

Finding FROVA'S SPOT



The Right Triptan for the Right Patient

Instead of trying to conquer the entire anti-migraine market, Frova will stake its claim by focusing on a niche market segment that can benefit from the drug's unique half-life and superior safety profile

Frova isn't the drug for every migraine patient. The marketers of the latest triptan to enter the anti-migraine market — UCB Pharma and Elan — are making a point of telling that to physi-

cians. The \$1.7 billion U.S. market for anti-migraine treatments already has five triptans and four powerful marketers fighting for market share (see related box on page 42 for more information). Instead of going head-to-head against these well-established brands, the strategic marketing plan for Frova is to carve out a niche by highlighting the drug's two main attributes: the longest half-life of approved triptans and the least drug-to-drug interactions in the triptan class of medicines.

Frova received U.S. marketing approval in November 2001 for the acute treatment of migraine attacks with or without aura in adults. The newly approved drug was developed by Vernalis Group Plc., a U.K.-based biopharmaceutical company, and is being marketed in the U.S. by UCB Pharma Inc. and Elan Corp.

"We're really going to be very specific in helping physicians select the appropriate

patient for Frova," says Dan Setar, former director of marketing for Elan Biopharmaceuticals. "Frova's unique half-life will be an important option for physicians to consider when looking at patient types and migraine attack profiles, especially patients who have longer duration type migraine and patients who may have a slower-building migraine."

About 23 million Americans experience migraine. Of this number, Frova's marketers estimate that 15% to 30% have long-duration migraine — the niche population best suited to Frova therapy.

One of Frova's major benefits is its long duration of action, thus reducing the rate of migraine recurrence, and benefiting patients who experience long-duration headaches, such as migraine associated with a menstrual cycle.

"For some individuals the headache goes on," says Arthur Elkind, M.D., director of the



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Elkind Headache Center and the principal investigator for six Frova clinical trials. "The other drugs have a very short duration, usually measured in several hours. Frovatriptan lasts up to 26 hours, so that will be a great benefit."

As part of Frova's marketing strategy, Elan and UCB Pharma are creating tools to help physicians get a better handle on specific migraine-attack profiles to help them prescribe the right triptan.

"We're taking a little different approach than some of the other triptans that have been launched recently," Mr. Setar says. "We're talking to physicians about looking at specific patients and their migraine types and attack profiles and asking them to prescribe 'the right triptan.' Frova is not the triptan for everybody, but Frova is the right triptan for the right type of patient."

Analysts believe that this approach may allow Frova to create a place for itself in the anti-migraine market.

"It is a crowded market, however, we think Frova has some differentiating features," says Sally Bennett, VP of biotechnology equity research at ING Financial Markets. "Particularly with the salesforces of UCB and Elan, which have specific experience with CNS drugs, we think Frova will be able to carve out a niche for itself in the market."

Under the terms of the co-promotion agree-

ment, UCB and Elan are marketing Frova to neurologists using their combined CNS salesforce of 265 field personnel. UCB also will promote Frova with its primary-care salesforce of about 475 field representatives.

"With these established salesforces we can expand on the current relationships we have with physicians in primary care and neurology and make sure that we generate nationwide awareness of the fact that Frova is available and that it is filling a need within the medical community," says Sue Curro, director of marketing at UCB Pharma Inc.

Greater Efficacy Through Long Half-Life

Frova's developers and marketers believe there is a definite need for the long-acting triptan in the market.

"There are a fair amount of patients who haven't gotten the pain relief that they want, even though there are five other triptans on the market," Ms. Curro says. "Patient satisfaction with pain relief is still pretty low ... this market is not completely satisfied and that's why we think Frova presents a unique therapeutic option in the triptan marketplace — it's really the first product in a long time that has a different pharmacokinetic profile, specifically related to its half-life."

The biggest difference between Frova and other marketed triptans is its half-life — the presence of active compound in the blood. Frova has a half-life of 26 hours. No other currently marketed triptan has a half-life of more than six hours.

Frova's long half-life translates into longer migraine relief for patients, as well as a lower incidence of returning migraine.

"Frova has the lowest recurrence rate of migraine within a 24-hour period," says John Hutchison, MRCP, Ph.D., FFPM, senior VP of development and chief medical officer at Vernalis. "In our five pivotal FDA trials, Frova's recurrence rate, averaged 17%, which compares with an average of 30% for the other triptans."

