HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

23 May 2012

GYNERGENE CAFEINE, tablets
B/20 (CIP code: 304 678-7)

Applicant: CENTRE SPECIALITÉS PHARMACEUTIQUES

Ergotamine tartrate
Anhydrous caffeine
ATC code: N02CA52 (ergot alkaloid)

List I

Date of validated Marketing Authorisation: 15 May 1991

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.
- Renewal of inclusion on the list of medicinal products refundable by National Health Insurance

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Ergotamine tartrate
Anhydrous caffeine

1.2. Indication

“Treatment of migraine attacks.”

1.3. Dosage

Adults:
The usual recommended dose is two tablets (i.e. 2 mg of ergotamine tartrate) as soon as the prodrome of the attack occurs.

If the pain persists beyond half an hour, this administration may be repeated. However, under no circumstances must the maximum daily dose of six tablets, i.e. 6 mg of ergotamine tartrate, be exceeded.

It is strongly recommended not to exceed, in one week, the equivalent of ten tablets of Gynergene caffeine.

Children:
The usual dosage is half the adult dosage. However, Gynergene caffeine is not recommended for children under the age of 10 years.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

N : Nervous system
02 : Analgesics
C : Antimigraine preparations
A : Ergot alkaloids
52 : Ergotamine

2.2. Medicines in the same therapeutic category

These are rye ergot derivatives indicated in the treatment of migraine attacks:
DIERGOSPRAY (dihydroergotamine), nasal spray solution
DIHYDROERGOTAMINE AMDIPHARM 1 mg/ml solution for injection

2.3. Medicines with a similar therapeutic aim

These are proprietary medicinal products with Marketing Authorisation in the treatment of migraine attacks.

NSAIDS indicated in the treatment of migraine attacks:
- MIGADVIL 400 mg (ibuprofen), soft capsule;
- BIPROFENID 150 mg (ketoprofen), scored tablet;

SALICYLATE combinations:
- CEPHALGAN (calcium carbasalate + metoclopramide), effervescent powder for oral solution in a sachet.
- MIGPRIV (lysine acetylsalicylate + metoclopramide), powder for oral solution in a sachet.

Triptans:
- ALMOGRAN (almotriptan), film-coated tablet
- RELPAX 20 mg and 40 mg (eletriptan), film-coated tablets
- NARAMIG 2.5 mg (naratriptan), film-coated tablet
- IMIGRANE (sumatriptan), tablet and nasal spray solution
- ZOMIG 2.5 mg (zolmitriptan), film-coated tablet
- ZOMIGORO 2.5 mg (zolimitriptan), orodispersible tablet

3 ANALYSIS OF AVAILABLE DATA

Prescription data:
According to IMS data (moving annual total November 2011), 33,000 prescriptions were issued for GYNERGENE CAFFEINE.
The small number of prescriptions is insufficient to allow a qualitative analysis of the data.
This proprietary medicinal product was first introduced to the world market in 1948.

Efficacy
The efficacy of ergotamine in the treatment of migraine attacks was shown in placebo-controlled studies.[1,2,3]

One double-blind study[4] evaluated the efficacy of ergotamine versus naproxen in 79 migraine subjects. Naproxen was more effective in relieving headache (primary endpoint), but with no difference as regards the duration and severity of the attack.

AFSSAPS data
Following a pharmacovigilance survey concerning ergot derivatives and based on data gathered between 1 January 1994 and 31 March 2011, the Regional Pharmacovigilance Centres found four cases associated with taking this proprietary medicinal product (two of them resulting from chronic use over a period of more than 180 months):
- one case of retroperitoneal fibrosis,
- one case of pleural fibrosis,
- one case of pulmonary hypertension with no further details,
- one case of multiple valve disease in a patient who had in addition been receiving dexfenfluramine and benfluorex.

According to AFSSAPS, the literature confirms that prolonged use of this substance, which is not indicated for the treatment of migraine attacks, and drug dependence favour the onset of valve disease. There is no known estimate of the number of patients treated long-term in France.

The AFSSAPS rapporteur concluded that a re-assessment of the risk/benefit ratio of this proprietary medicinal product in migraine was essential in light of its off-label use as a preventative treatment – and therefore not just for the treatment of migraine attacks.
Little is known about the actual use of ergotamine, especially in prolonged treatment, where the risk appears to be greatest.
This vote in favour of a re-assessment of the risk/benefit ratio of ergotamine was unanimous.

Applicant's pharmacovigilance data
The applicant provided pharmacovigilance data covering the period from 1 December 2006 to 30 November 2009. During this period, 110 cases of adverse events, 43 of them serious, were observed.

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[1] Dahlof C. Placebo-controlled clinical trials with ergotamine in the acute treatment of migraine. Cephalalgia. 1993; 13:166-71.
[2] Kinnunen et al. Placebo-controlled double-blind trial of pirprofen and an ergotamine tartrate compound in migraine attacks.
[3] Bigal ME, Tepper SJ. Ergotamine and dihydroergotamine: a review. Curr Pain Headache Rep. 2003; 7: 55-62.
[4] Treves TA, Streiffler M, Korczyn AD. Naproxen sodium versus ergotamine tartrate in the treatment of acute migraine attacks. Headache. 1992; 32: 280-2.

Two deaths were reported during this period: one diagnosed case of valve disease and one case of poisoning with ergotamine administered by injection.

Conclusion

The old data for the efficacy of ergotamine in the treatment of migraine attacks were established versus placebo. The efficacy seems to have been minimal.
Use of this proprietary medicinal product exposes the patient to the risks of fibrosis, hypertension, and valve disease, especially in cases of prolonged use, that is to say extending beyond treatment of the attack.

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 is intended as symptomatic treatment.

The efficacy/adverse effects ratio of this medicinal product in its indication is poor.

Drug alternatives to this proprietary medicinal product do exist, in particular the triptan-based products.

The actual benefit offered by this product in the treatment of migraine attacks **is moderate.**

4.2. Transparency Committee recommendations

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.

Packaging: The present pack of 20 tablets is inappropriate for the treatment of migraine attacks and constitutes an encouragement to continue taking the treatment. It would be desirable to have a smaller pack in order to prevent prolonged use.