CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Minocycline Eurogenerics 50 mg and 100 mg film-coated tablets Eurogenerics N.V., Belgium

minocycline (as hydrochloride dihydrate)

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/2448/001-002/DC
Registration number in the Netherlands: RVG 110440-110441

26 March 2013

Pharmacotherapeutic group:	antibacterials for systemic use, tetracyclines
ATC code:	J01AA08
Route of administration:	oral
Therapeutic indication:	50 mg - severe inflammatory acne vulgaris; 100 mg - uncomplicated non-gonococcal urethritis, acute tracheobronchitis caused by Mycoplasma pneumonia, trachoma (ocular infection caused by *Chlamydia trachomatis*), syphilis, actinomycosis or anthrax in patients allergic to penicillin.
Prescription status:	prescription only
Date of authorisation in NL:	1 November 2012
Concerned Member States:	Decentralised procedure with BE, 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 Minocycline Eurogenerics 50 mg and 100 mg film-coated tablets from Eurogenerics N.V. The date of authorisation was on 1 November 2012 in the Netherlands.

The 50 mg product is indicated for severe inflammatory acne vulgaris.

The 100 mg product is indicated for:
- uncomplicated non-gonococcal urethritis
- acute tracheobronchitis caused by Mycoplasma pneumonia
- trachoma (ocular infection caused by *Chlamydia trachomatis*)
- syphilis, actinomycosis or anthrax in patients allergic to penicillin.

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.

Minocycline has a bacteriostatic effect based upon inhibition of the protein synthesis. Minocycline and doxycycline have a greater *in vitro* activity on Gram-positive bacteria than tetracycline, as a result of which some tetracycline resistant strains *in vitro* are still sensitive to minocycline and doxycycline. Minocycline is also effective against many staphylococcal strains resistant to penicillin G. *In vitro* susceptibility has been shown for Listeria monocytogenes. No clinical trials on *in vivo* efficacy against Listeria monocytogenes infections have been reported. Bacteria which are resistant to minocycline *in-vitro* are usually also resistant to the other tetracyclines.

This decentralised procedure concerns a generic application claiming essential similarity with the historical innovator products Minocin-50 and Minotab-100 tablets (NL License RVG 11640, 13414), which were registered in the Netherlands by Wyeth Pharmaceuticals B.V. from 1988 until 2003.
In addition, reference is made to Minocin and Minotab 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 two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Minocin 50 mg, obtained from the Netherlands, and Minocin 100 mg, obtained from Spain and Portugal. The reference product has meanwhile been withdrawn in some European countries, including the Netherlands. Therefore, for the RMS, reference is made to *historical* reference medicinal products. 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 a generic 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 minocycline hydrochloride dihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a yellow, hygroscopic crystalline powder, and is sparingly soluble in water.

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 CEP, with no additional requirements. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for four pilot-scale and three full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for four full-scale batches stored at 25°C/60% RH (18 months) and at 40°C/75% RH (6 months). All results remained within the specification limits. Based on the stability data provided the proposed re-test period of 18 months and the proposed storage condition ‘Protect from light, store below 25°C, with excursion up to 30°C permitted’ can be granted.

** 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
Minocycline Eurogenerics 50 mg contains as active substance 57.93 mg minocycline hydrochloride dihydrate equivalent to 50 mg minocycline base. It is a light yellow, round, biconvex tablet with a smooth, mat surface with a diameter of approximately 7.1 mm.
Minocycline Eurogenerics 100 mg contains as active substance 115.85 mg minocycline hydrochloride dihydrate equivalent to 100 mg minocycline base. It is a light yellow, oblong-formed, biconvex tablet with a smooth, mat surface (approximately 11.25 mm by 5.25 mm).

The film-coated tablets are packed in PVC/PVDC/Aluminium blister packs.

