The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

23 May 2012

TAMIK Ge 3 mg, soft capsule
B/60 (CIP code: 322 714-1)

Applicant: IPRAD
dihydroergotamine mesylate
ATC code: N02CA01 (ergot alkaloid)

List II

Date of Marketing Authorisation (national procedure): 4 April 1979

Reason for request: Re-assessment of Actual Benefit of proprietary medicinal products based on dihydroergotamine, in accordance with Article R 163-21 of the social security code.
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Dihydroergotamine mesylate

1.2. Indications

“ - Preventative treatment of migraine attacks.
  - Offered in the treatment of orthostatic hypotension.
  - Alleviation of symptoms of venous and lymphatic insufficiency (heavy legs, pain, restless legs syndrome).
  - Offered in the treatment of orthostatic hypotension.”

The only indication qualifying for reimbursement is that of the preventative treatment of migraine (Decree of 9 August 2007 – Official Gazette of 28 August 2007) which is being put forward for re-assessment of actual benefit.

1.3. Dosage

One capsule three times daily, to be taken during mealtimes, with a glass of water.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

N : Nervous system
02 : Analgesics
C : Antimigraine preparations
A : Ergot alkaloids
01 : Dihydroergotamine

2.2. Medicines in the same therapeutic category

These are rye ergot derivatives indicated in the preventative treatment of migraine.
  - based on dihydroergotamine:
    DIHYDROERGOTAMINE AMDIPHARM 3 mg, tablet
    DIHYDROERGOTAMINE AMDIPHARM 2 mg/ml, oral solution in drops
    IKARAN LP 5 mg, tablets
    IKARAN Ge 2 mg/ml, oral solution in drops (generic)
    SEGLOR 5 mg, hard capsule
    SEGLOR LYOC 5 mg, oral lyophilisate
  - based on methysergide: DESERNIL 1.65 mg, tablet
2.3. Medicines with a similar therapeutic aim

Beta-blockers:
- metoprolol (LOPRESSOR, SELOKEN)
- propranolol (AVLOCARDYL). Propranolol is also indicated in the preventative treatment of cluster headache

Antidepressant: amitriptyline (LAROXYL)

Anticonvulsant: topiramate (EPITOMAX)

Other products indicated in the preventative treatment of migraine:
- flunarizine (SIBELIUM),
- indoramine (VIDORA),
- oxetorone (NOCERTONE),
- pizotifen (SANMIGRAN).

3 ANALYSIS OF AVAILABLE DATA

Prescribing data:
According to IMS data (moving annual total November 2011), 72,000 prescriptions were issued for TAMIK.
The small number of prescriptions is insufficient to allow a qualitative analysis of the data.

Efficacy
The first proprietary medicinal products based on dihydroergotamine (DHE) in the preventative treatment of migraine appeared in the late 1940s. The efficacy data available at this time are incomplete.

The available efficacy data concerning DHE are as follows:
- one non-comparative study,¹
- one non-comparative study at an off-label dosage,²
- one study with an intravenous form in the treatment of migraine attacks,³
- one study conducted with a form of DHE for nasal use in the treatment of migraine attacks.⁴

These studies were not taken into consideration by the Transparency Committee because their clinical relevance was insufficient to permit an assessment of the magnitude of the effect of the DHE in the Marketing Authorisation indication of preventative treatment of migraine. Moreover, an open-label study evaluating DHE versus flunarizine, with no identified

primary endpoint, published in Spanish (with only the abstract in English) and published in 1989, was not taken into account.

- The efficacy of DHE was evaluated in a randomised, double-blind study versus placebo. This unpublished study was carried out in 1984 in 40 adults having at least three migraine attacks per month. The diagnosis of migraine was based on the presence of paroxysmal headaches with at least two of the following criteria: hemicranial location, ophthalmoplegic migraine, family history of migraine, migraine starting before the age of 20 years. These out-of-date inclusion criteria no longer meet present-day standards. DHE was administered to a group of 20 subjects at a dosage of 5 mg twice daily, i.e. the dosage given in the Marketing Authorisation, the other group being on placebo. Not a single primary endpoint was identified among the 5 assessment criteria. After 30 days of treatment, the number of attacks during the treatment was reduced by 1.95 attacks in the IKARAN group and by 0.42 in the placebo group (p < 0.0001). In view of the short treatment duration, the inclusion criteria, and the lack of a primary endpoint, these results need to be interpreted with caution.

- A combined analysis of clinical studies in which DHE was evaluated was conducted in 2010. Most of the studies were open-label, uncontrolled and evaluated the efficacy of DHE in the treatment of migraine attacks and in the preventative treatment of migraine. In addition, it combined phase I, II and III studies. The forms administered were oral, nasal, subcutaneous and intravenous. No information is available concerning dosages and treatment durations. In light of these methodological shortcomings, this combined analysis did not permit any assessment of the extent of the effect of DHE in the preventative treatment of migraine.

