HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

27 April 2011

QUININE VITAMINE C GRAND, coated tablets
B/24 (CIP code: 308 874-5)

Applicant: DU GOMENOL

quinine (bisulfate) heptahydrate
ascorbic (acid)
ATC code: M09AA (Drugs for disorders of the musculo-skeletal system / quinine and derivatives)

List I

National Health Insurance (15%)

Date of Marketing Authorisation (national procedure): Licensed 1951, confirmed 31 December 1997

Reason for the request: Removal following the joint request from the French Ministry of Health and of the Social Security Directorate, in accordance with article R.163-7 of the French Social Security Code.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredients

quinine (bisulphate) heptahydrate: 50 mg (i.e. 40 mg of anhydrous quinine bisulfate)
ascorbic (acid): 50 mg

1.2. Indication

"Second-line treatment for primary muscle cramps."

1.3. Dosage

"FOR USE BY ADULTS ONLY
A maximum of four tablets daily, taken in one dose in the evening."

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 which contain the combination of quinine bisulfate and vitamin C.

2.2.2. Not-strictly-comparator medicines

Other proprietary medicinal products containing quinine are included on the list of medicines refundable by National Health Insurance in this indication:

- HEXAQUINE ADULTES, suppositories: quinine benzoate 300 mg / thiamine hydrochloride 90 mg (1 suppository/day)
  (AB low, opinion of 19 November 1999)
  HEXAQUINE, coated tablets: quinine benzoate 120 mg / thiamine hydrochloride 32 mg (2-3 tablets/day)
  (AB low, opinion of 19 November 1999)
- OKIMUS, coated tablets: quinine benzoate 80 mg / dry hawthorn extract 60 mg (4-6 tablets/day)
  (AB low, opinion of 18 October 2006)

2.3. Medicines with a similar therapeutic aim

There are no other medicinal products with the same 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

Committee opinion of 19 November1999 – Reassessment

"Actual benefit contributed by this proprietary medicinal product: low".

Committee opinion of 4 January 2006 – Renewal of listing

"In view of the absence of clinical data on the efficacy of vitamin C in the treatment of primary muscle cramps, or on its role in the action of quinine, the benefit of vitamin C in this proprietary medicinal product has not been established.
The efficacy of the combination of vitamin C and quinine in the indication for this proprietary medicinal product has not been established.

The actual benefit of this proprietary medicinal product is insufficient."

Committee opinion of 22 September 2010 – Renewal of listing

"The available clinical trials were carried out with higher doses of quinine than the maximum dosage recommended by the French Marketing Authorisation for the proprietary medicinal product QUININE VITAMINE C GRAND, coated tablets (up to 160 mg of quinine a day). In addition, there are no relevant clinical data on the efficacy of vitamin C in the treatment of primary muscle cramps, or on its role in the action of quinine. So the efficacy of the combination of vitamin C and quinine contained in the proprietary medicinal product QUININE VITAMINE C GRAND in muscle cramps has not been established.

The efficacy/adverse effects ratio for this proprietary medicinal product has not been clearly established

The actual benefit of this proprietary medicinal product is insufficient."

4 USAGE DATA

According to IMS-EPPM data (moving annual total November 2010), QUININE VITAMINE C GRAND was the subject of 4 000 prescriptions. The low number of prescriptions prevents qualitative analysis of the data.

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 (Katzberg HD, *et al*. 2010[1]) on various treatments for muscle cramps.
- a Cochrane meta-analysis assessing the efficacy and tolerance of quinine for the treatment of muscle cramps (2010) [2].
- two clinical trials[3,4] to assess the efficacy of vitamin C supplements in treating muscle cramps:
    - o One comparative study in 60 patients on haemodialysis, randomised into 4 groups of 15 patients, receiving either vitamin C (250 mg/day), or vitamin E, or the combination vitamin C + vitamin E, or placebo. All also received a vitamin B complex.
    - o One study which compared the efficacy of vitamin C (2 g/day) with that of calcium in muscle cramps in pregnant women.

The design of these studies makes it impossible to establish the efficacy of vitamin C in primary muscle cramps, recommended by the Marketing Authorisation at a maximum dosage of 4 x 50 mg/day.
There are no clinical data which would make it possible to assess the efficacy of the combination quinine + vitamin C in muscle cramps.

- 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.

- 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.

[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.
[3] Khajehdehi P, *et al*. A randomized, double-blind, placebo-controlled trial of supplementary vitamins E, C and their combination for treatment of haemodialysis cramps. Nephrol Dial Transplant. 2001 Jul; 16(7): 1448-51.
[4] Hammar M, *et al*. Calcium and magnesium status in pregnant women. A comparison between treatment with calcium and vitamin C in pregnant women with leg cramps. Int J Vitam Nutr Res. 1987; 57(2): 179-83.

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]), 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' points out those 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.
It should be noted that the dose most frequently used in the clinical trials included in this meta-analysis was 300 mg/day, which is higher than the maximum recommended dosage given in the French Marketing Authorisation for the proprietary medicinal product QUININE VITAMINE C GRAND (maximum 160 mg of anhydrous quinine bisulfate a day).

5.2. Adverse effects / Tolerance

5.2.1. Summary of tolerance data in the 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, dizziness, 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: PSUR covering the period 01 January 2007 to 31 December 2010. This report does not contain any cases of adverse effects reported in this period.

5.2.3. Data from the National pharmacovigilance database

Although HEXAQUINE and QUININE VITAMINE C GRAND 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 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[5,6]

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 the 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.
It should be noted that the dose most frequently used in the clinical trials included in this meta-analysis was 300 mg/day, which is higher than the maximum recommended dosages given in the French Marketing Authorisation for the medicinal product QUININE VITAMINE C GRAND (maximum 160 mg of anhydrous quinine bisulfate a day).
There are no data demonstrating the efficacy of quinine in combination with vitamin C in muscle cramps.

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).

[5] Food and Drug Administration: http://www.fda.gov/ (viewed 24 February 2011)
[6] 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.
It should be noted that the maximum dosage recommended in the French Marketing Authorisation for the proprietary medicinal product QUININE VITAMINE C GRAND is 160 mg of quinine a day, which is lower than the doses of quinine used in most of the available clinical trials.
In addition, there are no relevant data on the efficacy of vitamin C in the treatment of primary muscle cramps, nor on its value in combination with quinine in this indication.
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 of this proprietary medicinal product remains insufficient.

6.2. Therapeutic use

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

6.3. Transparency Committee recommendations

The Transparency Committee approves its removal from the list of medicines refundable by National Health Insurance.