



HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

23 May 2012

OKIMUS, coated tablets

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 MUSCULO-SKELETAL SYSTEM/QUININE AND DERIVATIVES)

List I

Date of Marketing Authorisation: confirmed 30 August 1991 (national procedure), first authorisation on 5 January 1953

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance.

1. BACKGROUND

The transparency Committee, in its Opinion of 27 April 2011, recommended that renewal of the inclusion of proprietary medicinal products containing quinine indicated in the adjuvant treatment of idiopathic muscle cramps should not be granted. Taking into account the low efficacy of these proprietary medicinal products and their purely symptomatic action, the Committee took the view that patients should not be exposed to a rare, but serious immunoallergic risk associated with quinine.

The proprietary medicinal product OKIMUS was deleted from the list of medicines refundable by National Insurance on 1 December 2011 (Official Gazette of 5 October 2011). The pharmaceutical company has consequently applied for its inclusion.

Quinine is available on prescription in this indication in the UK and is non-reimbursable in Germany. In the United States, quinine has not been approved for the treatment of cramps since 1995.

2. CHARACTERISTICS OF THE MEDICINAL PRODUCT

2.1. Active ingredient

Quinine benzoate: 80 mg – equivalent as quinine anhydrous base: 60.56 mg

Hawthorn dry extract: 60 mg

2.2. Indication

“Adjuvant treatment of idiopathic night cramps in adults after failure of non-pharmacological measures.

The decision to prescribe a proprietary medicinal product containing quinine must be taken after aetiological assessment and based on the frequency of night cramps and their impact on quality of life and on the assessment of all specific risks for the individual patient.”

2.3. Dosage and method of administration

“FOR USE BY ADULTS ONLY

Dosage

Up to 3-4 tablets per day, to be taken at bedtime, i.e. 180 mg to 240 mg of quinine base per day.

Patients should be monitored during the first weeks of treatment in case of undesirable effects [...]. An improvement must be observed within a period of days after starting treatment. If no improvement is observed after four weeks, quinine treatment must be stopped permanently.

Quinine therapy is not a long-term treatment for idiopathic night cramps.

Method of administration

For oral use.

Severe renal impairment

The dosage should be reduced in patients with severe renal impairment.

2.4. Contraindications

This medicinal product is contraindicated in the following situations:

- history of hypersensitivity to quinine or to one of the other constituents,
- myasthenia,
- intraventricular conduction disorders,
- concomitant administration of quinine or its derivatives, including consumption of beverages containing quinine.

2.5. Special warnings and precautions for use

Special warnings

The occurrence of immunoallergic events of the thrombocytopenia, hepatitis or allergy type necessitates the immediate and permanent discontinuation of this treatment and subsequent avoidance of quinine, particularly in beverages that contain it.

Quinine can lead to the occurrence of potentially life-threatening immunoallergic events that are not possible to predict. It must not be used in patients with a history of such reactions after its administration, either in drug form or in beverages that contain it.

Precautions for use

Before using quinine in the treatment of idiopathic night cramps, all risks (see section 4.8) must be carefully weighed against the expected potential benefit. These risk factors are especially common in the elderly.

Treatment of very painful and frequent cramps with quinine should be considered only once other possible causes of the cramps have been ruled out and if non-pharmacological measures were unsuccessful. Quinine must not be used in this indication during pregnancy.

Use of quinine can lead to the development of cinchonism, which is generally more serious in the event of overdose, but can also occur at therapeutic doses during routine use.

Patients must be warned not to exceed the prescribed dose, because of the possibility of serious and irreversible adverse effects in the event of overdose.

Any treatment of idiopathic night cramps with quinine must be stopped if symptoms associated with cinchonism develop. Such symptoms include dizziness, tinnitus, headache, nausea and visual disturbances (see sections 4.8 and 4.9).

This medicinal product contains sucrose. Its use is inadvisable in patients with fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency."

