HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

Opinion

23 July 2014

NIVAQUINE 100 mg, scored tablet

B/20 (CIP: 34009 307 311 7 8)
B/100 (CIP: 34009 307 310 0 0)

Applicant: SANOFI-AVENTIS France

INN	Chloroquine
ATC code (2014)	P01BA01 (synthetic antimalarials)
Reason for the review	**Renewal of inclusion in rheumatoid arthritis**
List concerned	**National Health Insurance (French Social Security Code L.162-17)**
Indication concerned	**“Long-acting symptomatic treatment of rheumatoid arthritis.”**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (national procedure)	Date initiated: 7 March 1974 validated on 30 January 1998
Prescribing and dispensing conditions /special status	List II

ATC Classification	2014 P: Antiparasitic products, insecticides and repellents P01: Antiprotozoals P01B: Antimalarials P01BA: Aminoquinolines P01BA01: chloroquine

02 BACKGROUND

In the last Opinion for the renewal of the inclusion of these proprietary medicinal products on 3 October 2012, the Committee gave a ruling on all the indications of the Marketing Authorisation except for rheumatoid arthritis, for which the actual benefit (AB) was still being assessed.

The Committee's last Opinion in RA is dated 8 November 2006 (renewal of inclusion), in which the AB was rated as substantial.

03 CHARACTERISTICS OF THE MEDICINAL PRODUCT

03.1 Therapeutic indications

That are the subject of this assessment
In rheumatology:
Long-acting symptomatic treatment of rheumatoid arthritis.

Not affected by this assessment because already assessed in October 2012:
"In parasitology:
Curative and preventive treatment of malaria.
It is necessary, when prescribing antimalarials, to take account of the guidelines of the national and international health authorities regarding changing parasite resistance.
In dermatology:
Discoid lupus erythematosus.
Subacute lupus erythematosus.
Adjuvant or preventive treatment of relapses of systemic lupus erythematosus.
Prevention of polymorphous light eruption."

03.2 Dosage

Treatment of rheumatoid arthritis:
Two to three tablets a day for treatment of an attack, in divided doses, (i.e. 200 to 300 mg chloroquine).
One to two tablets a day for maintenance treatment, in divided doses, (i.e. 100 to 200 mg chloroquine).

04 ANALYSIS OF NEW AVAILABLE DATA

04.1 Efficacy

The company has not provided any new clinical data on the efficacy of chloroquine in rheumatoid arthritis.

The literature search carried out by the HAS documentation department did not identify any acceptable clinical methods data published since the Committee's last opinion that could be used to assess the efficacy of chloroquine in the treatment of rheumatoid arthritis.

04.2 Safety/Adverse effects

◗ The company has provided pharmacovigilance data covering the period from 22.02.2009 to 31.05.2013.

◗ Since the Committee's last assessment in 2012 of the safety data for chloroquine, there have been no amendments to the SPC concerning the safety of chloroquine.
For information purposes, however, it must be pointed out that amendments that have not yet been validated by the ANSM [French National Agency for Medicines and Health Products Safety] concerning adverse effects (AEs) are awaiting to be added to the SPC, in particular: extrapyramidal disorders, maculopathy and macular degeneration, DRESS (application to change information submitted by the company to the ANSM in March 2013). Moreover, a review of cases of pneumopathy and DRESS (hypersensitivity syndrome) reported with chloroquine and hydroxychloroquine is currently being analysed at the ANSM. The minutes of the pharmacovigilance committee's meeting of 18 June 2013 proposed amendments to the SPC with the addition of these AEs (DRESS and eosinophilic pneumonia) and of warnings and precautions for use to the SPC. The addition of contraindications was not accepted. These amendments, which have not yet been validated, are at present still being assessed at the ANSM.

◗ **Overall, these new data do not seem likely to change the efficacy/adverse effect ratio of these proprietary medicinal products.**

04.3 Usage/prescription data

The prescription data (EPPM Permanent Survey on Medical Prescriptions, winter 2013 – moving annual total) show that 17,631 prescriptions were issued for NIVAQUINE. This small number of prescriptions does not allow a reliable analysis to be made of these data, particularly by indication. There are no data on the use of this proprietary medicinal product in RA.

