may occur</td>
</tr>
<tr>
<td>Tension type</td>
<td>Infrequent episodes of headache lasting minutes to days; typically bilateral, pressing or tightening in quality; mild/moderate intensity; does not worsen with routine physical activity; no nausea, but photophobia or phonophobia may be present</td>
</tr>
<tr>
<td>Cluster</td>
<td>Attacks of severe, unilateral pain at orbital, supraorbital, and/or temporal sites; lasts 15–180 minutes and occurs once every other day to 8 times a day; associated with lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, eyelid edema</td>
</tr>
</tbody>
</table>


Other than performing a simple blood chemistry test to observe for metabolic abnormalities, further evaluation using
specific, migraine-specific medication based on headache frequency and duration, disability, non-headache symptoms, previous treatment response, and patient preference—regardless of the immediate severity of symptoms. With stratified care, the initial treatment is more likely to control pain, reduce disability, and improve patient satisfaction.12

Results from the Disability in Strategies for Care (DISC) study13 showed superior outcomes with stratified care compared with step care; it also showed stratified care to be cost-effective. The DISC study assessed 835 migraineurs for treatment effectiveness across six migraine attacks. It compared the clinical benefits of three strategies—stratified care at the outset of symptoms, step care at the outset of symptoms, and step care within attacks in the study population. Patients were randomly assigned to receive (1) stratified care—in which those with a history of severe attacks were treated with a migraine-specific triptan; (2) step care across attacks—with a salicylate analgesic as the initial treatment; those patients who did not obtain relief in at least two of the first three attacks were then switched to a triptan to treat the remaining three attacks; or (3) step care within attacks—in which initial treatment for all attacks was aspirin. The results showed that head-ache response at 2 hours was significantly greater across six attacks in the stratified-care treatment group receiving a migraine-specific triptan (53%) than in the step-care groups—either the across-attacks group (41%) or the within-attacks group (36%). Disability time was significantly lower in the stratified-care group than in either of the step-care groups (P<.001).

Such results indicate that stratified care is more likely to provide the best initial treatment for migraine in order to avoid a series of failed therapeutic attempts.

PHARMACOTHERAPY FOR ACUTE ATTACKS

The triptans are the treatment of choice for migraine headaches (Table 2). The triptans are considered migraine-specific because of their agonist actions at specific 5-HT receptors in the brain, which are localized at strategic sites through the trigeminovascular system.13 Triptans are believed to dilate the meningeal vessels, inhibit the release of inflammatory neuropeptides, and interrupt pain impulses that travel from the periphery, thereby preventing central sensitization.14,15

For aborting mild-to-severe migraine pain, good evidence exists for the effectiveness of the oral triptans sumatriptan (Figure 3),16-18 naratriptan,19 rizatriptan,20 zolmitriptan,21 frovatriptan,22 eletriptan,23 and almotriptan.24 Subcutaneous15,26 and intranasal27,28 sumatriptan are also options for patients with nausea and vomiting (Table 3). Triptans are not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine.

Another, less-versatile treatment option for migraine attacks is opioid drugs. Opioids are narcotic analgesics with widespread effects throughout the central nervous system. While the opioids work well as analgesics, good evidence exists only for the efficacy of butorphanol nasal spray.29 Although opioids are commonly used to treat migraine headaches, these drugs are best reserved for use when other medications cannot be employed due to treatment failure or contraindications, opiate-related sedative side effects are not a concern, and the risk for opioid abuse has been addressed.
MIGRAINE PROPHYLAXIS

The goal of migraine prophylaxis is to decrease the frequency and severity of attacks. Prophylactic migraine medications are indicated if:26:

- Attacks occur >2 to 3 times a month
- Attacks last more than 48 hours
- Attacks are so severe that the patient is psychologically unable to cope
- Abortive therapies are inadequate or cause significant side effects
- Prolonged aura is present.

In the majority of migraineurs, preventive medications reduce attack frequency suboptimally—eg, from five a month to three a month.30 Patients should be advised that prophylaxis is rarely curative so that their expectations are realistic.31

Four agents are approved by the FDA for use in migraine prophylaxis: the beta-blockers propranolol32 and timolol,33 and the anticonvulsants topiramate34 and divalproex.35 The efficacy of these prophylactic agents during an emerging migraine attack has not been established and the drugs are not indicated for the onset of acute symptoms. But even for prophylaxis, all four drugs have side effects that foster patient non-adherence. Adverse effects include nausea, asthenia, dyspepsia, dizziness, somnolence, and diarrhea.36 As such, adherence to migraine prophylactic drugs is generally poor, especially with the availability of the “rescue” medications, such as sumatriptan, that can abort an attack in its early stages.

