LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Hydroxyzine Orion
(hydroxyzine hydrochloride)

SE/H/1578/01-02/DC

This module reflects the scientific discussion for the approval of Hydroxyzine Orion. The procedure was finalised on 2016-09-28. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

The application for Hydroxyzine Orion, 10 mg and 25 mg, film-coated tablet, 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, NO, PL, FI (25 mg only) and IS (25 mg only) as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Atarax, 10 mg and 25 mg, film-coated tablet authorised in SE since 1957, with UCB Nordic A/S as marketing authorisation holder.
The reference product used in the bioequivalence study is Atarax, 10 mg and 25 mg, film-coated tablet from SE with UCB Nordic A/S as marketing authorisation holder.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug 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 confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

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 have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

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

To support the application, the applicant has submitted two bioequivalence studies. One bioequivalence study was performed with the 10 mg strength and one bioequivalence study was performed with the 25 mg strength, see below:

Pharmacokinetic study with the 10 mg strength
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 28 healthy male volunteers, comparing hydroxyzine hydrochloride, 10 mg, tablet with Atarax, 10 mg, tablet under fasting conditions.. Blood samples were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of hydroxyzine were determined with an adequately validated LC/MS/MS method. The use of an achiral analytical method is agreed. The bioequivalence study was planned as a study with two stage design where the study met the bioequivalence criteria in stage 1, thus stage 2 was not conducted.
For AUC_{0-t} and C_{max} both the 90 % and 94.12 % confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for hydroxyzine as well as for the main metabolite cetirizine. Bioequivalence data for cetirizine was only considered as supportive data.

Pharmacokinetic study with the 25 mg strength
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 28 healthy male volunteers, comparing hydroxyzine hydrochloride, 25 mg, tablet with Atarax, 25 mg, tablet under fasting conditions.. Blood samples were collected pre-dose and up to72 hours post-dose. The study design is considered acceptable. Plasma concentrations of hydroxyzine were determined with an adequately validated LC/MS/MS method. The use of an achiral analytical method is agreed. 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% for hydroxyzine as well as for the main metabolite cetirizine. Bioequivalence data for cetirizine was only considered as supportive data.

Based on the submitted bioequivalence studies, Hydroxyzine Orion is considered bioequivalent with Atarax.

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.

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 Hydroxizyne Orion.

Safety specification

Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	• Cardiac dysrhythmias/QT prolongation • Use in patients with moderate or severe renal impairment • Use in patients with hepatic impairment • Use in elderly • Use in patients with electrolyte imbalances • Porphyria • Anticholinergic effect • Convulsions • Interaction with alcohol • Administration during pregnancy or breastfeeding • Effects on allergy tests
Important potential risks	• Effects on ability to drive and use machines • Cerebrovascular events in patients with risk of stroke
Missing information	• Use in children under 5 years of age

Risk minimisation measures

Safety concerns origin from the proposed SmPC for Hydroxyzine Orion. Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The MAH has satisfactorily responded to the question raised and updated the RMP accordingly.

The RMP is acceptable.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. 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 Hydroxyzinhydrochlorid EQL Pharma, DK/H/2313/01/DC for content and Topiramat Orion, DE/H/1325/01-04/DC for layout. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Hydroxyzine Orion, is found adequate. There are no objections to approval of Hydroxyzine Orion, from a non-clinical and clinical point of view.

Bioequivalence between the test and reference product has been adequately demonstrated.

The product information is acceptable.

The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Hydroxyzine Orion, 10 mg and 25 mg, film-coated tablet was positively finalised on 2016-09-28.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se