The excipients are: povidone K25, lactose monohydrate, microcrystalline cellulose (E460), croscarmellose sodium, colloidal silicon dioxide (E551), magnesium stearate (E470b), hypromellose 2910, macrogol 6000 (E1521), yellow iron oxide (E172), titanium dioxide (E171).

The two tablet strengths are fully dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies were manufacturing process trials. The choice of manufacturing process and packaging has been adequately justified.
The batch used in the bioequivalence study with the 100 mg formulation has the same composition and is manufactured in the same way as the future commercial batches. The BE batch is of sufficient size in relation to the intended commercial batch size. The pivotal BE study was performed against the Portuguese and Spanish reference products.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is divided into the following steps wet granulation, blending, lubrication, compression, two film coatings and packaging.
The product is manufactured using conventional manufacturing techniques. Adequate process validation data of three full-scale batches of each strength has been provided.

Control of excipients
The excipients comply with relevant Ph.Eur. monographs, except for ferric oxide which complies with the USP-NF monograph. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification of minocycline, hardness, disintegration time, average mass, loss on drying, related substances, assay, dissolution, mass variation, microbial contamination and identification of ferric oxide and titanium dioxide. The release and shelf life limits are identical except for loss on drying. This difference is justified. The drug product specification is acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on two pilot-scale and two full-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three full-scale batches of each strength stored at 25°C/60% RH (36 months). Furthermore stability data has been provided for two lab scale batches of each strength stored at 40°C/75% RH (6 months). The condition used in the stability studies is according to the ICH stability guideline. The batches were stored in PVC-PVdC/Al blisters.
At long term conditions the same trends were observed in both strengths. However, all results remained within specification limits. At accelerated conditions out of specification results were observed for appearance in both lab scale batches of the 100 mg tablets after 3 months of storage. Based on the photostability data provided, storage protected from light is not considered necessary
On the basis of the stability data provided, a shelf life of 36 months with the storage condition ‘Store below 25°C’ can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate and magnesium stearate are the only excipients used of human or animal origin. Declarations on the TSE/BSE safety have been provided.

II.2 Non-clinical aspects

This product is a generic formulation of Minocin 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 member states 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 minocycline 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

Minocycline 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 member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Minocycline Eurogenerics 50 mg is compared with the pharmacokinetic profile of the reference product Minocin obtained from the Netherlands, and a study with the 100 mg product compared to Minocin 100 mg, obtained from Portugal and Spain. The MAH of the reference products is TeoFarma S.R.L.

The batch size for the biobatch used the 50 mg study is not representative for the commercial batch size and is not in line with the guidelines. The study with the 100 mg strength is considered the pivotal study. Data in support of a biowaiver have been provided.

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 in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study I – 50 mg tablet
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 21-38 years. Each subject received a single dose (200 mg, 4 tablets) of one of the 2 minocycline formulations. The tablet was orally administered with 200 ml water after an overnight fast. A subsequent fasting period was applied for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 15, 24, 36 and 48 hours after administration of the products.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject withdrew due to an adverse event and was replaced by a spare subject. Twenty-four subjects completed the study and were included in the analysis.

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

Treatment N=24	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h

Test	39.0 ± 7.0	42.7 ± 9.0	3.1 ± 0.4	1.5 (1 – 3)	13.6 ± 2.4
Reference	40.2 ± 7.9	44.0 ± 9.7	3.2 ± 0.6	2.0 (1 – 2.5)	13.6 ± 2.3
***Ratio (90% CI)**	0.97 (0.94 - 1.01)	0.97 (0.94 - 1.01)	0.99 (0.94 - 1.03)	--	--
CV (%)	6.4	6.8	9.3	--	--

$AUC_{0-\infty}$ 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*

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. Based on the pharmacokinetic parameters of minocycline under fasted conditions, it can be concluded that Minocycline Eurogenerics 50 mg and Minocin 50 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study II – 100 mg tablet

Design

A single-dose, randomised, three-period, three-treatment, three-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 (+3) healthy male subjects, aged 19-36 years. Each subject received a single dose (100 mg) of one of the 3 minocycline formulations: the test product and the reference products obtained from Spain and Portugal, respectively. The tablet was orally administered with 200 ml water after an overnight fast. A subsequent fasting period was applied for 4 hours after dosing. There were 3 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 48 and 72 hours after administration of the products.

