LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Hydroxizin Omet Pharma
(hydroxyzine hydrochloride)

This module reflects the scientific discussion for the approval of Hydroxizin Omet Pharma. The procedure was finalised on 2022-04-13. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Hydroxizin Omet Pharma, 10 mg, 25 mg, Film-coated tablet.

The active substance is hydroxyzine hydrochloride, hydroxyzine. A comprehensive description of the indication and posology is given in the SmPC.

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

The application for Hydroxizin Omet Pharma, 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, Omet Pharma AB applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is

- For 10 mg: Atarax, 10 mg, film-coated tablet authorised in Sweden since 1957, with UCB Nordic A/S as marketing authorisation holder.
- For 25 mg: Atarax, 25 mg, film-coated tablet authorised in Sweden since 1957, with UCB Nordic A/S as marketing authorisation holder.

The reference product used in the bioequivalence studies are Atarax, 10 mg, film-coated tablet from Sweden with UCB Nordic A/S as marketing authorisation holder and Atarax, 25 mg, film-coated tablet from Sweden with UCB Nordic A/S as marketing authorisation holder.

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of hydroxyzine hydrochloride are well known. As hydroxyzine hydrochloride is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Hydroxizin Omet Pharma is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Hydroxizin Omet Pharma from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the application, the applicant has submitted two single dose bioequivalence studies comparing Hydroxyzine with the reference product Atarax. One bioequivalence study was performed with the 10 mg strength (study 177-13) and one bioequivalence study was performed with the 25 mg strength (study 176-13).

Pharmacokinetic properties of the active substance
Absorption: Hydroxyzine has an oral bioavailability of approximately 80% compared to intramuscular administration. Following an oral dose of hydroxyzine maximal plasma concentrations occur at approximately 2 hours.

There are no restrictions with respect to food in the SmPC of the originator.

Elimination: The terminal half-life for hydroxyzine is approximately 14 hours (7-20 hours).

Study 177-13
Methods
This was a single-dose, two-way crossover study conducted in 28 healthy volunteers, comparing Hydroxyzine, 10 mg, film-coated tablet with Atarax, 10 mg, film-coated tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72.00 hours post-dose. Plasma concentrations of hydroxyzine and its metabolite cetirizine were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 4 October 2013 and 15 October 2013.

Only the results of hydroxyzine are discussed in the overview since data for the metabolite cetirizine is not pivotal.

The bioequivalence study was planned in two cohorts (two-stage design). The study met bioequivalence criteria in cohort 1 (stage 1). Hence cohort 2 (stage 2) was not conducted.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for hydroxyzine, n=28.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**192.8±54.18**	**11.65±3.502**	**2.39 (1.0-5.0)**
Reference	**198.0±56.45**	**12.02±4.418**	**2.38 (1.25-8.05)**
***Ratio (90% CI)**	**97.53 (93.74-101.48)**	**98.83 (90.80-107.56)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

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%.

Study 176-13
Methods
This was a single-dose, two-way crossover study conducted in 28 healthy volunteers, comparing Hydroxyzine, 25 mg, film-coated tablet with Atarax, 25 mg, film-coated tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72.00 hours post-dose. Plasma concentrations of hydroxyzine and its metabolite cetirizine were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 11 January 2014 and 24 January 2014.

Only the results of hydroxyzine are discussed in the overview since data for the metabolite cetirizine is not pivotal.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 2.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for hydroxyzine, n=28.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**604.9±197.7**	**41.09±17.43**	**2.0 (1.25-4.0)**
Reference	**617.7±200.3**	**42.50±14.24**	**2.0 (1.25-5.0)**
***Ratio (90% CI)**	**97.89 (92.13-104.0)**	**95.41 (85.39-106.59**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

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%.

Discussion and overall conclusion

The bioequivalence studies and their statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Study 177-13 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. The applicant has provided evidence that the applied two-stage design controls the risk for false positive conclusions resulting from the interim analysis.

Based on the submitted bioequivalence studies, Hydroxizin Omet Pharma is considered bioequivalent with Atarax.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Hydroxizin Omet Pharma.

Safety specification

The MAH has submitted the version 0.2 RMP dated 9th July 2021 and proposed the following summary safety concerns:

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 patients • Use in patients with electrolyte imbalances • Anticholinergic effect • Convulsions • Interaction with alcohol • Effects on allergy tests
Important potential risks	• Cerebrovascular events in patients with risk of stroke
Missing information	• None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version 0.2 dated 9th July 2021 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the MPA;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PlL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Hydroxizin Omet Pharma, is found adequate. There are no objections to approval of Hydroxizin Omet Pharma, 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 benefit/risk is considered positive, and the application is therefore recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

Hydroxizin Omet Pharma, 10 mg, 25 mg, Film-coated tablet was approved in the national procedure on 2022-04-13.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

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