Public Assessment Report

Scientific discussion

Clindamycin EQL Pharma
(clindamycin hydrochloride)

Asp no: 2017-1222-23

This module reflects the scientific discussion for the approval of Clindamycin EQL Pharma. The procedure was finalised on 2018-11-01. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

The application for Clindamycin EQL Pharma, 150 mg and 300 mg, capsule, hard, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, EQL Pharma AB, applies for a marketing authorisation in Sweden through a National Procedure.

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

The reference product used in the bioequivalence study is Dalacin, 300 mg, capsule, hard, from Sweden with Pfizer AB as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

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 have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.
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 has an oral bioavailability of 90 %, but the bioavailability is non-linear and decreases with increasing doses. Following a dose of 600 mg the absolute bioavailability is 53+14 %. Following an oral dose of clindamycin maximal plasma concentrations occur at approximately 45 minutes. The pharmacokinetics of clindamycin is not significantly 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 2.4 hours.

Study BE/CLN-009-1-2016 with the 300 mg strength
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 28 healthy volunteers, comparing Clindamycin ABR, 300 mg, hard capsules, manufactured by Balkanpharma-Razgrad AD, Bulgaria with Dalacin, 300 mg, hard capsules, by Pfizer AB, Sweden from the Swedish market under fasting conditions. The study was conducted between 23rd June and 15 July 2016. 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 LC/MS/MS method. For $\text{AUC}_{0-t}$ and $C_{\text{max}}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.
Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \(t\)\(_{\text{max}}\) median, range) for clindamycin, \(n=28\).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>(\text{AUC}_{0-t}) µg*h/ml</th>
<th>(C_{\text{max}}) µg/ml</th>
<th>(t_{\text{max}}) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>10.17±5.84</td>
<td>2.78±0.93</td>
<td>0.63 (0.50-1.02)</td>
</tr>
<tr>
<td>Reference</td>
<td>10.68±5.31</td>
<td>2.81±0.82</td>
<td>0.75 (0.50-2.00)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>93.76 (88.26-99.61)</td>
<td>97.19 (90.16-104.76)</td>
<td>-</td>
</tr>
</tbody>
</table>

\(\text{AUC}_{0-t}\) area under the plasma concentration-time curve from time zero to \(t\) hours
\(C_{\text{max}}\) maximum plasma concentration
\(t_{\text{max}}\) time for maximum plasma concentration

*calculated based on ln-transformed data

Based on the submitted bioequivalence study, Clindamycin 300 mg capsules are considered bioequivalent with Dalacin 300 mg capsules.

**Biowaiver for the 150 mg strength**

For the 150 mg strength, the applicant applied for a BCS class I based biowaiver, although reference is also given to the conditions for biowaiver of additional strengths according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1). Both aspects are considered below.

**Strength biowaiver**

According to the SmPC of the Swedish originator the bioavailability is non-linear with a less than proportional exposure following administration of higher doses. For drugs characterised by a less than proportional increase in AUC with increasing dose over the therapeutic dose range, the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1) states that bioequivalence should in most cases be established both at the highest strength and at the lowest strength. If the non-linearity is not caused by limited solubility but is due to e.g. saturation of uptake transporters, it is sufficient to demonstrate bioequivalence at the lowest strength.

An article by Metzler and co-workers referred to by the applicant states that the dose-bioavailability relations of clindamycin bioactivity are linear but not proportional and that the pharmacokinetic variables for the different dose-levels are on a straight line but the response does not double when the dose is doubled. Thus, this article does not support dose proportionality since there is a less than proportional increase in AUC and Cmax with increasing dose.

Although the information in various SmPCs available on the European market differ in the information regarding dose-proportionality, the data submitted by the applicant does not unambiguously support a proportional increase in AUC or Cmax with increasing dose, and does not disprove the information stated in the SPC for the Swedish originator that the bioavailability is non-linear with a proportionally lower exposure following administration of higher doses. Thus, waiving bioequivalence studies with the 150 mg strength based on the study with the 300 mg strength is not acceptable from a pharmacokinetic perspective.

**BCS based biowaiver**
According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr), a BCS class I-based biowaiver is applicable for an immediate release product if the drug substance is not considered to have a narrow therapeutic index and has been proven to exhibit high solubility and complete absorption (BCS class I). Also, in-vitro dissolution characteristics of the test and the reference product should be either very rapid or similarly rapid and the excipients that might affect bioavailability should be quantitatively and qualitatively the same.

