Public Assessment Report

Scientific discussion

Pivmecillinamhydrochlorid "LEO"
400 mg film-coated tablets

(Pivmecillinam hydrochloride)

DK/H/2327/001/DC

18 September 2015

This module reflects the scientific discussion for the approval of Pivmecillinamhydrochlorid "LEO". The procedure was finalised on 10 September 2014. 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 Pivmecillinamhydrochlorid "LEO" 400 mg film-coated tablets from LEO Pharma A/S.

The product is indicated for adults in the treatment of acute uncomplicated cystitis caused by bacteria sensitive to mecillinam.
A comprehensive description of the indications and posology is given in the SmPC.

Pivmecillinamhydrochlorid "LEO" is an oral antibiotic containing pivmecillinam hydrochloride. Pivmecillinam hydrochloride is a pro-drug of the active drug mecillinam. The oral administered picmecillinam is well absorbed and subsequently hydrolysed to mecillinam. Pivmecillinam hydrochloride is a betalactam antibacterial agent that is indicated in the treatment of mecillinam sensitive organisms including urinary tract infections and salmonellosis caused by bacteria sensitive to mecillinam.

This decentralised application concerns a generic version of pivmecillinam hydrochloride. The present application is a so-called "auto-generic" - a generic application submitted by the originator company.

The originator product is Selexid 400 mg film-coated tablets by LEO Pharma A/S, registered since 3 December 2010. The first product in this global marketing authorisation is, however, Selexid 200 mg capsules which has been registered since16 November 1976. Selexid 200 mg film-coated tablets has been registered since 26 September 1977.

The marketing authorisation is granted based on article 10.1 of Directive 2001/83/EC.

In the Concerned Member States in this decentralised procedure, there is no current registration for pivmecillinam hydrochloride film-coated tablets and consequently a European reference product (ERP) is applicable for the present application: Selexid 400 mg film-coated tablets, approved in the Reference Member State.
Selexid 400 mg film-coated tablets was registered in Denmark in December 2010 as a line extension to Selexid 200 mg film-coated tablets approved in Denmark in September 1977. Hence, the European reference medicinal product chosen for this application belongs to the global marketing authorisation for Selexid and is a valid reference product concerning the data protection period.

II. QUALITY ASPECTS

II.1 Introduction

Each film-coated tablet contains 400 mg pivmecillinam hydrochloride.
The product is a white capsule-shaped, film-coated tablet, size 8 x 17 mm.

The excipients in the tablet core are: Cellulose, microcrystalline; Hydroxypropylcellulose and Magnesium stearate. The film-coating consists of Hypromellose 6 cps; Simethicone emulsion 30% and Paraffin, synthetic.

The tablets are packed in Aluminium/PVC-aluminium blisters in pack sizes of 10, 15, or 20 tablets. However, not all pack sizes may be marketed.

The RMS 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.

II.2 Drug Substance

The active substance, pivmecillinam hydrochloride, is described in the European Pharmacopoeia. It is a white or almost white, crystalline powder. It is freely soluble in water, in anhydrous ethanol and in methanol and slightly soluble in acetone. According to the monograph for pivmecillinam hydrochloride the active substance should be protected from light, at a temperature of 2 ºC to º8 C.

The manufacturer of the active substance has obtained a Certificate of Suitability, a copy of which is presented in the documentation.

The drug substance specification for the drug product manufacturer is presented and includes additional requirements reported in the CEP. Batch analysis data are provided which demonstrate the conformity with the Ph. Eur. monograph.

Based on the stability data presented, an appropriate re-test period has been set.

II.3 Medicinal Product

The finished product is pivmecillinam hydrochloride 400 mg capsule shaped film-coated tablets (size 8x17 mm) to be marked in a single-dose tamper evident aluminium-aluminium blister packaging.

It contains the excipients cellulose microcrystalline, hydroxypropylcellulose and magnesium stearate for the core and the film coating contains hypromellose, simethicone emulsion 30% and paraffin. All excipients comply with Ph.Eur. except for synthetic paraffin and simethicone emulsion 30%. Simethicone emulsion 30% complies with USP.

The analytical control methods are adequately described. Validation data provided are sufficient. Batch analysis data are given showing compliance with set specifications.

Stability results for long-term conditions over 36 months, for intermediate conditions over 12 months and for accelerated conditions over 6 months are provided. A shelf life of 36 months with no special storage conditions is accepted.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of pivmecillinam hydrochloride are well known. As pivmecillinam hydrochloride is a widely used and well-known, the applicant has not provided additional studies and none are required. An overview based on a literature review is therefore appropriate.