REFERENCES

34. Depakote [prescribing information]. N. Chicago, IL: Abbott Laboratories; 2006.

Table 3. Three Formulations of IMITREX (Sumatriptan)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Indication</th>
<th>Dosages available</th>
<th>Onset of action</th>
<th>Most common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMITREX Tablets Formulated with RT Technology®</td>
<td>For migraine sufferers who prefer the ease and convenience of a tablet</td>
<td>100-mg, 50-mg, and 25-mg tablets</td>
<td>With 100-mg tablets, 6% of migraineurs experience relief within 15 minutes, 64% at 2 hours, vs 7% and 38%, respectively, with placebo</td>
<td>Tingling and warm/cold sensations; side effects are usually mild and generally short-lasting</td>
</tr>
<tr>
<td>IMITREX STATdose System® Injection</td>
<td>For migraines that demand fast relief, such as early-morning migraines or migraines that come on suddenly</td>
<td>4-mg and 6-mg strength</td>
<td>With 6-mg injections, 16% of migraineurs experience relief at 10 minutes, 49% at 30 minutes, vs 4% and 12%, respectively, with placebo</td>
<td>Soreness and redness at the injection site (usually lasts 1 hour or less), unusual sensations (eg, tingling, warm/hot sensations), dizziness, and flushing</td>
</tr>
<tr>
<td>IMITREX Nasal Spray</td>
<td>For times when it is difficult to swallow a tablet due to nausea or vomiting</td>
<td>Preloaded with 1 dose of 5-mg, 10-mg, or 20-mg strength</td>
<td>With 20-mg dose, 12% of migraineurs experience relief within 15 minutes, 64% at 2 hours, vs 7% and 38%, respectively, with placebo</td>
<td>Bad or unusual taste in the mouth</td>
</tr>
</tbody>
</table>

IMITREX Tablets, formulated with RT Technology™: dissolve fast and absorb fast

Conventional IMITREX Tablet vs IMITREX Tablet, with RT Technology

Stomach

Small intestine

Scintigraphy* at 9 minutes

IMITREX Tablets, with RT Technology, disperse completely in 9.5 minutes vs 33.4 minutes for conventional IMITREX Tablets

Radiolabeled images of IMITREX emptying from the stomach into the small intestine during a migraine (n=1).

On average, IMITREX Tablets, formulated with RT Technology, absorbed faster than the conventional tablet during the critical early phase of a migraine

Mean times for all patients tested during a migraine (N=5).

*Scintigraphy and plasma levels: Images of radiolabeled tablets were obtained at various intervals with a scintillation camera as they disintegrated in the small intestine. Images are from a single patient for illustrative purposes only.

IMITREX Tablets, formulated with RT Technology, are bioequivalent to conventional IMITREX Tablets as measured by AUC0 to 24 and Cmax.

The clinical significance of this data is unknown.

Important Information

IMITREX is indicated for the acute treatment of migraine attacks, with or without aura, in adults. IMITREX should be used only where a clear diagnosis of migraine headache has been established.

IMITREX is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes and in patients with other significant underlying cardiovascular diseases. IMITREX should not be given to patients in whom unrecognized coronary artery disease is predicted by the presence of risk factors without a prior cardiovascular evaluation (see WARNINGS in complete Prescribing Information).

References:
IMITREX Tablets, formulated with RT Technology™, work fast

Combined results from 2 studies show rapid onset of pain relief with IMITREX Tablets, formulated with RT Technology™.

100 mg—Onset as early as 20 minutes (6% vs 4% for placebo, P<0.05)

Even when patients waited to treat at moderate or severe pain, 72% had pain relief at 2 hours with IMITREX 100-mg Tablets, formulated with RT Technology™.

Onset in as fast as 20 minutes with IMITREX 100-mg Tablets™

At 2 hours with conventional IMITREX Tablets, significant pain relief was achieved in 56% to 62% of patients with IMITREX 100 mg, and in 50% to 61% of patients with IMITREX 50 mg (17% to 27% for placebo, P<0.05).

Important Information

IMITREX is indicated for the acute treatment of migraine attacks with or without aura in adults. It should be used only where a clear diagnosis of migraine headache has been established.

IMITREX is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes and in patients with other significant underlying cardiovascular diseases. IMITREX should not be given to patients in whom unrecognized coronary artery disease is predicted by the presence of risk factors without a prior cardiovascular evaluation (see WARNINGS in complete Prescribing Information).

References:
IMITREX has a long track record of worldwide experience

- More than 764 million migraine headaches treated worldwide
- Treated 2 migraine headaches per second for the past decade
- Demonstrated clinical tolerability profile in clinical trials with more than 100,000 patients taking IMITREX

IMITREX 100-mg Tablets

#1 are the prescribed Rx acute migraine treatment in the United States

IMITREX is indicated for the acute treatment of migraine attacks, with or without aura, in adults. It should be used only where a clear diagnosis of migraine headache has been established.

IMITREX is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes and in patients with other significant underlying cardiovascular diseases. IMITREX should not be given to patients in whom unrecognized coronary artery disease is predicted by the presence of risk factors without a prior cardiovascular evaluation (see WARNINGS in complete Prescribing Information).