A BCS class III-based biowaiver is applicable for an immediate release product if the drug substance is not considered to have a narrow therapeutic index and has been proven to exhibit high solubility and limited absorption (BCS class III). Also, in-vitro dissolution characteristics of the test and the reference product should be very rapid and excipients that might affect bioavailability should be quantitatively and qualitatively the same and all other excipients should be qualitatively the same and quantitatively very similar.

Clindamycin is not considered to have a narrow therapeutic index in the sense that narrowed acceptance ranges would be necessary in bioequivalence studies performed with clindamycin.

The Swedish SmPC for the originator states that clindamycin has an oral bioavailability of 90%, but it is not stated at what dose this has been established. It is also stated that the bioavailability is non-linear and decreases with increasing doses. Following a dose of 600 mg the absolute bioavailability is stated to be 53±14%. This information has been taken from a study published by Gatti et al (Antimicrobial agents and chemotherapy, May 1993, p. 1137-1143) which was a cross-over study investigating a clindamycin dose of 600 mg in healthy volunteers following oral and IV administration and with a specific chromatographic assay.

In a study by Boazza et al an absolute bioavailability of 87.6% following a 600 mg dose was determined using a population pharmacokinetic model. The figure of 87.6% is clearly different from the figure of 53±14% stated in the Swedish SmPC for the same dose. It should be noted that the study by Boazza is a retrospective study using parallel design and sparse sampling while the figure in the SmPC is taken from a dedicated absolute bioavailability study using cross-over design and rich sampling. Thus, we are not prepared to agree that the study by Boazza et al disproves the figure of oral bioavailability of a 600 mg dose stated in the SmPC.

Complete absorption should normally be demonstrated for the entire therapeutic dose range in order to allow a BCS class I-based biowaiver. However, since the applicant has submitted a bioequivalence study with the 300 mg strength, the main concern in this particular case would be to demonstrate that the absorption is complete following a 150 mg dose. As stated above, it is not clear from the information in the SmPC at what dose the oral bioavailability figure of 90% has been established. However, since the substance is stated to have a non-linear bioavailability with proportionally lower exposure following administration of higher doses, it can be concluded that the lowest therapeutic dose (150 mg) should most likely have a degree of absorption above the cut-off of 85%. Thus, a BCS class I based biowaiver can be accepted for the lower strength. It is not clear if the absorption can be regarded as complete in the entire therapeutic range, but since the applicant has submitted a BE study for the higher strength (300 mg) it is considered sufficient to demonstrate complete absorption for the 150 mg dose.

There is one qualitative difference regarding the capsule fill, since the reference product contains talc as glidant while the test product contains colloidal anhydrous silica. There are also quantitative differences. The differences in excipients are acceptable for a BCS class I biowaiver.
The quality criteria for BCS class I biowaiver (solubility and dissolution) have been fulfilled. Thus, a BCS class I biowaiver for the lower strength is acceptable.

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.

IV.3 Risk Management Plan

The MAH has submitted an updated risk management plan (version 0.2 dated 2018-05-22), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Clindamycin EQL Pharma.

Safety specification

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
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<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
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<tr>
<td>Severe skin reactions</td>
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<tr>
<td>Clostridium difficile-associated diarrhoea (CDAD) and Pseudomembranous colitis</td>
</tr>
<tr>
<td>Impaired liver, kidney and bone marrow function</td>
</tr>
<tr>
<td><strong>Important potential risks</strong></td>
</tr>
<tr>
<td><strong>Missing information</strong></td>
</tr>
</tbody>
</table>

The Applicant has presented a list of safety concerns as in the table above, which is acceptable.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 0.2, dated 2018-05-22 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the MPA;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk
profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Clindamycin Actavis 150 mg, 300 mg hard capsules and Acetazolamid EQL Pharma 250 mg tablets. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product, Clindamycin EQL Pharma, is found adequate. There are no objections to approval of product name, from a non-clinical and clinical point of view. Based on the submitted bioequivalence study, Clindamycin 300 mg capsules are considered bioequivalent with Dalacin 300 mg capsules. A BCS class I biowaiver for the lower strength 150 mg is acceptable. The product information is acceptable. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Clindamycin EQL Pharma, 150 mg and 300 mg, capsule, hard was approved in the national procedure on 2018-11-01.
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<table>
<thead>
<tr>
<th>Procedure number*</th>
<th>Scope</th>
<th>Product Information affected</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Summary/ Justification for refuse</th>
</tr>
</thead>
</table>

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)