IKARAN LP 5 mg, tablets
B/30 (CIP: 339 287-4)

IKARAN Ge 2 mg/ml, oral solution in drops
Vial of 50 ml (CIP: 321 064-3)

Applicant: PIERRE FABRE

dihydroergotamine mesylate
ATC code: N02CA01 (ergot alkaloid)

List II

Date of Marketing Authorisation (national procedure):
IKARAN LP 5 mg, tablets: 19 September 1995
IKARAN Ge 2 mg/ml, oral solution in drops: 21 March 1977

Reason for request:
- Renewal of inclusion on the list of proprietary medicinal products refundable by National Health Insurance.
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Dihydroergotamine mesylate

1.2. Indications

- Preventive treatment of migraine attacks
- 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 and the application for continued inclusion on the list of reimbursable items.

1.3. Dosage

One tablet twice daily or 30 drops three times daily.

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
- based on dihydroergotamine:
  DIHYDROERGOTAMINE AMDIPHARM 3 mg, tablet
  DIHYDROERGOTAMINE AMDIPHARM 2 mg/ml, oral solution in drops
  SEGLOR 5 mg, hard capsule
  SEGLOR LYOC 5 mg, oral lyophilisate
  TAMIK Ge 3 mg, soft capsule (generic)
- 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), 77,000 prescriptions were issued for IKARAN. The small number of prescriptions is insufficient to allow a qualitative analysis of the data.

3.1. 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 dihydroergotamine 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. Furthermore, 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.

  IKARAN 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, with the other group being on placebo. Not a single primary efficacy endpoint was identified among the five 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\(^5\) of clinical studies that had evaluated DHE was carried out in 2010. Most of the studies were uncontrolled, in open-label mode and evaluated the efficacy of DHE in the treatment of migraine attacks and in the preventative treatment of migraine. In addition, it combined studies of phase I, II and III. The forms administered were oral, nasal, subcutaneous and intravenous. No information is available concerning dosages or treatment durations. In light of these methodological shortcomings, this combined analysis did not permit any assessment of the size of the effect of DHE in the preventative treatment of migraine.

- PROMISE Study\(^6\)

  This was a 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 of less than 80 on the MSQ scale, which corresponds to patients with a high degree of functional disability, liable 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 \textit{a posteriori}.

  In view of these shortcomings, these results cannot be taken into account by the Transparency Committee.

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\(^6\) Pradalier et al. ‘The PROMISE: PROphylaxis of Migraine with Seglor in French Primary Care » Drugs 2004; 18: 1149-63.
3.2. Adverse effects

**AFSSAPS data**

In 2007, the SPCs of dihydroergotamine-based proprietary medicinal products 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 started on 4 April 2011.

Between 1 January 1994 and 31 March 2011, the CRPVs 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, 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.

Taking ergot derivatives as a whole, the Pharmacovigilance Committee has noted that there was already an awareness of the risk of fibrosis 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 of dihydroergotamine in the preventative treatment of migraine was unfavourable. 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 was initiated with a view to having an assessment carried out at European level. It will lead to a European Commission decision that will be binding on all Member States.

**Applicant’s pharmacovigilance data**

The applicant provided pharmacovigilance data (PSUR) covering the period from 1 April 2006 to 31 December 2011. During this period, 60 adverse events involving 31 patients were observed.

The adverse effects most commonly related to cases of overdose, ergotism, nausea, vomiting, rash and pruritus.
These data also report on one case of valve disease and two cases of pulmonary disorders (one case of fibrosis and the other without an established diagnosis).

In addition, two cases of congenital heart defects were reported in children whose mother had been treated with IKARAN during pregnancy. According to the imputability method used, the causal relationship with IKARAN was judged doubtful in both cases.

3.3. 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 cardiac valve fibrosis.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

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

These proprietary medicinal products fall into the category of preventive therapy.

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

There are medicinal treatment alternatives to these proprietary medicinal products with a higher level of evidence of efficacy and better safety, in particular products based on propranolol and metoprolol.

The actual benefit offered by this proprietary medicinal 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.