MIGRAINE MARKET FACTS

- Americans with migraine: more than 23 million, about 10% of the population
- Migraine prevalence in children: 4% to 5%
- Missed workdays: 112 million a year

- Migraine gender prevalence: Before puberty, migraines occur equally in boys and girls. Following puberty, migraines occur in 6% of all men and about 18% of all women

- Migraine age prevalence: increases up to age 40 and then declines
- Frequency of migraine attacks: as often as once or twice weekly

- Healthcare costs for migraine care in the U.S.: estimated at more than \$1 billion a year
- Loss in productivity due to absenteeism and reduced effectiveness at work: \$13 billion

- Heredity factor: About 70% of migraineurs relate a positive family history of migraine. Genetic influence is most striking in migraine with aura

Consequently, a low recurrence of headaches results in a low re-medication rate. Because Frova stays in a patient's system longer than other triptans, the number of tablets taken per migraine attack is lower, which Frova's developers say benefits patients in terms of cost of treatment.

"Frova provides the same relief with only one pill," Dr. Elkind says. "Patients only take one pill instead of taking multiple doses, or even sometimes changing from one class of drug to another class. Thus far in clinical practice, patients taking Frova take fewer other types of medications."

In addition to a long duration of action, Frova has been found to have a good safety profile and no drug-to-drug interactions. In addition, other triptans require dosing adjustments if patients take other medications, Frova does not.

"One of the biggest advantages to the agent is that Frova has a good safety record and there is very little in the way of drug interactions," says Dr. Elkind. "For instance, with another triptan patients taking propranolol, a beta blocker, had to take a lower dosage. They don't have to do that with frovatriptan. Also, if patients are on an oral contraceptive or other drugs to prevent migraine they don't have to take a lower dosage or amount of Frova."

Also, according to Dr. Elkind, Frova's one dose size, 2.5 milligrams, can be used for all patients, which means that physicians do not have to modify the dose for elderly people or those with moderate organ impairment.

Getting a Piece of the Triptan Pie

Triptans have been referred to as "miracle" drugs. The first in this class of drugs was Imitrex (sumatriptan), followed by Zomig (zolmitriptan), Amerge (naratriptan), Maxalt (rizatriptan), and Axert (almotriptan). Relpax (eletriptan), in development by Pfizer, is expected to be released soon.

Before the introduction of triptans, available pain medications worked by masking the pain. Triptans, however, work in the brain to stop the cause of the pain. By raising the level of serotonin in the brain, triptans reduce the dilation of surrounding blood vessels, ending the source of the pain.

The triptan class of medicines is the most commonly prescribed for migraine relief, claiming a 96.2% share of the retail market for migraine medications in 2002, according to Scott-Levin Associates. The three best-selling triptans — GlaxoSmithKline's Imitrex, Merck & Co.'s Maxalt, and AstraZeneca's Zomig — collectively generated more than

\$1.5 billion in sales last year, and accounted for 89% of the anti-migraine market, according to IMS Health. The best-selling migraine treatment, GlaxoSmithKline's Imitrex, dominated the market in 2001 with sales of \$798 million.

"Yes, migraine is a crowded market and it's hard to grow," Mr. Setar says. "But from our perspective, we've identified a segment of the patient population that would be very well-suited for Frova therapy and our growth will be pretty good and we'll be very competitive as far as where we stand in the marketplace."

Vital Healthcare, a division of Saatchi and Saatchi, holds the professional account for Frova. Frova's marketers believe that the agency is an excellent choice because of its experience in the migraine category.

ING Financial analysts estimate Frova's 2002 sales will be between \$20 million and \$25 million, with peak sales at \$200 million.

In July, ING Financial reported that Frova generated 224 new prescriptions at the end of its launch week, with representatives from UCB conducting 75% to 80% of the detailing. Analysts believe that heavy sampling will be a key part of the Frova launch strategy, as well as the drug's price per tablet of \$15.40, which analysts say is less expensive than Imitrex, but not in line with the heavy discount strategy that Pharmacia has employed with Axert, an oral triptan for the acute treatment of migraine with or without aura in adults, which was approved for U.S. marketing in May 2001.

Treatment Options

Migraine treatments are divided into two main types: preventative and abortive. Preventative drugs are used by a patient on a regular basis to prevent a migraine before it starts. Only four drugs have been approved to prevent migraine: the beta blockers propranolol and timolol, ergot alkaloid methysergide maleate, and most recently, Abbott Laboratories' anti-epilepsy drug Depakote.

Preventative treatments make up a very small part of the overall market for migraine medicines. The choice between preventative and abortive drugs depends on the frequency of the migraine attacks.

