TRANSPARENCY COMMITTEE

OPINION

23 May 2012

DIHYDROERGOTAMINE AMDIPHARM 3 mg tablets
B/60 (CIP code: 364 381-0)
Bottle/60 (CIP code: 364 631-7)

DIHYDROERGOTAMINE AMDIPHARM 2 mg/ml oral solution
Vial of 50 ml (CIP code: 364 386-2)

DIHYDROERGOTAMINE AMDIPHARM 1 mg/ml solution for injection
ampoules
B/2 ampoules (CIP code: 364 383-3)

Applicant: CENTRE SPECIALITES PHARMACEUTIQUES (CSP)

dihydroergotamine (mesylate)
ATC code: N02CA01 (ergot alkaloids)

List II

Date of Marketing Authorisation (national procedure):
DIHYDROERGOTAMINE AMDIPHARM 3 mg tablets: 20/06/1986
DIHYDROERGOTAMINE AMDIPHARM 2 mg/ml oral solution: 20/06/1986
DIHYDROERGOTAMINE AMDIPHARM 1 mg/ml solution for injection: 23/10/1986

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

DIHYDROERGOTAMINE AMDIPHARM 3 mg tablets and 2 mg/ml oral solution:
- Preventative treatment of migraine.
- Improvement of symptoms related to venous and lymphatic insufficiency (heavy legs, pain, restless legs syndrome).
- Suggested for the treatment of orthostatic hypotension.”

The only reimbursable indication is preventative treatment of migraine (Order of 9 August 2007 – Official Gazette of 28 August 2007), which is the subject of this re-assessment of actual benefit.

DIHYDROERGOTAMINE AMDIPHARM 1 mg/ml solution for injection:
“Treatment of acute migraine.”

1.3. Dosage

Tablets or oral solution
One tablet three times per day or 30 drops three times per day.

Solution for injection
One ampoule (1 ml) via the IM, SC or IV route.
A second injection may be given after 30-60 minutes if the response to the first injection is insufficient.
In children aged under 6 years: ½ ampoule per day.

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

DIHYDROERGOTAMINE AMDIPHARM 3 mg tablets and DIHYDROERGOTAMINE AMDIPHARM 2 mg/ml oral solution:

Ergot derivatives indicated in the preventative treatment of migraine.
- Dihydroergotamine-based drugs:
  IKARAN LP 5 mg prolonged-release tablets
  IKARAN Gé 2 mg/ml oral solution (generic)
  SEGLOR 5 mg capsules
  SEGLOR LYOC 5 mg oral lyophilisate
  TAMiK Gé 3 mg soft gel capsules (generic)
- Methysergide-based drugs: DESERNIL 1.65 mg tablets

**DIHYDROERGOTAMINE AMDIPHARM 1 mg/ml solution for injection:**
Ergot derivatives indicated in acute migraine:
DIERGOSPRAY (dihydroergotamine) nasal spray
GYNERGENE CAFEINE tablets

**2.3. Medicines with a similar therapeutic aim**

**DIHYDROERGOTAMINE AMDIPHARM 3 mg tablets and DIHYDROERGOTAMINE AMDIPHARM 2 mg/ml oral solution:**
Beta blockers:
- metoprolol (LOPRESSOR, SELOKEN)
- propranolol (AVLOCARDYL)

Antidepressants: amitriptyline (LAROXYL)

Anticonvulsants: topiramate (EPITOMAX)

Other products indicated in the preventative treatment of migraine:
flunarizine (SIBELIUM)
indoramin (VIDORA)
oxetorone (NOCERTONE)
pizotifen (SANMIGRAN)

**DIHYDROERGOTAMINE AMDIPHARM 1 mg/ml solution for injection:**
Medicines with Marketing Authorisation for the treatment of acute migraine.

NSAIDs indicated in the treatment of acute migraine:
- MIGADVIL (ibuprofen) 400 mg soft gel capsules
- BIPROFENID (ketoprofen) 150 mg scored tablets

Related SALICYLATES:
- CEPHALGAN (carbasalate calcium + metoclopramide) effervescent powder for oral solution in sachets
- MIGPRIV (lysine acetylsalicylate + metoclopramide) powder for oral solution in sachets

Triptans:
- ALMOGRAN (almotriptan) film-coated tablets
- RELPAX (eletriptan) 20 mg and 40 mg film-coated tablets
- NARAMIG (naratriptan) 2.5 mg film-coated tablets
- IMIGRANE (sumatriptan) tablets and nasal spray
- ZOMIG (zolmitriptan) 2.5 mg film-coated tablets
- ZOMIGORO (zolmitriptan) 2.5 mg orodispersible tablets
Prescription data:
According to IMS data (moving annual total, November 2011), 2000 prescriptions have been issued for DIHYDROERGOTAMINE AMDIPHARM oral solution. The other forms were not included in the sample. The low number of prescriptions is insufficient for qualitative data analysis.

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.

\(^3\) Charles JA, Von Dohn P. Outpatient home-based continuous intravenous dihydroergotamine therapy for intractable migraine. Migraine 2010; 50: 852-862.
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 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 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.

Pharmacovigilance data from the pharmaceutical company

The pharmaceutical company has supplied pharmacovigilance data (PSUR) covering the period from 1 May 2006 to 30 April 2009. During this period, 169 adverse effects, including 84 serious adverse effects, were reported in 62 patients. The most common serious adverse effects came under the MedDRA SOCs of “nervous system disorders” (n=17), “general disorders and administration site conditions” (n=10) and “gastrointestinal disorders” (n=8).

In addition, three cases of abnormalities (hydrocephalus, hypothyroidism and heart defect) were reported in children whose mothers were treated with dihydroergotamine during pregnancy.

Conclusion

The efficacy data for DHE-based medicinal products are old and patchy. The level of evidence demonstrating the efficacy of dihydroergotamine in the preventative treatment of migraine remains very weak.

As with all ergot derivatives, there are risks of retroperitoneal, pleuropulmonary, pericardial and cardiac valve fibrosis.
4.1. Actual benefit

Migraine is a painful condition that results in a marked deterioration in quality of life.

These proprietary medicinal products are intended as preventative therapy (orally administered forms) and curative therapy (solution for injection).

The efficacy/adverse effects ratio for the products indicated in the preventive treatment of migraine is unfavourable.

The efficacy/adverse effects ratio for the product indicated in the treatment of acute migraine is low.

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

The actual benefit of the proprietary medicinal products administered orally is insufficient in the preventative treatment of migraine.

The actual benefit of the medicinal product administered via injection is moderate in the treatment of acute migraine.

4.2. Transparency Committee recommendations

DIHYDROERGOTAMINE AMDIPHARM 3 mg tablets
DIHYDROERGOTAMINE AMDIPHARM 2 mg/ml oral solution

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.

DIHYDROERGOTAMINE AMDIPHARM 1 mg/ml solution for injection ampoules

The transparency Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance in the indication and at the dosage in the Marketing Authorisation.