HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

27 April 2011

OKIMUS, coated tablets
B/1 bottle of 40 tablets (CIP code: 381 377-8)
B/2 blister strips of 20 tablets (CIP code: 363 666-1)

Applicant: BIOCODEX

quinine benzoate + hawthorn dry extract
ATC code: M09AA (drugs for disorders of the musculosquelettal system/ quinine and derivatives)

List I

Data of Marketing Authorisation: confirmed 30 August 1991 (national procedure), first licensed on 05 January 1953

Reason for request: Reassessment of Actual Benefit in accordance with article R. 163-21 of the Social Security Code.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

quinine benzoate: 80 mg
hawthorn dry extract: 60 mg

1.2. Indication

"Second-line treatment for primary muscle cramps."

1.3. Dosage

FOR USE BY ADULTS ONLY
Up to 4-6 tablets daily, taken in two or three doses.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

M	: MUSCULO-SKELETAL SYSTEM
M09	: OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM
M09A	: OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM
M09AA	: QUININE AND DERIVATIVES

2.2. Medicines in the same therapeutic category

2.2.1. Strictly-comparator medicines

There are no other proprietary medicinal products that contain a combination of quinine benzoate and hawthorn dry extract.

2.2.2. Not-strictly-comparator medicines

Two other medicinal products containing quinine are included on the list of medicines refundable by National Insurance in this indication:

- quinine + vitamin C: QUININE VITAMINE C GRAND, coated tablets
(AB insufficient, opinion of 04 January 2006)
- quinine + thiamine hydrochloride: HEXAQUINE ADULTES, suppositories and HEXAQUINE, coated tablets
(AB low, opinion of 19 November 1999)

2.3. Medicines with a similar therapeutic aim

There are no other medicines with a similar therapeutic aim.

NB: Medicinal products indicated for the treatment of painful muscle contracture are not included in the comparators.

3 SUMMARY OF PREVIOUS TRANSPARENCY COMMITTEE OPINIONS

Opinion of 18 October 2006
Renewal of listing for QUINESIDINE (former name)

"The actual benefit contributed by this proprietary medicinal product remains low in the indication of the Marketing Authorisation."

4 USAGE DATA

According to IMS data (moving annual total, November 2010), this proprietary medicinal product was the subject of 290 000 prescriptions.
It was mainly (63%) prescribed in the indication "abnormal involuntary movements". The other reasons for its prescription were very varied and accounted for small proportions of the total prescriptions.

5 UPDATING OF DATA MADE AVAILABLE SINCE THE PREVIOUS OPINION

5.1. Efficacy

The company has provided new efficacy data:

- a literature review by the American Academy of Neurology on various treatments for muscle cramps (2010) [1]
- a Cochrane meta-analysis assessing the efficacy and tolerance of quinine for the treatment of muscle cramps (2010) [2].

There are no data on the efficacy of quinine in combination with hawthorn dry extract.

- Katzberg HD *et al*. 2010[1]

Katzberg H *et al.* of the American Academy of Neurology published a literature review of symptomatic treatment for primary muscle cramps. Twenty-four publications were included. The authors' recommendations and conclusions were:
Although likely effective (Level A) though modest, quinine derivatives should be avoided for routine use in the management of muscle cramps because of the potential of toxicity. Quinine derivatives should be considered only in select patients for an individual therapeutic trial, for patients with cramps that are very incapacitating, with a significant impact on quality of life, and only once potential adverse effects are taken into account. In this situation patients should be informed of the risks of adverse effects and they should be closely monitored. Existing data are insufficient for establishing the efficacy of stretching exercises in reducing the frequency of muscle cramps.

[1] Katzberg HD, et al. Assessment: Symptomatic treatment for muscle cramps (an evidence-based review). American Academy of Neurology. 2010; 74: 691-696.

[2] El-Tawil S, Al Musa T, Valli H, Lunn MPT, El-Tawil T, Weber M. Quinine for muscle cramps. Cochrane Database of Systematic Reviews 2010, Issue 12. Article no. CD005044. DOI: 10.1002/14651858.CD005044.pub2.

- Cochrane 2010[2]

Aim:
The aim of this meta-analysis was to assess the efficacy and tolerance of quinine in the treatment of muscle cramps.

Selection criteria:
The selection criteria were as follows: randomised controlled clinical trials in patients of all ages, with muscle cramps, irrespective of location or cause, treated with quinine or quinine derivatives.