"If an individual is having one or two migraines a month, I usually prescribe a triptan, unless there is a contraindication — triptans usually are the first line of treatment," Dr. Elkind says. "Once a patient begins to have more frequent headaches, four or more

SELECTED MIGRAINE MEDICATIONS ON THE MARKET

Beta Blockers

- **INDERAL** (propranolol hydrochloride): Wyeth-Ayerst
- **BLOCADREN** (timolol maleate): Merck & Co.

Ergots

- **CAFERGOT** (caffeine, ergotamine tartrate): Novartis
- **ERGOMAR** (ergotamine tartrate): New River
- **MIGRANAL** (dihydroergotamine mesylate): Novartis
- **WIGRAINE** (caffeine, ergotamine tartrate): Organon

Triptans

- **AMERGE** (naratriptan): Glaxo-SmithKline
- **AXERT** (almotriptan): Pharmacia
- **FROVA** (frovatriptan): Elan and UCB Pharma
- **IMITREX** (sumatriptan): Glaxo-SmithKline
- **MAXALT** (rizatriptan): Merck & Co.
- **ZOMIG** (zolmitriptan): AstraZeneca



The re-medication rate for **FROVA** is low, that is the number of tablets taken per migraine attack, and obviously that has benefits in terms of cost of treatment.

headaches a month, I usually suggest they start a preventive drug."

Frova may be able to capitalize on the markets for both types of treatment. Additional development for Frova is expected to focus on preventative use.

"The current studies are aimed at prophylaxis because when you have a long duration of action it makes it ideal for dosing in advance of the problem occurring," Dr. Hutchison says. "It is an opportunity that we can exploit with the profile of this drug."

Frova is a 5-HT receptor agonist that binds with a high affinity for the 5HT_{1B} and 5HT_{1D} receptors and is believed to act on extracerebral, intracranial arteries and inhibit excessive dilation of these vessels in migraine. Scientists at Vernalis discovered in preclinical trials that Frova was cerebral selective. This means that Frova is selective for cerebral vasculature as opposed to peripheral vessels, unlike most of the triptans, which have the same effect on both central and peripheral vessels.

"The drug acts on serotonin 1B and 1D

receptors in the same way that other triptans work," Dr. Hutchison says. "But in preclinical testing, we were able to show a separation between the doses that were effective on the vessels supplying the brain over the vessels that were supplying the heart."

The cerebral selective effect has not been confirmed in humans, so that aspect of Frova will not be marketed and the drug will carry the same warning as other triptans.

In addition to options about the type of treatment a migraineur should use, physicians have a number of options when it comes to method of delivery. The most commonly prescribed method of delivery is the oral route. Tablet formulations of triptans claim 72.2% of the anti-migraine market, according to Scott-Levin Associates.

However, other routes of administration, such as subcutaneous injection, quick-dissolving tablets, and nasal sprays, offer patients faster relief.

"It's an advantage to have multiple formulations — for individuals who vomit on the onset of a headache or frequently during the headache, a nasal spray or an injectable might be better served," says Dr. Elkind. "Also in individuals who have quite rapid onset of headache, an injectable drug is best used."

Currently, Frova is available only as a 2.5-milligram tablet. However, scientists at Vernalis are looking at developing additional formulations.

Although competing triptans, such as Imitrex, Maxalt, and Zomig are available in more than one formulation, Frova's marketers do not believe this will hurt their drug's success.

"About 90% of the migraine market resides in oral treatments because the oral route is the most preferred," Mr. Setar says. "Injectables and nasal sprays are for more severe migraine, where there is rapid onset — that is not the patient type that we are necessarily going after."

Looking Ahead

While Frova's marketers expect that the triptan will create a niche for itself, Vernalis scientists are looking to expand the drug's treatment possibilities. Trials investigating the use of frovatriptan in the prevention of menstrual migraine, according to Vernalis, will be completed ahead of schedule. The company expects to report findings from the study in early September 2002. In addition, Frova is being studied in adolescents 12 years old to 17 years old in the U.S.

"We have been conducting a U.S. trial in more than 400 women with menstrual-cycle associated migraine to prevent the headache, which is a slightly different approach than treatment once the headache has started," Dr. Hutchison says.

In January 2002, the mutual recognition

procedure for regulatory approval throughout the European Union was completed for Frova, with France acting as the reference member state. Menarini Group, an Italian-based pharmaceutical company, holds the exclusive marketing rights throughout Europe, where the drug will be marketed as Migard. A European rollout is expected by the end of the year. ♦

PharmaVoice welcomes comments about this article. E-mail us at feedback@pharmalinx.com.

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