LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Capecitabine PharOS Generics (capecitabine)

SE/H/1362/01/DC

This module reflects the scientific discussion for the approval of Capecitabine PharOS Generics. The procedure was finalised at 2014-04-23. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Capecitabine PharOS Generics, 150 mg, Film coated tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, PharOS Generics Ltd, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE, UK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Xeloda, 150 mg, film coated tablets authorised in EU since 2001, with Roche Registration Ltd as marketing authorisation holder.

The reference product used in the bioequivalence study is Xeloda, 500 mg, film coated tablets from DE with Roche Registration Ltd as marketing authorisation holder. The active substance is not considered a new active substance.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Capecitabine PharOS Generics is presented in the form of tablets containing 150 mg of capecitabine. The excipients are croscarmellose sodium, hypromellose, microcrystalline cellulose, magnesium stearate, silica colloidal anhydrous, titanium dioxide, talc, macrogol 400, 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

Capecitabine PharOS Generics is formulated using excipients described in the current Ph Eur, except for red and yellow iron oxides which are controlled according to acceptable in house

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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%, although the confidence interval for C_{max} is on the limit of acceptance (90% CI 80.00-98.94).

From a pharmacokinetic point of view, absence of studies with the additional strength 150 mg

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is acceptable, since data indicate that the pharmacokinetics of capecitabine is dose-proportional in the dose range 500 to 3500 mg/m^2/day.

Bioequivalence can be concluded and the pharmacokinetic documentation is considered sufficient.

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
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 Xeloda EMEA/H/C/316 (for content) and Capecitalox SE/H/1217/01-02/DC (for layout). The bridging report submitted by the applicant has been found acceptable.

The results of the conducted bioequivalence study can be extrapolated to the 150 mg strength since the criteria for biowaiver for additional strengths are fulfilled according to the Guideline on the investigation of Bioequivalence.

The risk/benefit ratio is considered positive and Capecitabine PharOS Generics, 150 mg, Film coated tablets is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Capecitabine PharOS Generics, 150 mg, Film coated tablets was successfully finalised on 2014-04-23.

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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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