The non-clinical overview report refers 60 publications up to year 2011. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

The MAH has discussed the genotoxic potential of pivmecillinam and the metabolites mecillinam, pivalic acid and formaldehyde. The MAH has not performed any in vitro or in vivo studies on pivmecillinam or mecillinam (the active moiety), but purely performed assessment of the genotoxic potential based on literature and in silico analysis (DEREK Nexus). This approach is not in line with the current guidelines on genotoxic evaluation of pharmaceuticals intended for human use (ICH S2(R1)),

however, as the compound have been developed prior to the implementation of the present guidelines, and has been used for more than 35 years, the lack of these studies, and a more theoretical approach to the genotoxicity discussion has been accepted.

The metabolite formaldehyde is recognised as potentially genotoxic. However, as formaldehyde is both an endogenous substance from amino acid metabolism, as well as present in the diet and a metabolite of dietary compounds, a low level of formaldehyde from pivmecillinam could be acceptable. EFSA has established that the formaldehyde intake resulting from the acceptable daily intake of 40 mg/kg/day of aspartame (4.1 mg/kg/day) is considered acceptable. Therefore, the daily intake of up to 1200 mg/day of pivmecillinam, which will result in 2.52 mg/kg/day formaldehyde in a 30 kg child, is considered acceptable. The applicant sufficiently justified that the formaldehyde possibly excreted in the milk following ingestion of pivmecillinam, would not exceed the formaldehyde excreted due to endogenous formation of formaldehyde. The amount of formaldehyde exposure due to ingestion of pivmecillinam would be less than that following ingestion of aspartame according to the ADI for aspartame, and would be within the metabolic capacity of the body. Therefore, it was concluded that no risk to the breastfeeding child would be expected.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Pivmecillinamhydrochlorid “LEO” 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Pivmecillinam hydrochloride is a well-known active substance with established efficacy and tolerability.

As pivmecillinam hydrochloride is a widely used, well-known active substances, the MAH has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The clinical overview report refers several publications up to year 2012. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

The MAH has presented evidence to support the efficacy of pivmecllinam in acute uncomplicated cysititis caused by bacteria sentitive to mecillinam with the posology for adults of 400 mg x 3 for 3 days.

IV.2 Pharmacokinetics

Since the dossier is identical to the dossier approved for the reference product, it is considered acceptable that no bioequivalence study is performed.

IV.3 Risk Management Plan

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 Pivmecillinamhydrochlorid “LEO”.

Table 1. Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	• Carnitine depletion (pivmecillinam only) • Cross-hypersensitivity to penicillins and cephalosporins
Important potential risks	• Pseudomembranous colitis
Missing information	None

Table 2. Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Carnitine depletion (pivmecillinam only)	Inclusion of contraindication and warning in the SmPC (sections 4.3, 4.4 & 4.5) and PIL	Not applicable
Cross-hypersensitivity to penicillins and cephalosporins	Inclusion of contraindication in the SmPC (section 4.3)	Not applicable

V. 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 test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pivmecillinamhydrochlorid “LEO” 400 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Selexid. Selexid is a well-known medicinal product with an established favourable efficacy and safety profile.

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

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Pivmecillinamhydrochlorid “LEO” with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 10 September 2014. Pivmecillinamhydrochlorid “LEO” was authorised in Denmark on 30 September 2014.

According to the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs), no PSURs are required for this product.

The date for the first renewal will be: 10 September 2019.

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

Public Assessment Report

Update

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400 mg film-coated tablets

(Pivmecillinam hydrochloride)

DK/H/2327/001/E/001

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

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
Repeat use procedure with IE as CMS	DK/H/2327/001/E/001	No	18-07-2016	16-10-2016	Approval	Y (Annex 1)

ANNEX 1 – Repeat use procedure (DK/H/2327/001/E/001)

The repeat use procedure started on 10-07-2016. There was no discussion in the CMDh.
Agreement between member states was reached during a written procedure. The concerned member State IE, on the basis of the data submitted, considered that a marketing authorization could be granted.

The applicant has provided an updated dossier based on the response-documents submitted during the initial procedure.

The repeat use procedure was finalised on 16-10-2016.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

Common renewal date
The common renewal date is 10-09-2019 based on the approval date of the initial DC procedure.