

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

**Clindamycine 10 mg/ml Teva, cutaneous solution
Teva Nederland B.V., the Netherlands**

clindamycin (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 108315

25 February 2013

Pharmacotherapeutic group:	antiinfectives for treatment of acne
ATC code:	D10AF01
Route of administration:	cutaneous
Therapeutic indication:	moderate to severe acne
Prescription status:	prescription only
Date of authorisation in NL:	31 January 2012
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 Clindamycine 10 mg/ml Teva, cutaneous solution from Teva Nederland B.V. The date of authorisation was on 31 January 2012 in the Netherlands.

The product is indicated for moderate to severe acne vulgaris when topical therapeutic treatment without antibiotics is insufficient.

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.

Clindamycin is a lincosamide antibiotic that inhibits bacterial protein synthesis. It binds to the 50S ribosomal subunit and affects both ribosome assembly and the translation process. Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

This national procedure concerns a hybrid application claiming essential similarity with several products containing clindamycin 10 mg/ml solution which are licensed in the Netherlands for the treatment of acne vulgaris. The reference product is Dalacin-T 10 mg/ml, cutaneous solution (NL License RVG 09728), which has been registered by Pfizer B.V. 29 December 1983.

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC, a hybrid application, as bioequivalence cannot be demonstrated through bioequivalence studies.

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. It concerns a locally applied, locally acting product, for which bioequivalence studies are not required. Test and reference product have the same qualitative and quantitative composition. The current 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.

No paediatric development programme has been submitted, as this is not required for a hybrid medicinal product.

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 clindamycin phosphate, an established active substance described in the European, United States and British Pharmacopoeia (Ph.Eur., USP, BP*). The active substance is a white or almost white, hygroscopic, crystalline powder, which is freely soluble in water, very slightly soluble in alcohol and practically insoluble in ether and methylene chloride. Since the drug substance is a 1% topical solution, properties such as particle size distribution and polymorphic form are not relevant to the performance of the drug product

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 MAH refers to the specifications of the Ph.Eur. monograph for clindamycin phosphate and the additional CEP requirements. The additional requirements on the CEP regard impurities and residual solvents. The specification is acceptable in view of the CEP. Certificate of analysis for three batches of the have been provided.

Stability of drug substance

The retest period for the active substance is 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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

Medicinal Product

Composition

Clindamycine 10 mg/ml Teva is a clear and colorless topical solution with pH 5.2-5.6. One ml of solution contains 10 mg clindamycin as clindamycin phosphate.

The cutaneous solution is packed in brown transparent 30 ml, 60 ml or 100 ml type III (Ph.Eur.) glass bottles with a polyethylene dropper and polyethylene closure.

The excipients are: isopropyl alcohol, propylene glycol (E1520), purified water, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment).

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The aim was to develop a product similar to the innovator product Dalacin-T (Pfizer). In the course of the development several activities were performed with regard to pH influence, isopropyl content and propylene glycol content. Results on the influence of the pH (when the product is stored) and efficacy of the antimicrobial preservation were satisfactory. No overage is present in the drug product. The choices of the packaging and manufacturing process are justified. The pharmaceutical development of the product has been adequately performed. Similarity between the innovator product and Clindamycine Teva is shown from a chemical-pharmaceutical point of view.

Manufacturing process

The manufacturing process consists of four major manufacturing steps: weighting of the active substance and excipients, preparation of the bulk solution, filling of the glass containers with the prepared mixture, labelling and packaging. The product is manufactured using standard manufacturing techniques. The manufacturing process has been adequately validated according to relevant European guidelines. Validation data on 6 commercial batches are provided, results are satisfactory.

Control of excipients

The excipients comply with their respective Ph.Eur. monographs. These specifications are acceptable.

Microbiological attributes

The product is intended for the topical use only. Therefore it is not sterile and bacterial endotoxins test is not performed. However, in order to guarantee the good quality of the product throughout the shelf-life, isopropyl alcohol is used as antimicrobial preservative agent. Microbiological purity is justified as per Ph.Eur. 5.1.3.

Quality control of drug product

The product specification includes tests for aspect of solution, refractive index, pH, relative density, identification of clindamycin phosphate, deliverable volume, assay, degradation products, identification and assay of isopropyl alcohol, closure integrity test and packaging and labelling. The limits are acceptable (release and end of shelf-life). The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 10 batches of the different bottle volumes (30 ml, 60 ml or 100 ml), demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on several pilot-scale and production-scale batches of the three different volumes stored at 25°C/60%RH (12-24 months), 30°C/65%RH (12 months), and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The product is stored in a brown transparent type III bottle, stoppered with a PE closure. No specific changes or patterns were noted for any of the parameters. The product was shown to be photostable. The approved shelf-life and storage conditions are 24 months, when stored below 25°C. Although it is not considered necessary on the basis of the stability data provided, this is in line with the innovator product.

In-use stability studies have been performed. Stability was tested for a period of 28 days; twice daily 10 drops (0.05 ml) were taken from the bottle. The product has to be applied twice daily; the amount to be taken depends on the part of the skin that is affected. The test procedure is similar to daily use of the product. Based on the satisfactory results, an in-use shelf life of 28 days was granted.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a hybrid formulation of Dalacin-T 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 clindamycin 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

Clindamycin 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.

Pharmacodynamics

No new studies were provided. A summary of the pharmacodynamics of clindamycin in acne vulgaris was submitted.