Results:
Twenty-three clinical trials were identified, with a total population of 1586 patients.
In these trials, quinine was used at dosages of 200-500 mg/day (the most common dose was 300 mg/day) and compared with placebo and/or other medicines (which did not have an indication in France).
Efficacy
Over a two-week period, it was shown that quinine reduced the number of cramps (relative reduction in number of cramps = 28% with an absolute difference of -2.45 cramps, 95% CI [-3.54 to -1.36]), reduced the severity of cramps by 10% (-0.12 units on a 3-point scale, 95% CI [-0.20 to -0.05]) and the number of days with cramps by 20% (-1.15 days with cramps, 95% CI [-1.93 to -0.38]) more than placebo. There was no statistically significant reduction in duration of cramps.
Adverse effects
More patients experienced minor adverse effects (mostly gastrointestinal symptoms) when treated with quinine than with placebo (statistically significant difference in risk of +3%, 95% CI [0-6]).
There was no statistically significant difference in major adverse effects. There was one case of thrombocytopenia under quinine.
Conclusion:
Quinine was shown with a moderate level of evidence to have a low level of efficacy on reduction in frequency of cramps, severity of cramp and the number of days with cramp.
In the clinical trials identified, the use of quinine for up to 60 days was not associated with a significantly higher incidence of serious adverse effects than the use of placebo (moderate level of evidence). However, the authors point out that adverse effects are rare but may be serious or even fatal, which accounts for the very low prescription of quinine in certain countries.
The authors also emphasise that there is no evidence to support any optimum dose or treatment duration.

5.2. Adverse events/Tolerance

5.2.1. Summary of tolerance data from the Summary of Product Characteristics (SPC)

Adverse effects
"Non-dose-dependent adverse effects: hypersensitivity reaction that may take the form of:
- skin reactions: pruritus, erythematous rash, purpura, photosensitivity, or even in rare cases, anaphylactic reactions,
- haematological reactions: thrombocytopenia, a few rare cases of thrombotic microangiopathy and very occasionally, pancytopenia,
- hepatic reactions: a few cases of granulomatous hepatitis have been reported.

Dose-dependent adverse effects (described for doses 500 mg/day or higher): cinchonism manifesting as tinnitus, high-frequency hearing loss, vertigo, visual disturbances, headache."

Overdose
"The most common signs of overdose are:

- Tinnitus, impaired hearing and vertigo. Irreversible deafness has occasionally been reported after administration of toxic doses.
- Blurred vision, visual field constriction, diplopia and night blindness. Recovery is slow but generally complete. Central retinal artery spasm has been reported.
- A quinidine-like effect resulting in hypotension, conduction disorders, symptoms of angina and ventricular tachycardia.
- Local irritation in the gastrointestinal tract causing nausea, vomiting, abdominal pain and diarrhoea.
- In adults, oral administration of more than 3 g in a single dose may cause serious or even fatal poisoning, preceded by central nervous system depression and convulsions. Lower doses may be fatal in children.
- Arrhythmia, hypotension and cardiac arrest may result from the cardiotoxic effects of quinine, while ocular toxicity may lead to blindness.

Treatment: gastric evacuation and lavage. Administration of activated charcoal.
Symptomatic treatment of disorders in a hospital setting."

Special warnings
"The occurrence of immune hypersensitivity response such as thrombocytopenia, hepatitis or allergy requires immediate and definitive withdrawal of treatment and avoidance of quinine in the future, particularly beverages containing quinine."

5.2.2. New tolerance data submitted by the applicant

The applicant submitted new tolerance data:

- the Cochrane meta-analysis evaluating the efficacy and tolerance of quinine in the treatment of muscle cramps including one report of thrombocytopenia under quinine (see below, section 5.1)
- periodic tolerance update reports (PSURs covering the period 01 July 2005 to 31 December 2010): the company reports that nine patients experienced a total of 16 adverse effects. All except one were unanticipated effects. For six patients, the adverse events were serious, involving various organ systems (heart, general disorders, skin, liver), with a doubtful (3) or possible (3) causal relationship. One of these patients died. Based on the information received, a causal relationship between this death and OKIMUS was doubtful, as the patient had general signs of infection before the start of treatment and no post-mortem examination was carried out. Since the end of the last PSUR period, one case of thrombocytopenia has been reported, for which a causal relationship was doubtful.

Overall, recent pharmacovigilance data for OKIMUS do not identify any new alerts but do report seven serious cases of diverse origins.

5.2.3. Data from the National pharmacovigilance database

Although HEXAQUINE and OKIMUS are not completely identical formulations, they both contain quinine benzoate and are indicated as second-line treatment for primary muscle cramps and are likely to have the same adverse effects.

