LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Lorpeda - SE/H/1203/01-02/DC

(capecitabine)

This module reflects the scientific discussion for the approval of Lorpeda. The procedure was finalised 2012-07-11. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

PharOS Generics Ltd has applied for a marketing authorisation for Lorpeda film-coated tablets 150 and 500 mg. The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Xeloda 150 mg and 500 mg film-coated tablets, centrally authorised since 2001, with Roche Registration Ltd, UK, as marketing authorisation holder.
The product contains capecitabine as active substance. The reference product used in the bioequivalence study is Xeloda 500 mg film-coated tablets from the German market with Roche Registration Ltd, UK, as marketing authorisation holder.
For approved indications see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Lorpeda is presented in the form of film-coated tablets containing 150 mg and 500 mg of capecitabine. The excipients are croscarmellose sodium, hypromellose, microcrystalline cellulose, magnesium stearate, silica colloidal anhydrous, titanium dioxide, talc, red iron oxide and yellow iron oxide.The film-coated tablets are packed in aluminium-PVC/PVDC or aluminium-PVC/PE/PVDC-blisters.

II.2 Drug Substance

Capecitabine is not described in the Ph. Eur.

Capecitabine is a white to off-white crystalline powder which is freely soluble in methanol, soluble in acetonitrile and alcohol, sparingy soluble in water. The structure of capecitabine 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 and 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

Lorpeda film-coated tablets are formulated using excipients described in the current Ph Eur, except for red and yellow iron oxides which are controlled according to acceptable in house specifications in the USP/NF monographs. All raw materials used in the product are of vegetable origin.

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, when stored below 30 °C.

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

Bioequivalence was evaluated in a multicenter, open label, randomised, two-treatment, two-sequence (R-T-R-T and T-R-T-R), four-period, replicate single-dose crossover study conducted in 61 male and female patients with solid tumours, comparing Capecitabine, 500 mg, film-coated tablets (manufactured by Remedica Ltd) with Xeloda 500 mg film-coated tablets (both given as a dose of 2000 mg) under fed conditions. Administration took place immediately after a standard non-high fat meal. The study was conducted at six different sites in Poland (five regular cancer clinics and one private clinic specialised in BE studies) between 24th August 2010 and 28th April 2011. Blood samples were collected pre-dose and up to 8 hours post-dose. Since the study was a part of the patients' regular therapy the dosage schedule was adjusted to fit into the regular scheme, with test or reference given in the mornings of day 1 and 2 of two normal treatment cycles (in the evenings the calculated therapeutic dose of commercially available capecitabine was given). The study design is considered acceptable.

Plasma concentrations of capecitabine and the metabolite 5'-DFCR were determined with a 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%. Bioequivalence has been shown.

From a pharmacokinetic point of view, absence of studies with the additional strength 150 mg is acceptable, since data indicate that the pharmacokinetics of capecitabine is dose-proportional in the dose range 500 to 3500 mg/m^2/day. In addition, since the lower strength 150 mg is not used alone but in combination with the higher strength in order to attain the desired dose level, a biowaiver for the lower strength 150 mg is considered justified from a clinical perspective.

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 results of the conducted bioequivalence study can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

The risk/benefit ratio is considered positive and the application for Lorpeda film-coated tablets 150 and 500 mg is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Lorpeda film-coated tablets 150 and 500 mg was successfully finalised 2012-07-11.

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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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