

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**A-CQ 100 Chloroquine 100 mg, tablets
ARTECEF B.V., the Netherlands**

chloroquine (as phosphate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.

It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 106659

7 January 2013

Pharmacotherapeutic group:	aminoquinolines
ATC code:	P01BA01
Route of administration:	oral
Therapeutic indication:	prophylaxis and treatment of malaria; rheumatoid arthritis; lupus erythematosus; hepatic amebiasis
Prescription status:	prescription only
Date of authorisation in NL:	28 June 2011
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for A-CQ 100 Chloroquine 100 mg, tablets from ARTECEF B.V. The date of authorisation was on 28 June 2011 in the Netherlands.

The product is indicated for:

- Prophylaxis and treatment of all types of malaria.
 - * Treatment of *Plasmodium vivax* en *P. ovale* should always be completed with primaquine treatment in order to eliminate the extraerythrocyte phase the plasmodium cycle.
 - * Chloroquine resistant *Plasmodium falciparum* is seen in many regions, which limits the usability of chloroquine in these areas.
 - * In prescribing malaria medication the WHO compliant guidance issued by the Health Care Inspectorate should be taken into account.
 - * Rheumatoid arthritis (and juvenile rheumatoid arthritis) that has not responded to six months of treatment with a prostaglandin synthetase inhibitor.
- Lupus erythematosus.
- Hepatic amebiasis in combination with a contact amebicide in case of insufficient response to a general amebicide (metronidazole, tinidazole) or in patients in whom these agents are contraindicated.

Initially, the MAH also applied for the indication 'chronic Q fever (caused by *Coxiella Burnetii*) in combination with doxycycline', an indication not accepted for Nivaquine. During the procedure the MEB advised the MAH to restrict the indications to those accepted for Nivaquine and to submit a variation procedure for an extension of this indication with supporting literature in due time.

A comprehensive description of the indications and posology is given in the SPC.

Chloroquine is a 4-aminoquinoline compound which has a high degree of activity against the asexual erythrocytic forms of all species of malaria parasites. It has rapid schizonticidal effect.

This national procedure concerns a hybrid application claiming essential similarity with the innovator product Nivaquine 100 mg tablets (NL License RVG 00303) which has been registered in the Netherlands by Sanofi-Aventis B.V. since 20 May 1990 (original product).

A-CQ 100 contains chloroquine phosphate, whereas the reference product Nivaquine contains chloroquine sulphate.

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC (hybrid application), as bioequivalence hasn't been demonstrated through a bioavailability study.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. The MAH sufficiently substantiated that no clinically relevant difference in efficacy and safety is expected between the test and reference product. This hybrid product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to this product and no paediatric development programme has been submitted, as this is not required for a hybrid application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

The active substance is chloroquine phosphate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white, crystalline powder, which is freely soluble in water and only very slightly soluble in alcohol and methanol. It has one chiral center and is used as racemate.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur. monograph for chloroquine phosphate and the additional CEP requirements. The specification is acceptable in view of the CEP and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches.

Stability of drug substance

Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). Based on the data obtained, a re-test period of 3 years is acceptable.

* *Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition

A-CQ 100 Chloroquine is a white, round, flat tablet. On one side it has a breakline and on the other side inscription "CQ 100". Each tablet contains 161.3 mg chloroquine phosphate equivalent to 100 mg chloroquine. The tablets can be divided into equal halves.

The tablets are packed in PVC/Alu blisters.

The excipients are: lactose monohydrate, maize starch, pregelatinised maize starch, crospovidone, magnesium stearate and colloidal anhydrous silica.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The objective was to obtain a formulation similar to the reference product Nivaquine®

100 mg tablets marketed by Sanofi-Aventis. The dissolution profiles of the test batch and the reference product were compared at three different pH's (pH 1.2, pH 4.5, pH 6.4). The test product showed dissolution of >80% after 10 minutes at the whole pH range. The reference product reached 80% dissolution at 30 minutes. The test product can be considered as an immediate release form with a faster dissolution profile than the reference. The test product and the reference product can not be considered equivalent with respect to dissolution.

The MAH has adequately shown that the score line is functional and in conformity with the Ph.Eur. requirements on subdivision of tablets. The pharmaceutical development has been sufficiently described.

Manufacturing process

The manufacturing process for A-CQ 100 tablets consists of weighing, wet granulation followed by sieving, drying, sieving and subsequently mixing/blending and compressing. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot batches and one full-scale batch. The product is manufactured using conventional manufacturing techniques. Process validation for two more full-scale batches will be performed post authorisation.

Control of excipients

The excipients comply with the specifications and analytical procedures of the corresponding monographs in the Ph.Eur. Silicium dioxide complies with the specification and analytical procedures of the corresponding monograph in the USP. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identity (chloroquine and phosphate), chloroquine content, related substances, uniformity of dosage units, disintegration, dissolution, loss of drying, resistance to crushing, friability, and microbial quality. The analytical methods have been adequately described and validated. The validation of the HPLC method showed that the method is stability indicating. Batch analyses data of three production-scale batches have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided one pilot-scale batch and two production- -scale batches stored at 25°C/60% RH (1 pilot and 1 production batch for 36 months; 1 production batch for 3 months) and 40°/75% RH (1 pilot and 1 production batch for 12 months; 1 production batch for 3 months). The batches were stored in the proposed blister packaging.