The single dose, crossover study under fasting conditions to assess bioequivalence is considered adequate. The replacement of drop outs by sparse subjects with the same administration sequence is in accordance with the protocol.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Three subjects did not complete the study. One subject was withdrawn before dosing in Period I due to an adverse event, one subject withdrew his consent before Period I and one subject did not report for Period III. Two subjects were replaced. A total of twenty-three subjects completed the study and were included in the analysis.

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

Treatment N=23	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h

Test	30.0 ± 5.8	32.7 ± 6.1	1.7 ± 0.2	2.1 ± 0.8	17.1 ± 2.9
Reference SPAIN	30.0 ± 5.1	31.9 ± 5.5	1.6 ± 0.2	2.4 ± 1.0	17.5 ± 2.6
Reference PORTUGAL	29.0 ± 5.4	30.9 ± 6.0	1.6 ± 0.3	2.0 ± 0.9	16.9 ± 2.6
***Ratio (90% CI) versus SPAIN**	1.01 (0.95 - 1.07)	1.04 (1.00 - 1.09)	1.05 (0.99 - 1.12)	--	--
CV (%) versus SPAIN	10.9	8.9	11.3	--	--
***Ratio (90% CI) versus PORTUGAL**	1.02 (0.96 - 1.09)	1.06 (1.01 - 1.11)	1.12 (1.06 - 1.18)	--	--
CV (%) versus PORTUGAL	12.5	8.9	9.8	--	--
$AUC_{0-\infty}$ 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*

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. Based on the pharmacokinetic parameters of minocycline under fasted conditions, it can be concluded that Minocycline Eurogenerics 100 mg and Minocin 100 mg tablets obtained from two countries, are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

As the 50 mg study does not comply with the guidelines regarding the small size of the biobatch, data were submitted to substantiate that minocycline can be considered a BCS Class I drug. Based upon the BCS classification, submitted dissolution data, formulation composition and the results of the bioequivalence study with the 100 mg tablet, it was concluded that the 50 mg test formulation can be considered bioequivalent.

Minocycline may be taken without reference to food intake. Absorption of minocycline is delayed (around 1 hour) when taken with food. The degree of absorption is scarcely affected. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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

Minocycline was first approved in 1986, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of minocycline 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 decentralised procedure is in accordance with those accepted for other minocycline products.

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 of a pilot test with 3 participants, followed by two rounds with 10 participants each. A questionnaire of 19 questions was used: 2 introductory questions were asked, to help the participant relax for the remainder of the interview; 14 questions specific to the medicinal product were drawn up, sufficiently addressing the key safety messages; and finally 3 questions on personal opinion were designed to determine the test person's overall impression of the PL as mock-up.
The results of the interviews showed that the PL could be rated as readable and comprehensible according to the requirements of the European Directive with an Independent Readability Index of 99.6 and a Dependent Readability Index of 99.3. To further improve readability, the MAH proposed to increase the size of the leaflet format and thus also the font size as far as allowed by printing necessities in future PLs. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Minocycline Eurogenerics 50 mg and 100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Minocin-50 and Minotab-100 tablets. Minocin/Minotab 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 and are in agreement with other minocycline containing products.

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 Minocycline Eurogenerics 50 mg and 100 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 4 October 2012. Minocycline Eurogenerics 50 mg and 100 mg film-coated tablets is authorised in the Netherlands on 1 November 2012.

The date for the first renewal will be: 4 October 2017.

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

<u>Quality - medicinal product</u>

- The MAH committed to perform accelerated stability studies on full-scale batches.

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