HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

8 November 2006

TIGREAT 2.5 mg, film-coated tablets
Box of 2 tablets (CIP : 357 553-4)
Box of 6 tablets (CIP : 357 554-0)
Box of 12 tablets (CIP : 361 564-7)

Applicant : MENARINI FRANCE

Frovatriptan
List I

Date of Marketing Authorisation(MA): 12 December 2000

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals

Health Technology Assessment Division

1 PROPERTIES OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Frovatriptan (succinate monohydrate)

1.2. Indication

Acute treatment of the headache phase of migraine attacks with or without aura.

1.3. Dosage

Adults (18 to 65)
The recommended dose is one 2.5-mg tablet of frovatriptan.

If the migraine symptoms recur after initial relief, a second tablet may be taken, provided there is an interval of at least two hours between the two doses.

The total daily dose must not exceed two 2.5 mg tablets.

Children and adolescents (under 18):
There is no data on the use of frovatriptan in children and adolescents. Therefore, its use in these age groups is not recommended.

Elderly patients (over 65 years):
Limited data is available on the use of this product in patients over 65. Therefore, its use in this category of patients cannot be recommended.

Patients with renal impairment:
No dose adjustment is required in patients with renal impairment.

Patients with hepatic impairment:
No dose adjustment is required in patients with slight or moderate liver impairment.
Frovatriptan is contraindicated in patients with severe liver impairment.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2005)

N : Central Nervous System
N02 : Analgesics
N02C : Antimigraine preparations
N02C C : Selective serotonin (5HT1) agonists
N02CC07 : Frovatriptan.

2.2. Medicines in the same therapeutic category

Triptans indicated in the treatment of migraine attacks:

- Almotriptan : Almogran®
- Eletriptan : Relpax®
- Naratriptan : Naramig®
- Sumatriptan : Imigrane®
- Zolmitriptan : Zomig®, Zomigoro®

2.3. Medicines with a similar therapeutic aim

All anti-migraine products.

3 ANALYSIS OF AVAILABLE DATA

The dossier submitted by the pharmaceutical company includes three studies performed on the treatment of moderate or severe migraine attacks:

- 2 studies[1] assessing the efficacy of frovatriptan versus placebo (studies which had already submitted in August 2001 and December 2002);
- 1 non-inferiority study assessing the efficacy of frovatriptan versus sumatriptan (study already submitted in August 2001 and December 2002)

One study[2] assessing the prophylactic efficacy of (which does not correspond to Marketing Authorisation Indication) frovatriptan versus placebo in patients suffering from menstrual migraines according to the criteria defined by the IHS was added to the dossier. This study will not be discussed in this opinion.

3.1. Studies comparing frovatriptan versus placebo

Two superiority versus placebo studies assessed the efficacy of frovatriptan during three successive migraine attacks.

The inclusion and non-inclusion criteria were similar in both studies.

[1] Ryan R, Géraud G, Goldstein J, Cady R, Keywood C. Clinical efficacy of frovatriptan : placebo-controlled studies. Headache 2002; 42 (suppl 2) : S84-S92.
[2] Silberstein SD, Elkind AH, Schreiber C, Keywood C. A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. Neurology 2004 ; 63 : 261-9.

The main efficacy criterion was patient relief after two hours (defined by a shift from moderate or severe headache to no or slight headache) expressed as percentage of patients.

In the second study, the recurrence rate after 24 hours was used as the second principal efficacy criterion.

Headache absence rates two and four hours after taking the product were among the secondary efficacy criteria assessed.

Percentages observed in the two studies (ITT populations):

	Study 1 (N=308)		**Study 2 (N=1,111)**	
	Placebo	**Frovatriptan**	**Placebo**	**Frovatriptan**
Relief after 2 hours	21 %	39 %	27 %	46 %
Relief after 4 hours	31 %	56 %	38 %	65 %
No headache after 2 hours	2 %	14 %	3 %	13 %
No headache after 4 hours	10 %	27 %	14 %	32 %

The rates of patients experiencing relief after 2 hours and 4 hours were significantly higher in the frovatriptan group than in the placebo group, as were the headache absence rates after 2 hours and 4 hours.