The stability data at accelerated conditions show out-of-specification results. A shelf-life of 3 years is justified, based on the out of specification at accelerated conditions, the storage condition is; 'do not store above 25 °C' and 'store in the original packaging in order to protect against moisture'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Only lactose is of animal origin. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non-clinical aspects

This product is a hybrid formulation of Nivaquine, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the Board agreed that no further non-clinical studies are required.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of chloroquine released into the environment. It

does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Chloroquine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the Board agreed that no further clinical studies are required.

Nivaquine has been authorised in the Netherlands for decades. Since 2004 availability was limited. To guarantee availability, the MAH of the current product - ARTECEF B.V - developed A-CQ 100, as a generic of Nivaquine, both contain 100 mg of chloroquine. A-CQ 100 contains 161.3 mg chloroquine phosphate and the reference, Nivaquine, contains chloroquine sulphate.

For this hybrid application, the MAH has submitted a rationale for not performing bioequivalence studies.

BCS class

Literature data on the properties of chloroquine phosphate, chloroquine sulfate, and chloroquine hydrochloride related to the Biopharmaceutics Classification System (BCS) are reviewed by Verbeeck et al (Pharm. Science (2005) 94: 1389-1394). The available information indicated that these chloroquine salts can be classified as highly soluble and highly permeable, i.e., BCS class I.

The qualitative composition of immediate release (IR) tablets consists of the same amount of Active Pharmaceutical Ingredients (APIs) as existing Marketing Authorisations (MA) in Belgium, Germany, Finland and the Netherlands (NL). The MAH considers these MAs with the same critical therapeutic indication as bioequivalent to the innovator.

In conclusion, the data indicate that chloroquine is well absorbed and can be considered to fulfill BCS Class I criteria regarding absorption. The quantitative and qualitative compositions of the A-CQ and Nivaquine tablets are not similar. However, as chloroquine can be considered a BCS Class I drug, excipients may differ. The excipients used are regularly used excipients and are considered not to impact bioavailability.

Dissolution study

A dissolution study has been performed. Dissolution tests were performed in order to show similarity with the reference medicinal product Nivaquine®. The dissolution of A-CQ 100 tablets was very rapid. In all three buffers (pH 1.2, 4.5, and 6.4) the dissolution was completed after 15 minutes. At 15 minutes each individual unit had a dissolution more than 85%.

The results for dissolution of the Nivaquine tablets at the three buffers remained less than 85% after 15 minutes. At 30 minutes only one individual unit had a dissolution of more than 85%. Dissolution was less than 50% after 15 minutes.

A-CQ 100 tablets are an immediate release form and have a faster dissolution profile than Nivaquine tablets. Clearly, there is a marked difference in dissolution between the A-CQ chloroquine and Nivaquine tablets.

Conclusion

Chloroquine is a BCS class I drug, meaning the drug is highly soluble over the pH range of 1 – 7, and highly permeable. Dissolution data showed that dissolution of A-CQ at a pH 1.2, 4.5 and 6.8 is very rapid (more than 85% within 15 min). Dissolution is more rapid than observed for Nivaquine, meaning that there is a theoretical possibility that compared to Nivaquine, C_{max} may be higher. The excipients used in the A-CQ tablet are commonly used excipients, and are considered not to affect the extent of absorption of chloroquine. Thus except for a possible higher C_{max} , the efficacy and safety are considered not clinically relevant affected and as such, the product is acceptable.

Risk management plan

Chloroquine has been used for many years and there is sufficient post-authorisation experience with the active substance. The safety profile of chloroquine can be considered to be well established and no

product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the national procedure has been adequately adapted in accordance with the MEB's comments and is in accordance with that accepted for Nivaquine.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted was conducted with 13 participants. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The readability test revealed that most information in the Patient Information Leaflet was "findable" for the participants. However some information was difficult to understand and not easily applied to an imaginary situation. The results on three questions were beneath 80%. This suggests that information about pregnancy, use of A-CQ 100 with disturbed renal function and the dose regimen for children is unclear.

The readability test has been sufficiently performed. However, as the PL is essentially identical to the Patient Information Leaflet of the innovator product Nivaquine, the outcome of the user test is acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

A-CQ 100 Chloroquine 100 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Nivaquine 100 mg tablets. Nivaquine is a well-known medicinal product with an established favourable efficacy and safety profile. A-CQ 100 contains chloroquine phosphate, whereas the reference product Nivaquine contains chloroquine sulphate.

No bioequivalence studies have been conducted as chloroquine is a BCS class I drug, meaning the drug is highly soluble and highly permeable. Efficacy and safety are considered not clinically relevant affected by the difference in dissolution profile.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations. A commitment was made (see below).

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

In the Board meeting of 28 April 2011, the dissolution profile of the test product versus the innovator was discussed. The Board concluded that the difference in dissolution does not affect efficacy or safety.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. A-CQ 100 Chloroquine 100 mg, tablets was authorised in the Netherlands on 28 June 2011.

The following post-approval commitment has been made during the procedure:

Pharmacovigilance

- The MAH committed to provide an update of the Detailed Description of the Pharmacovigilance System (DDPS). This commitment has been fulfilled.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Update of the DDPS as part of a commitment to a registration procedure.	--	II	27-7-2011	3-4-2012	Approval	N