LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Capecitabine Orion (capecitabine)

SE/H/1212/01-02/DC

This module reflects the scientific discussion for the approval of Capecitabine Orion. The procedure was finalised at 2014-01-09. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Capecitabine Orion, 150 mg and 500 mg, film-coated tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orion Corporation, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and FI 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 and 500 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.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Capecitabine Orion is presented in the form of tablets containing 150 mg and 500 of capecitabine. The excipients are of pharmacopeia grade. The tablets will be packed in PVC/PVdC-aluminium blisters, Aluminium/Aluminium-blisters and HDPE containers.

II.2 Drug Substance

Capecitabine has a monograph in the Ph Eur.

Capecitabine is a white, to off white crystalline powder which is sparingly soluble in water. The structure of “drug substance” has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism, 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/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 Orion film coated tables is formulated using excipients described in the current Ph Eur, except for iron oxides which are controlled according to USP-NF. None of the materials, except lactose anhydrous, used in this formulation is of human or animal origin. There is no risk of transmissible spongiform encephalopathy (TSE) and bovine spongiform encephalopathy (BSE) associated with the active substance and excipients used in this formulation.

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as poor aqueous solubility, hygroscopic properties, polymorphism, stability.

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.

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 one single-dose, two-period, two-treatment crossover study conducted in 88 cancer patients, comparing Capecitabine, 500 mg, film-coated tablet with Xeloda, 500 mg, film-coated tablet, under fed conditions.
The study lasted through one treatment cycle of capecitabine (2 weeks of daily treatment followed by 1 week rest period); period-I was the first day of the first chemotherapy cycle of the study and Period-II was the first day of the next chemotherapy cycle of the study. Patients were on an overnight fast for at least 10 hours prior to serving of a standardized non high-fat breakfast prior to dosing in each period. At 30 minutes after serving of the breakfast, patients were administered a single oral dose of 1500 mg (3x500 mg) of either the test or reference product. Blood samples were collected pre-dose and up to 12 hours post-dose. The study design is considered acceptable. Plasma concentrations of capecitabine were determined with an adequately 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%.

Based on the submitted bioequivalence study, Capecitabine Orion, film-coated tablets is considered bioequivalent with Xeloda, film-coated tablets.

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 Venlafaxin Orion DE/H/1420/01-03/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 other strengths 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 Orion, film-coated tablet, 150 mg and 500 mg is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Capecitabine Orion, film-coated tablet, 150 mg and 500 mg, was successfully finalised on 2014-01-09.

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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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