CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Claritromycine retard CF 500 mg, prolonged-release film-coated tablets Centrafarm B.V., the Netherlands

clarithromycin (as citrate)

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 and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states 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.

EU-procedure number: NL/H/2042/001/DC
Registration number in the Netherlands: RVG 107530

24 October 2011

Pharmacotherapeutic group:	macrolides
ATC code:	J01FA09
Route of administration:	oral
Therapeutic indication:	treatment of the following infections caused by clarithromycin susceptible organisms: acute exacerbation of chronic bronchitis; mild to moderate community-acquired pneumonia; acute bacterial sinusitis (adequately diagnosed); bacterial pharyngitis; skin and soft tissue infections of mild to moderate severity
Prescription status:	prescription only
Date of authorisation in NL:	5 September 2011
Concerned Member States:	Decentralised procedure with AT, BE, IT, LU
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

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 member states have granted a marketing authorisation for Claritromycine retard CF 500 mg, prolonged-release film-coated tablets, from Centrafarm B.V. The date of authorisation was on 5 September 2011 in the Netherlands. The product is indicated for the treatment of the following infections caused by clarithromycin susceptible organisms:

- Acute exacerbation of chronic bronchitis
- Mild to moderate community-acquired pneumonia
- Acute bacterial sinusitis (adequately diagnosed)
- Bacterial pharyngitis
- Skin and soft tissue infections of mild to moderate severity

Consideration should be given to official guidance on the appropriate use of antibacterial agents

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

Clarithromycin is an antibiotic belonging to the macrolide antibiotics group. It exerts its antibacterial action by inhibiting the intracellular protein synthesis of susceptible bacteria. It selectively binds to the 50S subunit of bacterial ribosomes and thus prevents the translocation of activated amino acids.

The 14(R)-hydroxy metabolite of clarithromycin, a product of parent drug metabolism in humans, also has antimicrobial activity. The metabolite is less active than the parent compound for most organisms, including Mycobacterium spp. An exception is *Haemophilus influenzae* against which the metabolite is 1 to 2 times more active than the parent compound. Clarithromycin combined with the metabolite showed a strain-dependent additive or synergistic effect both *in vitro* and *in vivo*.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Klacid XL 500 mg (NL license RVG 17902) which has been registered in the UK by Abbott since 1996 (original product). In addition, reference is made to Klacid authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

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. To this end the MAH has submitted three bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Klaricid XL 500 mg tablets, registered in the UK, under various conditions. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic 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 these products, and no paediatric development programme has been submitted, as this is not required for generic medicinal products.

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 clarithromycin citrate. Although the citrate form of clarithromycin is not described in the European Pharmacopoeia, clarithromycin itself is an established active substance described in the European Pharmacopoeia (Ph. Eur.*). Clarithromycin citrate is soluble in methanol, sparingly soluble in water and in alcohol and slightly soluble in acetone, methylene chloride and in acetonitrile. Clarithromycin citrate has ten chiral centres in the main clarithromycin macrolide ring. The polymorphic form of clarithromycin citrate is claimed as Polymorphic Form-A.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacture
Clarithromycin citrate is manufactured in six steps from the starting material. The manufacturing process has been described in sufficient detail. Clarithromycin citrate has been adequately characterized.

Quality control of drug substance
The specification is in line with the requirements of the Ph.Eur. and USP* monograph for clarithromycin, with modifications for the presence of the citrate group where necessary and additional requirements for residual solvents. A test for specific optical rotation has been included in the drug substance specification. The polymorphic form has been demonstrated to remain stable during storage. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.
The MAH has committed to re-evaluate the current limits for the clarithromycin assay and to possibly tighten these when more data has become available.

Stability of drug substance
Stability studies were conducted on three consecutive pilot batches and two full-scale batches packed into the commercial packaging under long-term and accelerated ICH conditions as well as under stress conditions.
At long term conditions for 48 months and at accelerated conditions for 6 months all parameters comply with the proposed specification and no significant changes have been observed. A re-rest period of 48 months is granted, when stored in the original containers in order to protect from moisture.
The MAH has committed to continue the long term studies (on the two full-scale batches) as per provided stability protocol (60 – 72 months). Furthermore one additional full-scale batch will be placed in long-term stability studies.

** Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and the USA.*

Medicinal Product

Composition
The product at issue is clarithromycin 500 mg prolonged-release tablets. The tablets are yellow colored, oblong shaped, biconvex film-coated tablets. Lactose monohydrate, hypromellose, hypromellose phthalate, talc and magnesium stearate are used as excipients, the tablets are coated with Opadry coating system.
The tablets are packed into Transparent PVC/PVDC film/ Aluminium blisters. The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The pharmaceutical development of the product has been adequately performed; the choice of the active substance and excipients is justified. The test product was compared to the innovator product with respect to active substance, ionic behaviour, dissolution and impurity profile, demonstrating similar behaviour.
Results of *in vitro* dissolution testing, obtained with the batches of the test and reference product used in the bioequivalence study have been provided, as well as comparative dissolution profiles with the Dutch, German, and French reference products. It has been demonstrated that the dissolution of the reference products is similar to the UK reference product and the test product.

Manufacturing process
The clarithromycin extended release tablets are made by wet granulation followed by direct compression and film coating. Validation studies have been performed on three consecutive pilot-scale batches and three consecutive commercial-scale batches.
The MAH has committed to retain lager batches sizes to validate the manufacturing process with the first three commercial batches. The validation report will be carried out in line with the guidance document "*CPMP/QWP/848/96 – Note for guidance on process validation*".

Excipients
The excipients comply with the Ph.Eur. and are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, length, width, thickness, average weight, uniformity of weight, loss on drying, dissolution, assay, related substances, uniformity of dosage units and microbial purity.
The release and end of shelf-life requirements are identical, except for related substances. The analytical methods have been adequately described and validated.
Batch analyses data has been provided on three production-scale batches. The results are in compliance with the release specification.

Microbiological attributes
The test for microbial contamination is included as a part of finished product specification to check the microbiological quality of the drug product, since some excipients may tend to support microbial growth.
The microbiological tests for Clarithromycin 500 mg Extended Release Tablets were performed as per the finished product specification and as per Ph. Eur. 2.6.12 method and Ph. Eur. 2.6.13 method. This is sufficient.

Stability tests on the finished product
Stability data on the product has been provided for three pilot-scale batches and three full-scale batches stored at 25°C/40% RH (36 months), at 30°C/65% RH (36 months), at 30°C/75% RH (36 months) and 40°C/25% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline.
The data provided shows that no significant changes occur in the parameters tested when the tablets are stored long term and accelerated conditions. An upward trend for total related and single related compounds can be seen for the pilot-scale batches, but the results remain well within the requirements. For the full-scale batches these trends were less pronounced. The assay values show some variability and a downward trend can be observed. Results remain within the proposed limits. A photostability study has been carried out on three pivotal batches of finished product. The results for the directly exposed

tablets (outside immediate pack) demonstrate that the product is not sensitive to light. The proposed shelf-life of 36 months is granted. No special storage conditions are required.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only excipient of animal origin. Statements of the suppliers of the excipients regarding BSE/TSE safety have been provided.

II.2 Non-clinical aspects

This product is a generic formulation of Klacid XL, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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 clarithromycin citrate 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

Clarithromycin citrate is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted three bioequivalence studies in which the pharmacokinetic profile of the test product Claritromycine retard CF 500 mg, prolonged-release film-coated tablets (Centrafarm B.V., NL) is compared with the pharmacokinetic profile of the reference product Klaricid XL 500 mg tablets (Abbott, UK), under various conditions.

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products (if applicable) in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study 1 - single dose, fasted conditions
A randomized, single dose, two treatment, two sequence, two period, two-way crossover comparative bioequivalence study was carried out under fasted conditions in 80 healthy male volunteers, aged 19-45 years. Each subject received a single dose (500 mg) of one of the 2 clarithromycin formulations. The tablets were administered in solid form with 200 ml water after an overnight fast of at least 10 hours. Fasting was continued for 4 hours after dosing. For each subject there were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected predose and at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 12, 16, 24, 36, and 48 hours after administration of the products. The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

The results for metabolite 14-OH-clarithromycine are considered supportive.