3. SIMILAR MEDICINAL PRODUCTS

3.1. 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

3.2. Medicines in the same therapeutic category

3.2.1 Comparator medicines

The proprietary medicinal products containing quinine indicated in the treatment of muscle cramps (OKIMUS, HEXAQUINE and QUININE VITAMINE C GRAND) are no longer reimbursable as of 1 December 2011 (Official Gazette of 5 October 2011).

3.3. Medicines with a similar therapeutic aim

There are no other reimbursable medicinal products indicated in the treatment of idiopathic night cramps in adults after failure of non-pharmacological measures.

NB: Medicinal products indicated in the treatment of painful muscle contractions are not included in the comparator medicines.

4. REVIEW OF COMMITTEE OPINIONS AND CONDITIONS OF INCLUSION

Opinion on the renewal of inclusion of OKIMUS of 27 April 2011

AB: “Idiopathic muscle cramps are painful but benign complaints that resolve spontaneously. This proprietary medicinal product is a symptomatic treatment.

The efficacy of quinine in cramps is low.

The benefit of quinine in combination with hawthorn dry extract has not been demonstrated.

Quinine can result in serious adverse effects, in particular allergic thrombocytopenia, hepatitis and rash.

The efficacy/tolerance ratio for this medicinal product is low.

Public health benefit:

Idiopathic muscle cramps are a relatively common, but nonserious symptom. The public health burden which they represent is low.

The available data demonstrate that this proprietary medicinal product has a low impact on the reduction in symptoms, whereas the impact on patients' health remains uncertain due to the risks associated with poor tolerance.

There is no public health need.

This proprietary medicinal product is not therefore expected to benefit public health.

Given the low efficacy of this proprietary medicinal product and action that is purely symptomatic, the Committee considers it unjustified to put patients at risk of rare, but serious adverse effects.

The actual benefit of this proprietary medicinal product is insufficient to justify reimbursement by National Health Insurance.”

Therapeutic use: “This proprietary medicinal product has no place in therapeutic use.”

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

The transparency Committee recommends deletion from the list of medicines refundable by National Health Insurance.”

5. ANALYSIS OF AVAILABLE DATA

The assessment of the efficacy of OKIMUS is based primarily on a literature analysis (2010) and a meta-analysis (2010), previously submitted with the application for renewal of inclusion in April 2011.

OKIMUS, in common with all proprietary medicinal products containing quinine indicated in the treatment of idiopathic muscle cramps, underwent re-assessment of its risk/benefit relationship by AFSSAPS (French Health Product Safety Agency) in 2011, as presented below.

In support of its reapplication, the pharmaceutical company has also submitted periodic safety update reports (PSURs) covering the period from 1 July 2005 to 31 December 2010, previously submitted with the application for renewal of inclusion in April 2011.

5.1. Efficacy

The efficacy data supplied comprise in particular:

- an American Academy of Neurology literature analysis of the different treatments for cramps (2010)¹
- a Cochrane meta-analysis evaluating the efficacy and tolerance of quinine in the treatment of cramps (2010).²

There are no efficacy data for quinine in combination with hawthorn dry extract.

5.1.1 Katzberg HD et al. 2010

Katzberg H. et al. of the American Academy of Neurology have published an analysis of the literature on the symptomatic treatment of idiopathic cramps. A total of 24 publications were included and the authors proposed the following recommendations and conclusions:

Despite their probable (level A), though weak efficacy, systematic use of quinine derivatives in the management of muscle cramps should be avoided because of their risk of toxicity. The use of quinine derivatives should be considered only on a case-by-case basis, in patients in whom the cramps are very incapacitating, with a significant impact on quality of life, and only once potential adverse effects have been taken into account. In such cases, patients must be informed of the risk of adverse effects and they should be closely monitored.

5.1.2 Cochrane meta-analysis 2010

Objective: The objective of this meta-analysis was to evaluate 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, regardless of localisation or aetiology, treated with quinine or quinine derivatives.

