LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Hydroxyzine Bluefish AB
(hydroxyzine, hydroxyzine hydrochloride)

SE/H/2305/01-02/DC

This module reflects the scientific discussion for the approval of Hydroxyzine Bluefish AB. The procedure was finalised on 2023-11-27. 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 Hydroxyzine Bluefish AB, 10 mg, 25 mg, Film-coated tablet.

The active substance is hydroxyzine, hydroxyzine hydrochloride. 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 Hydroxyzine Bluefish AB, 10 mg, 25 mg, Film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and Austria and Poland as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Atarax® 25 mg film coated tablets authorised in Spain since 1956, with UCB Pharma SA as marketing authorisation holder.

The reference product used in the bioequivalence study is Atarax® 25 mg film coated tablets from Spain with UCB Pharma SA as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS Austria for the application of Hydroxyzine Bluefish AB, 10 mg: Atarax 10 mg filmdragerade tabletter authorised in Sweden since 1957, with UCB Nordic A/S as marketing authorisation holder. The justification to use this product is based on RMS's own files.

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 Hydroxyzine Bluefish AB 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 Hydroxyzine Bluefish AB from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Hydroxyzine Bluefish AB with the reference product Atarax.

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 C12291
Methods
This was a single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Hydroxyzine, 25 mg, film-coated tablets with Atarax, 25 mg, film-coated tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of hydroxyzine 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 2013-08-29 and 2013-09-16.

Results

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

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for hydroxyzine, n=24.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**576.5±177.5**	**40.28±12.93**	**2.00 (1.0-3.50)**
Reference	**587.8±197.4**	**43.19±16.64**	**2.13 (0.67-6.0)**
***Ratio (90% CI)**	**98.6 (92.89-104.69)**	**95.6 (85.54-106.76)**	**-**
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%.

A biowaiver was sought for the additional strength of 10 mg.

Discussion and overall conclusion

The bioequivalence study and its 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.

The availability of literature stating linear/nonlinear pharmacokinetics over the therapeutic range is very limited. However, there are no obvious signs of a less than proportional increase in AUC with increasing dose, which would be the case where a study with the lower strength would be necessary. The biowaiver for the lower strength can be accepted from a pharmacokinetic perspective.

Absence of studies with the additional strength of 10 mg is acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled.

Based on the submitted bioequivalence study, Hydroxyzine Bluefish AB 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 Hydroxyzine Bluefish AB.

Part II Safety specification

The MAH has submitted the version 1.1 RMP dated 2023-07-19 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 imbalance. • Anticholinergic effect • Convulsions • Interaction with alcohol • Effects on allergy tests
Important potential risks	• Cerebrovascular events in patients with risk of stroke
Missing information	• None

The Summary of safety concerns is in line with the most recent RMP version for hydroxyzine and is considered acceptable.

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

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

Part VI Summary of the RMP
The summary of the RMP is endorsed.

Conclusion of RMP assessment
The submitted Risk Management Plan, version 1.1 signed 2023-07-19 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 RMS;
- 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

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Hydroxyzinhydrochlorid

EQL Pharma 25 mg, film-coated tablets, DK/H/2313/001/DC, regarding content and Venlafaxine 37.5mg, 75mg and 150mg Capsules (MAH: Bluefish Pharmaceuticals) regarding 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 Bluefish AB, is found adequate. There are no objections to approval of Hydroxyzine Bluefish AB, 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

The decentralised procedure for Hydroxyzine Bluefish AB, 10 mg, 25 mg, Film-coated tablet was positively finalised on 2023-11-27.

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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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