Results
Two subjects withdrew because of personal reason before or after dosing in Period I. Analyses were carried out on the first 72 included subjects.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of clarithromycin under fasted conditions.

Treatment N = 72	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	10758 ± 6657	11197 ± 6727	829 ± 396	4.5 (2.0 – 9.0)	6.4 ± 3.8
Reference	9969 ± 5889	10394 ± 6003	749 ± 407	6.0 (2.0 – 16.0)	6.0 ± 2.9
***Ratio (90% CI)**	1.11 (1.00 – 1.24)	1.11 (1.00 – 1.24)	1.15 (1.06 – 1.25)	---	---
CV (%)	41.4	40.5	31.2	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 14-OH-clarithromycin under fasted conditions.

Treatment N = 72	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	6776 ± 3099	7191 ± 3323	469 ± 152	4.5 (2.0 – 8.0)	7.9 ± 2.8
Reference	5733 ± 2946	6227 ± 3154*	356 ± 139	5.5 (3.0 – 24.0)	8.1 ± 3.5*
***Ratio (90% CI)**	1.22 (1.12 – 1.34)	1.19 (1.08 – 1.30)	1.35 (1.26 – 1.45)	---	---
CV (%)	33.3	33.8	25.3	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*
*** N= 71*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25.

Bioequivalence study 2 - single dose, fed conditions

A randomized, single dose, two treatment, two sequence, two period, two-way crossover comparative bioequivalence study was carried out under fed conditions in 44 healthy Indian male volunteers, aged 19-42 years. Each subject received a single dose (500 mg) of one of the 2 clarithromycin formulations. The tablets were administered in solid form with 200 ml water 30 min after serving a high fat breakfast. For each subject there were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected predose and at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 12, 16, 24, 36, and 48 hours after administration of the products. The analytical method is adequately validated and

considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

The results for metabolite 14-OH-clarithromycine are considered supportive.

Results
There were no dropouts; all subjects completed the study. Analyses were carried out on the 44 included subjects.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of clarithromycin under fed conditions.

Treatment N = 44	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	15957 ± 4887	16248 ± 4870	1485 ± 443	5.0 (2.0 – 12.0)	5.6 ± 1.2
Reference	15871 ± 5047	16143 ± 4978	1396 ± 426	6.0 (4.5 – 16.0)	5.3 ± 0.9
***Ratio (90% CI)**	1.01 (0.96 – 1.07)	1.01 (0.97 – 1.06)	1.07 (1.00 – 1.14)	---	---
CV (%)	15	13.1	18.4	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 14-OH-clarithromycin under fed conditions.

Treatment N = 44	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	8579 ± 2989	8869 ± 3078	566 ± 169	5.5 (3.0 – 12.0)	7.4 ± 1.6
Reference	8159 ± 2719	8527 ± 278	498 ± 143	6.5 (4.5 – 16.0)	7.6 ± 1.8
***Ratio (90% CI)**	1.05 (0.99 – 1.11)	1.03 (0.98 – 1.09)	1.13 (1.07 – 1.19)	---	---
CV (%)	16.9	15.4	15.6	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*
*** N= 71*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25.

Bioequivalence study 3 - multiple dose, fed conditions

A randomized, two treatment, two period, two sequence, multiple dose, two-way crossover bioequivalence study was carried out under fed conditions in 36 healthy male volunteers, aged 21-44 years. Each subject received for six days, once daily a single dose (500 mg) of one of the 2 clarithromycin formulations. The tablets were administered in solid form with 200 ml water 30 minutes after serving a high fat breakfast. For each subject there were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were taken pre-dose at day 1 (-120h), day 2 (-96h), day 3 (-72h), day 4 (-48h), day 5 (-24h), day 6 (0h) and at day 6, 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 12, 16, 24, 36, and 48 hours after administration of the products. The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

The results for metabolite 14-OH-clarithromycine are considered supportive.

Results

One subject was withdrawn in Period I for medical reasons and one subject withdrew for personal reason in Period I. One of these subjects was replaced. Analyses were carried out on the 32 subjects.