Primary efficacy endpoint: Number of cramps.

Secondary endpoints: Intensity, number of days with cramps, duration of cramps, adverse effects.

Results: Twenty-three clinical trials were identified, with a total population of 1586 patients.

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. Art. No.: CD005044. DOI: 10.1002/14651858.CD005044.pub2.

In these studies, quinine was used at dosages of between 200 and 500 mg/day (the most common dose was 300 mg/day) and compared with placebo and/or other drug therapies (used off-label in France).

Efficacy

Over a two-week period, quinine was shown to reduce the number of cramps relative to placebo (primary efficacy endpoint) (-1.81 cramps, 95% CI [-2.20 to -1.42]), their intensity (-0.12 units on a 3-point scale, 95% CI [-0.20 to -0.05]) and number of days with cramps (-1.15 days with cramps, 95% CI [-1.93 to -0.38]). No statistically significant reduction was observed in the duration of cramps. There were differences between the trials (dosages, patient characteristics). Statistical tests also revealed significant heterogeneity in treatment effects between studies for the endpoints “difference in number of cramps” ($I^2 = 89\%$; $p < 0.0001$) and “difference in number of days without cramps” ($I^2 = 86\%$; $p < 0.00001$), consequently a random-effects model was used. The examination of this heterogeneity by the authors of the meta-analysis did not allow formal identification of its origin.

Adverse effects

More patients experienced minor adverse effects (mainly gastrointestinal symptoms) when treated with quinine than with placebo (+3%, 95% CI [0% to 6%]).

No statistically significant difference in major adverse effects was observed. One patient treated with quinine developed thrombocytopenia.

Conclusion: In this meta-analysis, quinine was found to show weak efficacy in reducing the frequency of cramps, cramp intensity and number of days with cramp. Given that the statistical tests demonstrated heterogeneity in treatment effects between studies, the results must be treated with caution. In the clinical studies identified, use of quinine for up to 60 days was not associated with a significantly higher incidence of serious adverse effects compared with placebo (moderate level of evidence). However, the authors point out that although adverse effects are rare, they can be serious or even fatal, which is the reason why prescription of quinine is severely restricted in some countries.

The authors also stress that there is no evidence on which to base an optimum dose or duration of treatment.

5.2. Adverse effects

5.2.1 Data from the Summary of Product Characteristics (SPC)

Additions to adverse effects made since the previous assessment by the Transparency Committee are underlined.

Non-dose-dependent adverse effects:

- Hypersensitivity reactions:
 - dermatological: pruritus, erythematous rash, purpura, eczema, photosensitisation,
 - general: anaphylactic shock, angioedema.
- Haematological reactions: thrombocytopenia, some rare cases of thrombotic microangiopathy and very rarely pancytopenia.
- Hepatic reactions: cholestatic or cytolytic symptoms or both, some cases of granulomatous hepatitis have also been reported.

Dose-dependent adverse effects:

Cinchonism, manifested as tinnitus, hypoacusis, dizziness, visual disturbances, headache.

Overdose

The most common signs of overdose are:

- Tinnitus, loss of auditory acuity and dizziness. Permanent deafness has sometimes occurred after administration of toxic doses.
- Amblyopia, narrowing of the visual field, diplopia and hemeralopia. Recovery is slow, but generally complete. Cases of central retinal artery spasm have been reported.
- Quinidine-like effects resulting in hypotension, conduction disturbances, anginal symptoms and ventricular tachycardia.
- Local gastrointestinal irritation causing nausea, vomiting, abdominal pain and diarrhoea.

In adults, oral administration of more than 3 g in a single dose can cause serious or even fatal poisoning, preceded by central nervous system depression and seizures. In children, lower doses can be fatal.

QT prolongation, arrhythmia, hypotension and cardiac arrest can result from the cardiotoxic effects of quinine. Its ocular toxicity can lead to blindness.

