

Public Assessment Report

Scientific discussion

Quetiapin Orion **(quetiapine fumarate)**

SE/H/1115/01-04/DC

This module reflects the scientific discussion for the approval of Quetiapin Orion. Please note that the marketing authorisation was first approved with the name “Quetiapin Nevada” and therefore this name is used throughout the document. The procedure was finalised on 14 March 2012. For information on changes after this date please refer to the module ‘Update’.

I. INTRODUCTION

Nevada Pharma AB has applied for a marketing authorisation for Quetiapine Nevada Pharma 25 mg, 100 mg, 200 mg and 300 mg film-coated tablets claiming essential similarity to Seroquel 25 mg, 100 mg, 200 mg and 300 mg film-coated tablets marketed in Sweden by AstraZeneca AB. The product contains quetiapine fumarate as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Seroquel 25 mg and 100 mg film-coated tablets marketed by AstraZeneca Oy in Finland.

II. QUALITY ASPECTS

II.1 Introduction

Quetiapine Nevada Pharma is presented in the form of film-coated tablets containing 25, 100, 200 and 300 mg of quetiapine as quetiapine fumarate. The excipients are of pharmacopeia grade. The tablets are packed in blister.

II.2 Drug Substance

The drug substance does not have a monograph in the Ph Eur.

The drug substance, quetiapine fumarate, is a white to off-white, crystalline powder. It is slightly soluble in water and non-hygroscopic.

The structure of quetiapine fumarate has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and solubility in different pH 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

Quetiapine Nevada Pharma 25 mg, 100 mg, 200 mg and 300 mg film-coated tablets is formulated using excipients described in the current Ph Eur, except for iron oxides which are controlled according to acceptable *USP*. No excipients of human or animal origin or any novel excipients have been used.

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as poor aqueous solubility, hygroscopic properties, polymorphism and 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, with no special storage precautions.

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

Study 3092007 with quetiapine 25 mg

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 30 healthy male and female volunteers, comparing quetiapine, 25 mg, tablet with Seroquel, 25 mg, tablet under fasting conditions. The study was conducted at Clinical Research Services Turku in Finland between 21 December 2005 and 17 February 2006. Blood samples were collected pre-dose and up to 12 hours post-dose. The study design is considered as satisfactory.

Plasma concentrations of quetiapine were determined with an 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, Quetiapine Nevada Pharma 25 mg tablet is considered bioequivalent with Seroquel 25 mg tablet.

Study 3092004 with quetiapine 100 mg

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 25 healthy male volunteers, comparing quetiapine, 100 mg, tablet with Seroquel, 100 mg, tablet under fasting conditions. The clinical phase of the study was divided into two parts (part I and part II). An interim analysis was performed after the first part. If all the 12 subjects randomised in part I had completed the study and if the sample size had been enough for the achievement of bioequivalence, part II had not been performed. However, with only 11 subjects completing the first part bioequivalence could not be shown. Therefore thirteen new subjects were randomised and twelve subjects completed the part II. 23 subjects completed both study periods and were included in the pharmacokinetic analysis.

The study was conducted at Clinical Research Services Turku in Finland between 30 August 2005 and 7 November 2005. Blood samples were collected pre-dose and up to 12 hours post-

dose. The study design is considered as satisfactory. Plasma concentrations of quetiapine were determined with an 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%. However, no steps were taken to assure the preservation of the overall type I error. In using a conservative adjustment of the coverage probability (e.g. 95% CI) a conclusion of bioequivalence can however still be drawn.

Based on the submitted bioequivalence study, Quetiapine Nevada Pharma 100 mg tablet is considered bioequivalent with Seroquel 100 mg tablet.

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 the product Quemyl, Generics UK, film-coated tablets, DK/H/1371/001-004/MR regarding the language and the content. A second bridging regarding the layout was carried out on the product Pantoprazol Nevada Pharma, enteric coated tablets reference number 111:2008/56127 and 111:2008/56128. The bridging report submitted by the applicant has been found acceptable.

The results of the conducted bioequivalence study with the 100 mg strength can be extrapolated to the 200 mg and 300 mg strength since the criteria for biowaiver for additional strengths are fulfilled according to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)

The risk/benefit ratio is considered positive and Quetiapine Nevada Pharma 25 mg, 100 mg, 200 mg and 300 mg film-coated tablet is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Quetiapine Nevada Pharma 25 mg, 100 mg, 200 mg and 300 mg film-coated tablets was successfully finalised on 14 March 2012.

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)