The tolerance results of these studies were described in another publication[3]. This publication also includes the tolerance findings of a study which assessed the efficacy of various doses of frovatriptan in the treatment of a migraine attack, and the results of a long-term (12-month) open-label tolerance study.

The overall results of these studies show:
- 1% cessation of treatment as a result of adverse events in the placebo groups and the frovatriptan groups;
- 5% cessation of treatment in patients included in the long-term open-label tolerance study;
- 47% adverse effects in the frovatriptan groups (N = 1,554) compared to 34% in the placebo groups (N = 838);

The main adverse effects observed were nervous system disorders such as dizziness, forms of paresthaesia, and headache (18% in the frovatriptan group versus 12% in the placebo group), gastrointestinal disorders such as nausea, dry mouth, dyspepsia and vomiting (15% versus 13%), worsening of general state of health, particularly fatigue (12% versus 9%) and psychiatric disorders, mainly drowsiness (10% versus 7%).

3.2. Non-inferiority study of frovatriptan 2.5 mg versus sumatriptan 100 mg

This was a non-inferiority study of frovatriptan compared to sumatriptan 100 mg assessed over the course of three successive migraine attacks.

This study has not been published and the results took part of the study report supplied by the pharmaceutical firm.

It should be noted that the current recommended dose of sumatriptan is one 50-mg tablet.

[3] Géraud G, Spierings ELH, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. Headache 2002 ;42 (suppl 2) : S93-S92.

1,335 patients were randomised. The principal efficacy criterion was relief from the migraine attack after two hours. A second principal efficacy criterion was defined: the 24-hour recurrence rate (recurrence was assessed between 4 and 24 hours after the product was taken).

Frovatriptan was to be considered not inferior to sumatriptan 100 mg if the difference between the two groups (frovatriptan group minus sumatriptan group) in terms of the percentages of patients experiencing relief after two hours was less than 10%.

Patients were given frovatriptan 2.5 mg, sumatriptan 100 mg or placebo during their first migraine attack. They were given frovatriptan 2.5 mg during their second and third attacks (open-label treatment).

Results of the analysis of the principal efficacy criteria:

	Frovatriptan group	**Sumatriptan group**	**Placebo group**	**Difference between treatments**
Relief after 2 h (PP population)	156/420 37.1 %	206/435 47.3 %	49/211 23.2 %	- 10.2 %
Relief after 2 h (ITT population)	160/438 36.5 %	206/441 46.7 %	51/225 22.7 %	- 10.2 %
Recurrence after 24 h (ITT population)	25 %	31 %	31 %	- 6 %

The study report does not specify the 95% confidence intervals for the difference between treatments.

The per-protocol analysis did not show frovatriptan to be non-inferior to sumatriptan in terms of relief from the attack after two hours.

The intention to treat (ITT) results confirmed those observed in the per-protocol analysis.

Analytical results for recurrence after 24 hours are available for ITT but not for per-protocol.

Results of the ITT analysis on the secondary efficacy criteria (PP results not supplied):

	Frovatriptan group	**Sumatriptan group**	**Placebo group**	**Difference between treatments**
No headache after 2 hours	9 %	18 %	3 %	9 %
No headache after 4 hours	31 %	42 %	9 %	11 %

Tolerance results (N=1,206):

- Adverse effects were observed in 36% of patients in the frovatriptan group versus 43% of patients in the sumatriptan group during the first migraine attack (28% in the placebo group).

- After the first migraine attack, three cessations of treatment due to adverse events were reported in the frovatriptan group (N = 480) versus 5 in the sumatriptan group (N = 482) (there was one cessation of treatment in the placebo group). No serious adverse effects were reported.

- The most frequent adverse effects were:

	Sumatriptan	Frovatriptan	Placebo
Vertigo	4 %	5 %	2 %
Paresthaesia	5 %	3 %	2 %
Nausea	6 %	3 %	2 %
Fatigue	5 %	3 %	1 %
Chest pain	3 %	1 %	< 1%

- 8 cessations of treatment were reported during the open-label phase of treatment with frovatriptan.

3.3. Meta-analysis conducted by FERRARI 2002[4]

A meta-analysis published in 2002 compared 53 clinical trials involving triptans. As far as tolerance is concerned, the authors' analysis found that triptans have relatively similar levels of tolerance.