5.2.2 Cardiac disorders

In the event of overdose, QT prolongation due to quinidine-like effects may be observed.

One case of atrial flutter with faintness has been reported without overdose (unforeseen serious case, possibly connected with the drug) (PSUR).

5.3. International information^{3,4,5}

The US (FDA, August 2010) and UK (MHRA, June 2010) authorities recently renewed their warnings about use of medicinal products containing quinine in the treatment of muscle cramps, particularly in relation to the occurrence of serious cases of thrombocytopenia.

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

In the United Kingdom, quinine is licensed in the treatment and prevention of night cramps in adults and the elderly when this regularly causes interruption of sleep. The MHRA recently (June 2010) published the following guidelines:

- treatment must be restricted to very painful or frequent cramps regularly causing interruption of sleep, when aetiological treatment is not possible and non-pharmacological measures have proved ineffective.
- it recommends close monitoring at the start of treatment and therapeutic patient education about dosages and the clinical signs of thrombocytopenia (petechiae, bleeding or ecchymoses).
- the MHRA recommends paying close attention to the relative risks and potential benefits, to avoid using this treatment on a routine basis, to stop treatment after 4 weeks in the absence of any benefit, and to re-evaluate the need to continue with it about every three months.

³ Food and Drug Administration: <http://www.fda.gov/> (consulted 30 March 2012)

⁴ SPC. EMC website.

http://www.medicines.org.uk/EMC/medicine/24105/SPC/Quinine+Sulphate+Tablets+BP+200mg/#CLINICAL_PARTS (consulted 30 March 2012)

⁵ 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> (consulted 30 March 2012)

5.4. Re-assessment by AFSSAPS of the relative risks and benefits of medicinal products containing quinine indicated in the adjuvant treatment of idiopathic muscle cramps (2011)^{6,7}

The identification of a risk of serious allergic and hepatic adverse effects led AFSSAPS to re-evaluate the relative benefits and risks of proprietary medicinal products containing quinine indicated in the adjuvant treatment of idiopathic muscle cramps.

AFSSAPS concluded that, although all the clinical data suggested that quinine was effective in reducing the number of cramps, this effect was not precisely quantifiable.

These clinical data have been examined in the light of the haematological risk (pancytopenia and thrombocytopenia) and risk of cinchonism, even at standard doses, demonstrated by the cumulative tolerance data. Moreover, closer scrutiny of the safety data led to the identification of a risk of cholestatic or cytolytic liver symptoms or both and a risk of general hypersensitivity reactions such as anaphylactic shock and angioedema. The SPC and package leaflet for these proprietary medicinal products have been revised to take account of these risks. AFSSAPS states that the risk profile appears to correlate with the quinine dose and duration of treatment used.

The risk of a move towards medicinal products with unconfirmed efficacy in idiopathic muscle cramps (benzodiazepines, muscle relaxants, antiepileptics) was also considered; such a move would favour off-label use for which the risk profile is not inconsiderable.

In this context and taking into account all the efficacy data and cases documented by pharmacovigilance in France, the marketing authorisation committee took the view that the risk/benefit relationship for proprietary medicinal products containing quinine indicated in the adjuvant treatment of idiopathic muscle cramps remained favourable.

The conclusions of this re-assessment led AFSSAPS to take the following action:

- to restrict the indication for such proprietary medicinal products to “adjuvant treatment of idiopathic night cramps in adults after failure of non-pharmacological measures.”
- to harmonise the dosages of these proprietary medicinal products.
- to issue warnings, precautions for use and guidelines:

Before using quinine in the treatment of idiopathic night cramps, all risks must be carefully weighed against the expected potential benefit. These risk factors are especially common in the elderly.

