Ravimiamet
State Agency of Medicines

Hinnangu kokkuvõte

20.12.2013 anti müügiload KRKA d.d., Novo Mesto ravimitele Aclexa 100 mg ja 200 mg kõvakapslid.

Müügiload taotleti detsentraalse protseduuri kaudu, kus viidatavaks riigiks oli Eesti.

Tegemist on retseptiravimitega.

Aclexat kasutatakse täiskasvanutel reumatoidartriidi, osteoartroosi ja anküloseeriva spondüliidi nähtude ja sümptomite leevendamiseks.

Ravimi Aclexa toimeaine on tselekoksiib. Aclexa kuulub ravimite rühma, mida nimetatakse mittesteroidseteks põletikuvastasteks aineteks (MSPVA), täpsemalt alarühma, mida nimetatakse tsüklooksügenaas-2 (COX-2) inhibiitoriteks. Teie organism toodab prostaglandiine, mis võivad põhjustada valu ja põletikku. Selliste seisundite puhul nagu reumatoidartriit ja osteoartroos toodab teie organism neid rohkem. Aclexa pärsib prostaglandiinide tootmist ja vähendab sellega valu ning põletikku.

Ravimitele anti müügiload, kuna Aclexa kasutamisest oodatav kasu ületab võimalikud riskid.

Avalik hinnanguaruanne on leitav järgnevatelt lehekülgedelt.

Public Assessment Report

Scientific discussion

ACLEXA
Celecoxib

EE/H/0187/001-002/DC

Date: 08.01.2014

This module reflects the scientific discussion for the approval of Aclexa. The procedure was finalised at 7.11.2013. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Aclexa 100 mg and 200 mg hard capsule, from Krka, d.d., Novo mesto.
The product is indicated for the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

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

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC as amended.

II. QUALITY ASPECTS

II.1 Introduction

Celecoxib 100 mg and 200 mg hard capsules were formulated as immediate release oral dosage forms using well-known conventional excipients of pharmacopoeial quality. The excipients in the capsule core are lactose monohydrate, povidone K30, croscarmellose sodium, sodium laurilsulfate and magnesium stearate (E572). The excipients in the hard capsule shell are gelatin and titanium dioxide (E171) and additionally in the hard capsule shell of 200 mg iron oxide, yellow (E172). The development of the product has been described in sufficient detail, the choice of excipients is justified and their functions explained.

Celecoxib 100 mg hard capsules are size 3 capsules with white cap and white body filled with white or almost white granulated powder. Celecoxib 200 mg hard capsules are size 1 capsules with with brownish yellow cap and brownish yellow body filled with white or almost white granulated powder.
The capsules are packaged in PVC/Al blister.

II.2 2.2 Drug Substance

Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, is classified as a nonsteroidal anti-inflammatory drug (NSAID). Celecoxib appears as white or off-white crystalline powder and is non-hygroscopic in nature. It is freely soluble in methanol, acetone and ethyl acetate, sparingly soluble in isopropanol and practically insoluble in water at room temperature. Celecoxib is not a chiral molecule
since no stereogenic center, axis nor plane is considered in its molecule. It is optically inactive and it does not contain any optical isomers. Celecoxib is crystalline in nature, the polymorphic form III is used in the drug product. The stability of produced polymorphic form is proven.
Celecoxib monograph is included in the Ph. Eur. API manufacturer uses Certificate of suitability. The compliance with the monograph requirements has been evaluated by EDQM.
The finished product manufacturer`s active substance specification includes relevant tests and the limits are 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

Aclexa hard capsules are conventional oral dosage forms containing 100 mg or 200 mg of celecoxib. The finished product for 100 mg strength is white or almost white granulated powder in a capsule size 3 with white cap and white body. The finished product for 200 mg strength is white or almost white granulated powder in a capsule size 1 with brownish yellow cap and brownish yellow body.
The development of the product has been described, the choice of excipients is justified and their functions explained.
The information provided with regard to manufacturing process of the medicinal product is considered generally adequate, however the following follow- up measure (FUM) has been made.
The drug product specifications are considered acceptable. The analytical methods are described and validated. Batch analysis has been performed on 5 batches for 100 mg drug product and 5 batches for 200 mg drug product.
The capsules are packed in PVC/Al blisters.
The conditions used in the stability studies are according to the ICH stability guideline. The shelf-life of 24 months with storage condition store below 25°C is supported by the stability data and can be accepted.

There is also a possibility for the storage of the bulk product indicated in the documentation.

III. NON-CLINICAL ASPECTS

No new data were presented.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Aclexa is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Celecoxib are well known. As Celecoxib is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required.
The originator product for Aclexa is Celebrex (hard capsules 100 and 200 mg) by Pfizer AB authorised since 03.12.1999.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Bioequivalence studies
To support the application, the applicant has submitted one bioequivalence study and applied the biowaiver for additional strength.
The study was a randomised, open-label, two-treatment, two-sequence, two-period, crossover, single dose bioequivalence study conducted under fasting conditions with a wash out period of 7 days between two administrations. One capsule containing 200 mg of Celecoxib was administered in each period.