- PROMISE Study

This multicentre, randomised, double-blind study versus placebo. The migraine subjects were treated for 5 months with dihydroergotamine (10 mg/day) or received a placebo. This study, previously examined by the Committee in 2003 (see opinion of 2 April 2003), showed that DHE was no different from placebo in terms of reducing the frequency of migraine attacks (primary endpoint). A difference in favour of dihydroergotamine was observed in the following criteria: reduction in the mean duration of attacks, decreased intensity of attacks, patient preference. These results in terms of the secondary criteria endow them with no more than exploratory value.

The applicant’s dossier also comprises an analysis by subgroup of the PROMISE study involving 288 patients defined by a score below 80 on the MSQ scale, which corresponds to patients with a high degree of functional disability, who are likely to need preventative treatment. While this scale is cited in English-language publications, the only questionnaire validated in France is the QVM scale (Quality of life of migraine sufferers). Furthermore, the choice of a threshold of 80 is based on a “consensus of experts on the study’s scientific committee” and not on literature data. In any event, this sub-group of patients was defined a posteriori. In view of these shortcomings these results cannot be taken into account by the Transparency Committee.

Adverse effects – AFSSAPS data

In 2007, the SPCs of proprietary medicinal products based on dihydroergotamine were amended to include the risks of fibrosis and arterial vasoconstriction. The amendments concerned the sections on “Side effects”, “Contraindications”, “Warnings and precautions for use”, “Effects on ability to drive and use machines” and “Overdose”.

A pharmacovigilance survey of ergot derivatives was launched on 22 March 2011 on the risks of fibrosis, valve disease and arterial hypertension. At the same time, a re-assessment of the risk/benefit ratio of these products was initiated on 4 April 2011.

Between 1 January 1994 and 31 March 2011, the Regional Pharmacovigilance Centres identified 32 cases associated with the intake of dihydroergotamine, including:
- 21 cases of fibrosis: 11 retroperitoneal, 3 mediastinal, 4 pleural, 1 myocardial and 2 pulmonary. Two of the observations were cases of multiple fibrosis: mediastinal and retroperitoneal in one patient, and retroperitoneal and pleural in the other.
- 6 cases of valve disease. In 5 cases, another suspect medication was involved (Mediator or Celance). Since the end of the survey period, 7 new cases of valve disease have been reported (including 5 with Mediator as the suspect medication).
- 5 cases of PAH, unrelated to any valve disease. In 4 cases, concomitant use of an appetite suppressant was found.

Examination of the literature has revealed various cases of fibrosis after prolonged dihydroergotamine treatment, but not a single case of valve disease or PAH. Fibrosis tends to follow prolonged treatment and can be serious. It is mentioned in the SPCs of different proprietary medicinal products.

As regards valve disease and PAH, there is no particularly strong signal, but recent reports of new cases and the pharmacological mechanism of action of dihydroergotamine mean that this risk cannot be ruled out.

The Pharmaco-Toxico-Clinical Working Group of 6 October 2011 proposed withdrawing the indication of preventative treatment of migraine for dihydroergotamine.

For all ergot derivatives, the Pharmacovigilance Committee noted that the risk of fibrosis had already been reported and that the risks of hypertension and valve disease could not be ruled out. It came to the unanimous conclusion that the risk/benefit ratio for dihydroergotamine in the preventative treatment of migraine was not favourable. The Pharmaco-Toxico-Clinical Working Group of 6 October 2011 proposed removing this indication for proprietary medicinal products based on oral dihydroergotamine.

The Marketing Authorisation Committee concluded on 15 December 2011 that the risk/benefit ratio of dihydroergotamine in the preventative treatment of migraine was unfavourable.

Arbitration under Article 31 of Directive 2004/27/EC may be initiated with a view to an assessment being carried out at European level. It will lead to a European Commission decision which will be binding on all Member States.

Applicant’s pharmacovigilance data

The applicant provided a summary of the last pharmacovigilance report covering the period from 1 April 2008 to 4 April 2011. During this period, no spontaneous notifications were reported to the applicant.

Between 5 April 2011 and 26 January 2012, one case of valve disease was notified in one female patient who had no risk factors for valve disease.

Conclusion

The efficacy data relating to DHE-based products are out-of-date and incomplete. The demonstration of the efficacy of dihydroergotamine in the preventative treatment of migraine offers a very low level of evidence.
As with all ergot derivatives, there are risks of retroperitoneal, pleuropulmonary, pericardial and valve fibrosis.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Migraine is a painful condition characterised by a marked deterioration in quality of life.

This proprietary medicinal product falls into the category of a preventive therapy.

The efficacy/adverse effects ratio of these proprietary medicinal products in the preventive treatment of migraine is unfavourable.

There are treatment alternatives to this proprietary medicinal product with better evidence of efficacy and better safety, especially products based on propranolol and metoprolol.

The actual benefit offered by this product in the preventative treatment of migraine is insufficient.

4.2. Transparency Committee recommendations

The transparency Committee does not recommend continued inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services.