Treatment of very painful and frequent cramps with quinine should be considered only once other possible causes of the cramps have been ruled out and if non-pharmacological measures were unsuccessful. Quinine must not be used in this indication during pregnancy. The dosage should be reduced in patients with severe renal impairment.

Patients should be monitored during the first weeks of treatment in case of adverse effects. An improvement must be observed within a period of days after starting treatment. If no improvement is observed after four weeks, quinine treatment must be stopped permanently. Quinine therapy is not a long-term treatment for idiopathic night cramps.

Quinine can lead to the occurrence of potentially life-threatening immunoallergic events that are not possible to predict. It must not be used in patients with a history of such reactions after its administration, either in drug form or in beverages that contain it.

Use of quinine can lead to the development of cinchonism, which is generally more serious in the event of overdose, but can also occur at therapeutic doses during routine use. Such symptoms include dizziness, tinnitus, headache, nausea and visual disturbances. Any treatment of idiopathic night cramps with quinine must be stopped if symptoms associated with cinchonism develop.

⁶ AFSSAPS: Marketing authorisation committee, 21 July 2011.

⁷ AFSSAPS: Marketing authorisation committee, 13 October 2011.

Patients must be warned not to exceed the prescribed dose, because of the possibility of serious and irreversible adverse effects in the event of overdose.

We have been in contact with health professionals to inform them of the new procedures for the use of these products and to draw their attention to the risks.⁸

5.5. Conclusion

Idiopathic night cramps are diagnosed once organic causes have been ruled out. Treatment of this type of cramp with the proprietary medicinal product OKIMUS was not specifically the subject of the studies presented.

The most recent efficacy data on medicinal products containing quinine in idiopathic muscle cramps are based primarily on a Cochrane meta-analysis. This shows, with a moderate level of evidence, a reduction versus placebo after 2 weeks of treatment in the number of cramps: -1.81 cramps, 95% CI [-2.20 to -1.42]. Neither this reduction, nor the reduction in the number of days without cramps (relevant criterion for the patient: -1.15 days; 95% CI [-1.93 to -0.38]), is clinically relevant. There was no observed reduction in the duration of cramps compared with placebo.

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

Moreover, quinine can result in rare, but serious adverse effects, in particular immunoallergic effects (pancytopenia, thrombocytopenia, anaphylactic shock, hepatitis) or a form of cinchonism, particularly at the start of treatment.

⁸ AFSSAPS: Quinine indicated in the treatment of idiopathic cramps: restriction of the indication and revision of the safety data for the proprietary medicinal products concerned - Letter to health professionals. 16/01/2012

6. TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Actual benefit

Idiopathic night muscle cramps are painful, but benign complaints that resolve spontaneously. They are diagnosed on the basis of exclusion of an organic disorder.

This proprietary medicinal product is a symptomatic treatment.
It is an adjuvant treatment.

The efficacy of quinine in cramps is low and is not clinically relevant.
Quinine can result in serious adverse effects, in particular immunoallergic effects (pancytopenia, thrombocytopenia, anaphylactic shock, hepatitis) or a form of cinchonism, particularly at the start of treatment.
The benefit of combining quinine with hawthorn dry extract has not been demonstrated.

The efficacy/tolerance ratio for this medicinal product is low.

Public health benefit:

Idiopathic muscle cramps are a relatively common, but non-serious symptom. The public health burden which they represent is low.

The available data demonstrate that this proprietary medicinal product has a low impact on the reduction in symptoms, whereas the impact on patients' health remains uncertain due to the risks associated with poor tolerance.

There is no public health need.

This product is not therefore expected to benefit public health.

In view of the low efficacy of quinine, the lack of justification for combination with hawthorn dry extract, and the risk of rare, but serious adverse effects, the Committee considers that the actual benefit of this proprietary medicinal product is **insufficient**.

6.2. Transparency Committee recommendations

The transparency Committee does not recommend inclusion on the list of medicines refundable by National Health Insurance in the indication and at the dosages in the Marketing Authorisation.