04.4 Therapeutic use

Rheumatoid arthritis

The management of rheumatoid arthritis at present consists of the prescription of an immediate-acting antiinflammatory (NSAID, corticosteroid, etc.) and a disease-modifying medicine so as to induce clinical and biochemical remission. Methotrexate is the reference conventional disease-modifying medicine for rheumatoid arthritis. If there is an inadequate response to methotrexate or if it is contraindicated, depending on the clinical and biochemical presentation of the disease, and the patient's pathophysiological background, use is made of:
- another conventional disease-modifying treatment as monotherapy, or
- a combination of conventional disease-modifying treatments, or
- an anti-TNF agent.

Therapeutic use of chloroquine:
In the absence of any current national recommendations on the management of rheumatoid arthritis, the European recommendations of EULAR[1] (European League Against Rheumatism) were taken into account.

They recommend sulfasalazine and leflunomide as a first-line alternative to methotrexate if that substance is not tolerated or is contraindicated.

The antimalarials hydroxychloroquine and chloroquine are no longer included in the recommendations but the rationale states that they are used in RA, particularly in combination, but also in monotherapy in patients with moderate disease activity. They have the advantage that they can be used during pregnancy but have a moderate disease-modifying effect. Their effect in terms of slowing down radiographic progression seems to be less than that of other DMARDs (methotrexate, sulfasalazine and leflunomide), which is why they are not widely offered in these recommendations, even though patients with weak disease activity are fairly unlikely to have joint degradation.

The French Society of Rheumatology (SFR) was asked by the TC office for a statement on the use of non-biological disease-modifying medicines in the treatment of RA. Chloroquine (NIVAQUINE) is regarded as an alternative to hydroxychloroquine (PLAQUENIL) which is still indicated in benign forms and in combination with other disease-modifying medicines.

The recommendations of the American College of Rheumatology (ACR) of 2012[2] include hydroxychloroquine among the conventional DMARDs, for the same reasons as methotrexate, leflunomide and sulfasalazine.

In view of this information and of the available alternatives, the Transparency Committee believes that the place of chloroquine in the strategy for managing RA, as defined in its Opinion of 8 November 2006, has changed: **it is an alternative to hydroxychloroquine in benign, minimally active forms of rheumatoid arthritis and in combination with other disease-modifying treatments.**

[1] Smolen et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. **Ann Rheum Dis** 2014;73:492-509.
[2] Singh et al. 2012. Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis. Arthritis Care & Research 2012; 64: 625–639.

05 TRANSPARENCY COMMITTEE CONCLUSIONS

Considering all this information, the Committee believes that the conclusions of its earlier Opinion of 8 November 2006 on the indication RA have changed, as follows:

05.1 Actual clinical benefit

Disease-modifying treatment of rheumatoid arthritis

- Rheumatoid arthritis is a serious and disabling chronic disease.
- NIVAQUINE (chloroquine) is intended as symptomatic treatment.
- The efficacy/adverse effects ratio of NIVAQUINE remains high in the disease-modifying treatment of RA.
- There are numerous treatment alternatives, particularly other biological and non-biological disease-modifying treatments.
- This proprietary medicinal product is an alternative to hydroxychloroquine in benign, minimally active forms of rheumatoid arthritis and in combination with other disease-modifying treatments.

Taking account of these points, the Committee believes that the actual benefit of NIVAQUINE remains substantial in an indication limited to the disease-modifying treatment of benign, minimally active forms of rheumatoid arthritis and in combination with other disease-modifying treatments.

05.2 Transparency Committee recommendations:

The Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance in an indication limited to the "disease-modifying treatment of benign, minimally active forms of rheumatoid arthritis and in combination with other disease-modifying treatments".

- **Proposed reimbursement rate: 65%**

- **Packaging:**

Appropriate for the prescribing conditions as regards indication, dosage and treatment duration.