LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Hydroxyzine Orifarm
(hydroxyzine hydrochloride)

SE/H/1450/01-02/DC

This module reflects the scientific discussion for the approval of Hydroxyzine Orifarm. The procedure was finalised on 2015-09-30. 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 Orifarm, 10 and 25 mg, film-coated tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orifarm Generics A/S applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, NO and FI (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 and 25 mg, film-coated tablets 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 and 25 mg, film-coated tablets from SE with UCB Nordic A/S as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

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 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.

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.

Based on the submitted bioequivalence studies, Hydroxyzine Orifarm 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 Hydroxyzine Orifarm.

The summary of safety concerns consists of:

Important identified risks
• Hypersensitivity reactions
• Cardiac dysrhythmias/QT prolongation
• Use in patients with moderate or severe renal impairment
• Use in patients with hepatic impairment
• Use in elderly
• Convulsions
• Anticholinergic effect
• Interaction with alcohol
• Use in patients with electrolyte imbalances
Important potential risks
• Cerebrovascular events in patients with risk of stroke
Missing information
• Use in children under 5 years of age

Routine risk minimisation measures are suggested and no additional risk minimisation measures are suggested by the applicant, which is agreed by the assessor.

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) regarding content and Diclofenac Orifarm (SE/H/1142/01/DC) regarding lay-out. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Hydroxyzine Orifarm, 10 and 25 mg, film-coated tablet is 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 Orifarm, 10 and 25 mg, film-coated tablet was positively finalised on 2015-09-30.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

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)

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