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of clarithromycin under fed conditions.

Treatment N = 32	**AUC_τ** ng.h/ml	**C_{min}** ng/ml	**C_{max}** ng/ml	**t_{max}** h	**Cp**** ng/ml
Test	19883 ± 6676	227 ± 147	1842 ± 498	4.5 (2.0 – 9.0)	283 ± 74
Reference	19559 ± 8011	243 ± 164	1752 ± 566	5.0 (3.0 – 9.0)	295 ± 88
***Ratio (90% CI)**	1.05 (0.95 – 1.16)	0.94 (0.81 – 1.09)	1.07 (0.99 – 1.16)	---	---
CV (%)	24.1	35.0	18.7	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*
*** Calculated on the basis of the last 3 pre-dose concentrations (-48, -24 and 0 h)*

Table 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 14-OH-clarithromycin under fed conditions.

Treatment N = 32	**AUC_τ** ng.h/ml	**C_{min}** ng/ml	**C_{max}** ng/ml	**t_{max}** h	**Cp**** ng/ml
Test	6754 ± 1909	125 ± 59	476 ± 140	5.0 (3.5 – 9.0)	143 ± 36
Reference	6332 ± 2249	126 ± 65	432 ± 119	6.25 (3.5 – 9.0)	144 ± 39
***Ratio (90% CI)**	1.09 (0.99 – 1.20)	1.02 (0.90 – 1.17)	1.09 (1.02 – 1.18)	---	---
CV (%)	23.0	31.4	17.5	---	---

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life

**ln-transformed values*
*** Calculated on the basis of the last 3 pre-dose concentrations (-48, -24 and 0 h)*

Based on the pharmacokinetic parameters of the parent clarithromycin, the reference and test are considered bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for AUC_T, C_{min} and C_{max} of clarithromycine were inside the normal range of acceptability (0.80 – 1.25).

Overall conclusion bioequivalence studies 1, 2, and 3
It can be concluded that for this application three bioequivalence studies are submitted in accordance with the guideline on extended release formulations: one single dose bioequivalence under fasting conditions, one single dose bioequivalence under fed conditions, and one multiple dose bioequivalence study. In all three studies the 500 mg extend release formulation is used. For all three studies, the 90% confidence intervals were inside the normal range of acceptability. Based on the pharmacokinetic parameters of clarithromycin under both fasted and fed conditions, it can be concluded that Claritromycine retard CF 500 mg, prolonged-release film-coated tablets and the Klaricid XL 500 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Clarithromycin was first approved in 1989, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of clarithromycin 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

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 lay-out of the PIL, and the testing was set up in accordance with EU-Guidelines. The results were presented in a clear way, good results were achieved, well within the pre-determined limits. Based on the testing, the company considered that the PIL was acceptable. However, the analysis of the free oral opinion on the lay-out of the PIL led to the conclusion that the font size of the PIL has to be changed from 8 to 9 Didot. According to the company, 8 points Didot is the font size in accordance with the guideline on Readability, so no change in this is deemed necessary. However, for products authorized after February 2011, font size should be 9 points Didot. The PIL has to be adjusted in this respect by the MAH.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Claritromycine retard CF 500 mg, prolonged-release film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Klaricid XL 500 mg tablets. Klaricid XL tablets is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Claritromycine retard CF 500 mg, prolonged-release film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 14 July 2011. Claritromycine retard CF 500 mg, prolonged-release film-coated tablets is authorised in the Netherlands on 5 September 2011.

The date for the first renewal will be: 1 December 2015.

The following post-approval commitments have been made during the procedure:

Quality - active substance

- The MAH has committed to re-evaluate the current limits for the clarithromycin assay and to possibly tighten these when more data has become available.
- The MAH has committed to continue the long term studies (on two full-scale batches) as per provided stability protocol (60 – 72 months). Furthermore one additional full-scale batch will be placed in long-term stability studies.

Quality - medicinal product

- The MAH has committed to retain lager batches sizes to validate the manufacturing process with the first three commercial batches. The validation report will be carried out in line with the guidance document "*CPMP/QWP/848/96 – Note for guidance on process validation*".

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
$t_{½}$	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