LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Flukloxacillin Meda, 1 g, film-coated tablet (flucloxacillin)

Asp no: 2016-1463

This module reflects the scientific discussion for the approval of Flukloxacillin Meda. The procedure was finalised on 2016-10-27. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Flukloxacillin Meda, 1 g, film-coated tablet, is a line extension application (addition of new strength) made according to Article 8(3), Known active substance of Directive 2001/83/EC. The active substance flucloxacillin is the same as in Flukloxacillin Meda, 500 mg and 750 mg, film-coated tablet, marketed by Meda AB since 2005. No Public Assessment Report is available for Flukloxacillin Meda, 500 mg and 750 mg, film-coated tablet.

The applicant, Meda AB applies for a marketing authorisation in Sweden through a National Procedure.

The new strength is intended as an alternative to using multiple tablets of the already approved strengths.

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

Pharmacodynamic, pharmacokinetic and toxicological properties of flucloxacillin are well known. As flucloxacillin is a widely used, well-known active substance, no further data are required and the applicant provides none. The dosage of Flukoxacillin Meda 1 g film-coated tablets is not increased. Overview of the pharmacodynamic, pharmacokinetic and toxicological properties is thus considered sufficient.

III.1 Ecotoxicity/environmental risk assessment

Since Flukloxacillin Meda 1 g film-coated tablets are intended to replace other products on the market, approval of this product will not lead to an increased exposure to the environment.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Flucloxacillin is well absorbed following oral administration. Administration with food decreases absorption, and the product should therefore preferrably be taken between meals. The half-life is 80-90 minutes and the plasma protein binding is 94-95%. Elimination occurs mainly via tubular secretion and glomerular filtration in the kidneys.

The applicant has not submitted a bioequivalence study for the new 1 gram strength and requests a biowaiver.

A study by Nauta & Matie (1975), investigating urinary excretion following oral administration of 0.5 and 2 mg flucloxacillin, showed dose proportional amount excreted in urine thus indicating dose-proportional absorption of flucloxacillin, provided that there is no non-linearity in renal clearance. Since linear pharmacokinetics following iv administration of flucloxacillin has been demonstrated (Landersdorfer et al. 2007), non-linear renal clearance can be ruled out. The bioequivalence study comparing Heracillin 500 and 750 mg tablets that demonstrates bioequivalence (after dose adjustment) is considered as supportive evidence of linearity, although the dose range is limited. Thus, available data support that the pharmacokinetics of flucloxacillin is linear in the therapeutic dose range.

From a pharmacokinetic perspective, absence of studies with the new 1 gram strength is acceptable.

IV.2 Pharmacodynamics/ Clinical efficacy/ Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Additional data is not necessary.

IV.3 Risk Management Plans

The MAH has submitted a risk management plan, 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 Flukloxacillin Meda.

Safety specification

Summary table of safety concerns as approved in RMP

Table. Summary of safety concerns.	
Summary of safety concerns	
Important identified risks	Liver damage probably increasing with increasing age and duration of treatment Hypersensitivity including anaphylactic reactions, urticaria and exanthema. Pseudomembranous colitis caused by Clostridium difficile may occur.
Important potential risks	Decreased efficacy of warfarin during treatment with flucloxacillin
Missing information	None

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 RMP is approved.

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 RMS;
- 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 Heracillin 1 g tablets (MTnr 44918) leaflet which was reported in a bridging study, assessed and accepted in the procedure with Dnr: 111:2010/57507. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Flukloxacillin Meda, 1 g, film-coated tablet is 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

Flukloxacillin Meda, 1 g, film-coated tablet was approved in the national procedure on 2016-10-27.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

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