A total of 60 healthy subjects were enrolled in the study, all enrolled subjects completed the study and were included in the pharmacokinetic and statistical analysis. The primary pharmacokinetic parameters assessed were C_{max} and AUC_{0-t}. The 90% confidence intervals for the test and reference mean ratio of the log-transformed primary pharmacokinetic variables were within the conventional bioequivalence range of 80% to 125%.

The main results of the bioequivalence study are tabulated below.

Table 1. Pharmacokinetic parameters for Celecoxib (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	**AUC_{0-t}** xng/ml/h	**$AUC_{0-\infty}$** xng/ml/h	**C_{max}** xng/ml	****t_{max}** h
Test GM	**4747.782**	**5070.859**	**438.815**	**2.63**
Arithmetic mean ± SD	**5217.340 (±2559.5)**	**5556.972 (±2722.1)**	**502.580 (±295.3)**	
Reference GM	**4633.742**	**4865.676**	**465.648**	**2.46**
Arithmetic mean ± SD	**5084.609 (±2333.4)**	**5326.153 (±2437.4)**	**526.103 (±261.3)**	
***Ratio**	**102.46%**	**104.22%**	**94.24%**	**N.A.**
(90% CI)	**(98.78%-106.28%)**	**(100.05%-108.56%)**	**(85.79%-103.52%)**	
CV (%)	**12%**	**13.4%**	**31.5%**	**N.A.**

$AUC_{0-\infty}$ **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**
GM **Geometric mean**
****ln-transformed values***
***** median***

Based on the submitted bioequivalence study, Celecoxib 200 mg hard capsule by KRKA d.d., Slovenia, is considered bioequivalent with the reference product Celebrex® 200 mg capsule by Pfizer Manufacturing Deutschland GmbH, Germany.
Since the 100 mg strength of the product meet the criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.), the results and conclusions of the bioequivalence study on the 200 mg strength can be extrapolated to the 100 mg strength.

IV.2 Pharmacodynamics

No new data were presented.

IV.3 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

Follow-up measures - quality

3.2.P.8 Stability

The Applicant is committed to carry out stability studies at intermediate testing conditions with the dissolution test performed according to the new chosen method and revise the storage conditions of the finished product after additional stability results are available (not later than December 2014).

3.2.P.3 Manufacture

Two pilot scale batches (in-bulk capsules) have been investigated in stability studies for bulk product. Thus, the Applicant is committed to carry out in-bulk stability studies with commercial scale batches for according to the EMA Q&A guidance 'Stability issues of pharmaceutical bulk products' the data from pilot scale batches should be verified in post-approval stability commitments on commercial scale batches. The requested additional data should be provided not later than December 2014.

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 the applications for Aclexa 100 mg and 200 mg hard capsules are recommended for approval.

Public Assessment Report

Update

ACLEXA
Celecoxib

EE/H/0187/001-002/

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Variations/ Notifications

Procedure number	Scope /Type of Notification	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
EE/H/0187/001-002/IB/001/G	C.I.8a and A.2b	No	12.08.2014	Approved	N/A
EE/H/0187/001-002/IA/002	B.I.a.2a	No	10.11.2014	Approved	N/A
EE/H/0187/001-002/IA/003	B.III.1a2	No	02.03.2016	Approved	N/A
EE/H/0187/001-002/IB/004	B.II.d.2d	No	10.06.2016	Approved	N/A
EE/H/0187/001-002/IB/005	B.I.d.1a4	No	13.05.2016	Approved	N/A
EE/H/0187/001-002/P/001	Notification Art. 61(3) in order to updated new QRD Template 4.	Yes	12.01.2018	Approved	N/A
EE/H/0187/001-002/IB/006	B.III.1a3	No	26.02.2018	Approved	N/A
EE/H/0187/001-002/IB/007	B.II.b.3z	No	09.03.2018	Approved	N/A
EE/H/0187/001-002/IA/008	A.7	No	26.07.2018	Approved	N/A
EE/H/0187/001-002/IB/009	C.I.2a	Yes	31.08.2018	Approved	N/A

Other procedural steps

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
EE/H/0187/001-002/E/001	Repeat Use Procedure, CMS: MT	No	29.04.2014	Accepted, with remaining FUM (the same as for initial DCP, outlined in section V above)	N/A

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
N/A	Submission of FUM (as per initial DCP and RUP) in December 2014 and January 2018	No	30.01.2018	FUM resolved	N/A
EE/H/0187/001-002/R/001	Shortened Renewal Procedure	No	24.05.2018	Approved	N/A