In December 2010, the French Healthcare Product Safety Agency (AFSSAPS) examined pharmacovigilance data for HEXAQUINE proprietary medicinal products (the only other reimbursable medicinal product containing quinine in the same indication) based on data extracted from the French national pharmacovigilance database. Analysis of the 90 cases in which HEXAQUINE was the only medicinal product under suspicion showed that half the

effects were anticipated (haematological effects, skin effects, allergic reactions and dose-dependent visual disturbances and dizziness). Twenty-one of the forty-seven unanticipated cases were serious. These involved skin disorders (particularly eczema), allergic reactions (including three cases of anaphylactic shock) and hepatic disorders (cytolysis and/or cholestasis, half of which were serious).

5.2.4. International information[3,4]

Warnings were recently renewed by the United States (August 2010) and the United Kingdom (June 2010) authorities concerning medicinal products containing quinine in the treatment of muscle cramps, particularly related to the onset of severe thrombocytopenia.

In the United States, quinine has not been authorised for muscle cramps since 1995. In August 2010, following notifications of serious haematological adverse effects (mainly thrombocytopenia) associated with the off-label use of quinine sulphate in the treatment or prevention of muscle cramps, the FDA renewed its warnings against the use of quinine in muscle cramps. The FDA issued a reminder that quinine should not be used in muscle cramps, as its use could lead to serious or even fatal haematological adverse effects. It also emphasised that in the absence of evidence concerning the efficacy of quinine in this indication in actual practice, the risk associated with its use was greater than its potential benefit.

In the United Kingdom, the MHRA (Medicines and Healthcare products Regulatory Agency) published recommendations for restricting the target population and for increased patient follow-up with clinical monitoring for signs of thrombocytopenia (June 2010).

5.3. Conclusion

The recent efficacy data concerning medicinal products containing quinine in the treatment of primary muscle cramps are mainly based on the Cochrane meta-analysis[3]. This analysis shows a small reduction of 28% in the number of cramps, with a moderate level of evidence (-2.45 cramps, 95% CI [-3.54 to -1.36]), together with a reduction in severity by 10% (-0.12 units on a 3-point scale, 95% CI [-0.20 to -0.05]) and in the number of days with cramp by 20% (-1.15 days with cramp, 95% CI [-1.93 to -0.38]). There was no statistically significant reduction in duration of cramps.
There are no data on the efficacy of quinine in combination with hawthorn dry extract.

In addition, there is a known risk of onset of a rare and severe allergic reaction in the form of thrombocytopenia, and more rarely, granulomatous hepatitis or skin disorder. One report of thrombocytopenia was included in the meta-analysis.
In addition, AFSSAPS recently carried out a new examination of the French pharmacovigilance database in relation to the proprietary medicinal product HEXAQUINE, which confirmed the known effects of quinine, leading AFSSAPS to consider that HEXAQUINE had a role in new hypersensitivity reactions (anaphylactic shock, angioedema), hepatic effects (cytolysis and/or cholestasis) and skin effects (eczema).

[3] Food and Drug Administration: http://www.fda.gov/ (viewed 24 February 2011)

[4] Medicines and Healthcare products Regulatory Agency, Commission on Human Medicines. Drug Safety Update, Volume 3, Issue 11, June 2010. http://www.mhra.gov.uk/home/groups/pl-p/documents/publication/con084657.pdf (viewed 24 February 2011)

6 TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Actual benefit

Primary muscle cramp is a painful but benign disorder which resolves spontaneously.

This proprietary medicinal product is intended as symptomatic treatment.

The efficacy of quinine in muscle cramps is low.
The benefit of the combination of quinine with dry hawthorn extract has not been demonstrated.
Quinine may cause serious adverse effects, particularly allergic thrombocytopenia, hepatitis and skin disorders.
The efficacy/adverse effects ratio for this proprietary medicinal product is low.

Public health benefit:
Primary muscle cramp is a relatively common but non-serious symptom. The public health burden which it represents is small.
The available data show that this proprietary medicinal product has a low impact on symptom reduction, but the impact on patients' state of health remains uncertain because of the risks related to its poor tolerance profile.
There is no public health need.
Consequently, this proprietary medicinal product offers no benefit to public health.

In view of the low efficacy of these proprietary medicinal products and the fact that their action is only symptomatic, the Committee considers that it is not reasonable for patients to incur a risk of rare but serious adverse effects.
The actual benefit contributed by this proprietary medicinal product is insufficient for it to be refundable by National Health Insurance.

6.2. Therapeutic use

This proprietary medicinal product has no place in the treatment strategy.

6.3. Transparency Committee recommendations

The Transparency Committee does not recommend continued inclusion on the list of medicines refundable by National Insurance in the indication and at the dosage in the Marketing Authorisation.

The Transparency Committee recommends removal from the list of medicines refundable by National Insurance.