LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Clindamycin Actavis
(clindamycin hydrochloride)

SE/H/1538/001-02/DC

This module reflects the scientific discussion for the approval of Clindamycin Actavis 150 and 300 mg, hard capsules. The procedure was finalised on 2016-01-26. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The applications for Clindamycin Actavis, 150 mg and 300 mg, hard capsule, are generic applications made according to Article 10(1) of Directive 2001/83/EC. The applicant, Sigillata Limited applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is originator Dalacin 150 mg and 300 mg hard capsule, authorised in Sweden since 1974, with Pfizer AB as marketing authorisation holder.

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II. QUALITY ASPECTS

II.1 Introduction

Clindamycin Actavis is presented in the form of capsules containing 353 mg of clindamycin hydrochloride which corresponds to 300 mg of clindamycin. The excipients are lactose anhydrous, magnesium stearate, maize starch, talc, gelatin, sodium lauril sulfate, titanium dioxide, potassium hydroxide, propylene glycol, shellac and iron oxide black. The capsules are packed in/filled in blisters.

II.2 Drug Substance

Clindamycin hydrochloride has a monograph in the Ph. Eur.

Clindamycin hydrochloride is a white or almost white, crystalline powder which is very soluble in water and slightly soluble in ethanol. The structure of clindamycin hydrochloride has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Clindamycin Actavis, hard capsules are formulated using excipients described in the current Ph. Eur., except for iron oxide black which is controlled according to acceptable in house specifications. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal

Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Clindamycin is rapidly and almost completely absorbed (90%). Bioavailability is non-linear with a proportionally lower exposure following administration of higher doses. After a dose of 600 mg the absolute bioavailability is approximately 53%. Following an oral dose of clindamycin maximal plasma concentrations occur after 30 minutes to 2 hours. The pharmacokinetics of clindamycin is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator. The pharmacokinetics is non-linear with a less than proportional increase in AUC with increasing dose. The terminal half-life is 2-3 hours.

To support the application, the applicant has submitted 2 single-dose bioequivalence studies in the fasted state:

- Study BE-1177-14 with the 150 mg strength
- Study BE-1176-14 with the 600 mg strength (not applied for in this application)

For drugs with non-linear pharmacokinetics characterised by a less than proportional increase in AUC with increasing dose over the therapeutic dose range bioequivalence should in general be established at the lowest strength (or a strength in the linear range). If the non-linearity is caused by limited solubility bioequivalence should also be demonstrated at the highest strength (i.e. highest and lowest strength) (Guideline on the investigation of bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1). According to the monograph clindamycin is very soluble in water which indicates that the non-linearity is not caused by limited solubility, and thus the study with the 150 mg strength is considered to be the main pivotal study, and the study with the higher strength is considered supportive. Absence of studies with the additional strength

300 mg is acceptable from a pharmacokinetic point of view.

Both bioequivalence studies were single-dose, two-way crossover studies conducted in 32 healthy volunteers under fasting conditions. The studies were conducted at Watson Pharma Pvt. Ltd., Navi Mumbai, India between 1st and 5th September 2014 (study BE-1177-14) and between 25th and 29th November 2014 (study BE-1176-14) respectively. Study BE-1177-14 compared Clindamycin, 150 mg, capsules with Dalacin, 150 mg, hard capsules and study BE-1176-14 compared Clindamycin, 600 mg, capsules with Dalacin, 300 mg, hard capsules (at a dose of 600 mg). Blood samples were collected pre-dose and up to 24 hours post-dose. The study design is considered acceptable. Plasma concentrations of clindamycin were determined with an adequately validated LC/MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% in both studies.

Table 1: Results from the pivotal study with the 150 mg strength. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for clindamycin, n=32.

Treatment	**AUC_{0-t}** **ng*h/ml**	**C_{max}** **ng/ml**	**t_{max}** **h**
Test	**17101±5249**	**3581±774**	**0.75 (0.50-2.50)**
Reference	**16844±5557**	**3595±642**	**0.75 (0.50-1.50)**
***Ratio (90% CI)**	**101.89 (96.32-107.77)**	**98.87 (94.60-103.33)**	**-**
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 plasma concentration			

**calculated based on ln-transformed data*

Table 2: Results from the supportive study with the 600 mg strength (not applied for in the current application). Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for clindamycin, n=30.

Treatment	**AUC_{0-t}** **ng*h/ml**	**C_{max}** **ng/ml**	**t_{max}** **h**
Test	**42211±15029**	**7877±1788**	**1.00 (0.50-1.50)**
Reference	**42688±14236**	**7907±1915**	**1.00 (0.50-1.75)**
***Ratio (90% CI)**	**98.39 (95.29-101.58)**	**99.92 (96.60-103.36)**	**-**
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 plasma concentration			

**calculated based on ln-transformed data*

Based on the submitted bioequivalence study, Clindamycin Actavis 150 mg capsules are considered bioequivalent with Dalacin, 150 mg, hard capsules.

The results of study BE-1177-14 with 150 mg formulation CAN be extrapolated to the other strength 300 mg, according to conditions in the Guideline on the investigation of Bioequivalence; CHMP/QWP/EWP/1401/98 Rev. 1, section 4.1.6.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation
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 language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The risk/benefit ratio is considered positive and Clindamycin Actavis, 150 mg and 300 mg, hard capsule is recommended for approval.

VI. APPROVAL

Decentralised procedure for Clindamycin Actavis, 150 mg and 300 mg, hard capsule was successfully finalised on 2016-01-26.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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