With regard to efficacy, data published on frovatriptan indicates that it is less effective than other triptans, especially sumatriptan (the reference triptan used in most clinical studies).

3.4. Conclusion

Studies have showed frovatriptan to be more effective than placebo in offering relief from moderate or severe migraine attacks after two hours.

It should be noted that 50 mg is the current standard dose for sumatriptan.

In the non-inferiority study of frovatriptan compared to sumatriptan, the per-protocol analysis did not show frovatriptan not to be inferior to sumatriptan 100 mg in terms of relief from migraine attack after 2 hours.

Frovatriptan 2.5 mg caused fewer adverse effects than sumatriptan 100 mg (36% versus 43%).

The number of cessations of treatment as a result of adverse effects was similar in both groups of patients.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Migraine is a painful, disabling condition that has a marked negative effect on quality of life.

This medicine is a symptomatic therapy.

The efficacy/safety ratio for this medicine is high.

This medicine is a second-line treatment.

[4] Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-$HT_{1B/1D}$ agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. Cephalalgia 2002, 22 : 633-58.

There are alternative drug treatments that could be used instead of this proprietary product.

Public health benefit:

The public health burden due to migraine is significant.
Improving control of this condition is a public health priority (national technical objective definition group priority). There are many chemicals available offering relief to most patients and improving their quality of life. .
Regarding available data, frovatriptan is not expected to have a greater impact on morbidity and quality of life than other existing triptans.
TIGREAT is therefore unlikely to make any improvement to meeting the identified public health need.
Therefore, TIGREAT is not expected to have any public health benefit.

The actual benefit of this medicine is substantial.

4.2. Improvement in actual benefit

Frovatriptan does not offer any improvement in clinical benefit compared to other triptans used in the treatment of migraine attacks (IAB V).

4.3. Therapeutic use

The ANAES recommendations issued in 2002[5] on the diagnosis and treatment of migraine attacks draws a distinction between:

- non-specific treatments (analgesics and non-steroidal anti-inflammatories);
- and specific treatments (triptans and ergot derivatives) which, by acting on 5 HT1B/D receptors, inhibit the neurogenic inflammation and vasodilation which are thought to underlie migraine headache.

<u>Patients already being treated with non-specific treatments:</u>

During the first consultation, patients should be asked about about their usual treatment and the relief that this treatment brings (professional consensus):

- Do you obtain significant relief two hours after taking the product?
- Do you tolerate this drug well?
- Do you just take one dose?
- Does taking this drug allow you to rapidly resume your normal social, family and professional activities?

Patients who reply yes to these four questions should remain on the same treatment.

Patients who reply no to at least one of the four questions should be prescribed an NSAID and a triptan on the same prescription. Patients should be advised to start by taking the NSAID and to keep triptan in reserve in case they are still in pain two hours after taking the NSAID. Patients who experience no relief from the NSAID or who do not tolerate it should be prescribed a triptan for immediate use.

<u>Patients already being treated with specific treatments:</u>

• Ergotamine tartrate

The professional consensus is that patients who experience relief on taking ergotamine should remain on this treatment provided that it is not contraindicated and that they are not increasing doses.

[5] [Diagnosis and treatment of migraine in adults and children: clinical and economic aspects.]

• Triptans
There are minor (grade B) differences in efficacy and tolerance between the various triptans.

Patients who do not respond to one triptan may respond to another (professional consensus). Patients who do not respond to a triptan during the first attack may respond in subsequent attacks (grade A). Before concluding that a triptan is ineffective it is recommended that it be tried during at least three attacks, unless it is not well tolerated (professional consensus).

4.4. Target population

The target population has been estimated on the basis of the following assumptions:
- The prevalence of migraine among adults aged between 18 and 65 is estimated at between 12 and 15%[4];
- Data published by the French statistical office INSEE put the number of people aged between 18 and 65 living in France on 1 January 2006 at 37,442,095.
- About 50% of these patients experience relief when they take a standard painkiller.

In the light of this information, the target population would be 2.2 to 2.8 million.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services within the marketing authorisation indication.

4.5.1. Packaging
Appropriate for prescription conditions.

4.5.2. Reimbursement rate: 65%