In acne treatment, clindamycin reduces the population of *Propionibacterium acnes* on the surface of the skin and within the hair follicle, thus decreasing the percentage of pro-inflammatory free fatty acids in skin surface. The mechanism of action of clindamycin is thought to be an inhibition of protein synthesis: It binds reversibly to 50S ribosome sites usually occupied by the transfer RNA-amino acid complex and therefore causes competitive inhibition of protein synthesis by ribosomal blockade.

Once delivered to the skin, clindamycin phosphate is hydrolyzed topically by phosphatases to the active constituent clindamycin and clindamycin is found in comedone samples at sufficient levels to be active against most strains of *Propionibacterium acnes*.

The pharmacodynamic action of clindamycin is well-known and clindamycin is considered well-established use in the treatment of acne vulgaris.

Pharmacokinetics

No new studies were provided. A summary of literature references was submitted.

Topically administered 1% clindamycin has been found to have low bioavailability, with values differing considerably in different studies, including values from 4 to 5% to less than 1% (Akhavan et al. 2003¹).

In a comparative study of clindamycin hydrochloride versus clindamycin phosphate, each in a combination gel with tretinoin 0.025%, applied daily for 5 consecutive days to the faces of healthy volunteers, very few clindamycin was detected in plasma after the clindamycin phosphate preparation (0 to a maximum of 5 ng/mL), but clindamycin was detected in one volunteer receiving the clindamycin hydrochloride preparation (13 ng/mL). This was similar for clindamycin urinary excretion. When the penetration of the clindamycin phosphate/tretinoin gel was monitored after 4 and 12 weeks of daily treatment, in 87% of the samples there was no clindamycin detectable. The highest plasma concentration was 11 ng/mL, corresponding to a mean of 1.7% of absorption versus a mean value of 7.5% for the clindamycin hydrochloride. Interestingly, there was also no demonstrable notable enhancing effect of tretinoin on systemic uptake of clindamycin (13). The urinary excretion of clindamycin amounted to 5-18 µg/mL for clindamycin phosphate/tretinoin gel and 2-27 µg/mL for clindamycin phosphate 1% reference lotion (mean of 10 ± 6 µg/mL) over the 12h on day 5 versus 9-82 µg/mL for clindamycin hydrochloride/tretinoin gel (van Hoogdalem et al. 1998²).

¹ Akhavan A, Bershada S. Topical acne drugs: review of clinical properties, systemic exposure, and safety. American Journal of Dermatology. 2003;4:473-492

² Van Hoogdalem EJ, Baven TL, Spiegel-Melsen I, Terpstra IJ. Transdermal absorption of clindamycin and tretinoin from topically applied anti-acne formulations in man. Biopharm Drug Dispos 1998;19(9):563-9.

Pharmacokinetic properties are well-known and sufficiently summarised in the overview by the MAH. Systemic absorption is low (around 1.7%) when applied in accordance with the dosing regimen.

Clinical Efficacy

Topical antibacterial agents, including clindamycin, are widely used for treating acne. Clindamycin 1% solution is well established as an effective topical antibacterial in acne therapy. This is sufficiently described in the references presented in the clinical overview. No product specific therapeutic equivalence study is provided. No bioequivalence, neither clinical study is considered necessary as dermal absorption of the active ingredient is weak and the solution Clindamycine Teva and Dalacin-T 10 mg/ml cutaneous solution have the same qualitative and quantitative composition.

Use of clindamycin 1% solution is considered well established in acne therapy. The absence of a comparative clinical non-inferiority study with Clindamycine Teva versus Dalacin-T, lotion 1% m/v is accepted in this specific case since there are no clinically relevant differences regarding the quality of both products. The indication for the reference product Dalacin-T can therefore be extrapolated to the present application.

Clinical Safety

No specific study has been carried out to assess the safety of Clindamycin 10 mg/ml PCH.

Reference is made to the literature and known safety profile of the innovator product. The known adverse events are mostly minor. The most common site effect reported skin dryness, other reported side effects include skin irritation, itching, peeling erythema or staining of the skin, contact dermatitis, stinging of the eye, gastrointestinal disturbances and abdominal pain. Severe events like gastrointestinal events are rare. Absence of clinical safety data is regarded to be acceptable since there are no clinically relevant differences regarding the quality of both products.

Benefit/risk assessment

Clindamycine 10 mg/ml Teva cutaneous solution is considered well established as an effective topical antibacterial in acne therapy. Although no clinical studies have been carried out there seems to be sufficient evidence of essential similarity between the compositions of Clindamycin 10 mg/ml Teva and Dalacin-T lotion 1% m/v. The efficacy and safety data in the sought indication for the reference product can therefore in this specific case be extrapolated to the present application without specific clinical studies.

The benefit/risk balance for Clindamycin 10 mg/ml is regarded to be favourable.

Product information

SPC

The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product Dalacin-T cutaneous solution.

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. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Revisions were made based on the results obtained in the first round of testing. Overall, the result of the user test was satisfactory, as more than 90% of literate adults were able to locate the requested information, to explain the contents of the text and the readers knew how to act on it. The readability test has been adequately performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Clindamycine 10 mg/ml Teva, cutaneous solution has a proven chemical-pharmaceutical quality and is a hybrid form of Dalacin-T 10 mg/ml, cutaneous solution. Dalacin-T 10 mg/ml is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are locally applied, locally acting products, no bioequivalence study is deemed necessary.

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

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

The Board followed the advice of the assessors. 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. Clindamycine 10 mg/ml Teva, cutaneous solution was authorised in the Netherlands on 31 January 2012.

There were no post-approval commitments made during the procedure.

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