IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Hydroxyzine hydrochloride 25 mg film-coated tablets
Hydroxyzine hydrochloride
PA22749/025/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Hydroxyzine hydrochloride 25mg film-coated tablets, from Brillpharma (Ireland) Limited on 2nd December 2022.

They are licensed for the management of anxiety in adults. They are also indicated for the management of pruritus associated with acute and chronic urticarial, including cholinergic and physical types, and atopic and contact dermatitis in adults and children.

This application for a marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC. The reference product for this application was Atarax 25mg Film Coated Tablets, which has been licensed in accordance with Union provisions in force for not less than 6/10 years in the EEA. The date of authorisation was 24/07/1985, and it was licensed in the UK.

The product is subject to medical prescription and can only be supplied through pharmacies. Promotion of the product is to healthcare professionals only.

No scientific or procedural advice was requested by the applicant for this procedure.

The active substance had been the subject of an Article 31 referral on the risks of disturbances in heart rhythm (EMEA/H/A-31/1400)), which concluded in February 2015. The product information text for this product is in concordance with the agreed text from that procedure.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Hydroxyzine hydrochloride 25mg film-coated tablets
Name(s) of the active substance(s) (INN)	Hydroxyzine hydrochloride
Pharmacotherapeutic classification (ATC code)	N05BB01
Pharmaceutical form and strength(s)	25mg
Marketing Authorisation Number(s) in Ireland (PA)	PA22749/025/001
Marketing Authorisation Holder	Brillpharma (Ireland) Limited

II. QUALITY ASPECTS

II.1. Introduction

This application is for Hydroxyzine hydrochloride 25mg film-coated tablets.

II.2 Drug substance

The active substance is Hydroxyzine hydrochloride, an established active substance described in the European Pharmacopoeia; it is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of Good Manufacturing Practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to the relevant European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The finished product specification is based on the pharmacopoeial monograph for tablets and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical and Pharmaceutical Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Hydroxyzine hydrochloride 25mg film-coated tablets.

III. NON-CLINICAL ASPECTS

This active substance is a generic formulation of Atarax 25mg Film Coated Tablets on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.5 Ecotoxicity/environmental risk assessment

As this application is for a generic version of an established product, no additional use is anticipated but instead substitution of existing use. As such, no additional environmental risk is anticipated.

III.6 Discussion on the non-clinical aspects

The non-clinical aspects of this substance are well established and acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Hydroxyzine is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Atarax 25mg Film Coated Tablets.

For this generic application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the test product is compared with the pharmacokinetic profile of the reference product Atarax 25mg Film Coated Tablets.

A randomized, open label, balanced, two treatment, two period, two sequence, single dose, two way crossover, bioequivalence study in 28 healthy human adult male subjects, under fasting conditions was carried out to compare the bioavailability of Test product (A) [1 × Hydroxyzine Hydrochloride Tablets 10 mg of Ipca Laboratories Ltd. India] with Reference product (B) [1 × ATARAX (Hydroxyzine Hydrochloride) 10 mg Film Coated Tablets of UCB Pharma Limited].

Based on the pharmacokinetic parameters of active substance are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The 10mg strength dose proportional with the 25mg strength. The pharmacokinetics of the active substance are linear in the therapeutic range. The results of the bioequivalence study performed with the 10mg form therefore apply to the other strengths.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product and are in concordance with that agreed during the previously mentioned referral procedure.

IV.2 Pharmacokinetics

Absorption

Hydroxyzine is rapidly absorbed from the gastrointestinal tract.
After a single oral dose of hydroxyzine, 0.7 mg/kg (mean dose 39.0 +/- 5.4 mg) a mean maximum serum hydroxyzine concentration of 72.5 +/- 11.1 ng/ml has been shown to occur at a mean time of 2.1 +/- 0.4 hours.

Distribution

Distribution of hydroxyzine into human body tissues and fluids has not been fully characterised. Following administration of hydroxyzine to animals, the drug is widely distributed into most body tissues and fluids with highest concentrations in the liver, lungs, spleen, kidneys, and adipose tissue. The drug is also distributed into bile in animals.

Hydroxyzine crosses the placental barrier which may lead to higher foetal than maternal concentrations.

Serum hydroxyzine concentrations do not necessarily reflect hydroxyzine tissue binding or distribution to skin receptor sites. Suppression of wheals, flares, and associated pruritis has been shown to persist even when serum hydroxyzine concentrations are low.

First-generation H1 antagonists easily cross the blood-brain barrier.
In a study group of healthy adults, the mean apparent volume of distribution has been found to be 16.0 +/- 3.0 L/kg.

Biotransformation

Hydroxyzine is metabolised in the liver. Metabolites include cetirizine, which has antihistaminic activity. Cetirizine is formed from hydroxyzine via an oxidative biotransformation step.

Elimination

An elimination half-life of 20.0 +/- 4.1 hours and of 14.0 hours has been reported for hydroxyzine.

Total body clearance in adults is generally in the range of 5 to 12 ml/min/kg.
Hydroxyzine is eliminated by hepatic metabolism in humans. Cetirizine is mainly renally excreted.

Special populations

Elderly patients

The pharmacokinetics of hydroxyzine were studied in nine healthy elderly (mean age 69.5 +/- 3.7 years) subjects who ingested a single dose of hydroxyzine, 0.7 mg/kg (mean dose 49.0 +/- 6.7 mg). The mean serum elimination half life value of hydroxyzine in this elderly group was 29.3 +/-10.1 hours (range 20.2 to 53.3 hours), which was significantly longer than that reported in younger subjects. The mean apparent volume of distribution of hydroxyzine in this elderly group was 22.5 +/- 6.3 L/kg (range 13.4 to 30.7L/kg), which was significantly larger than that reported to be found in young adults. Hydroxyzine has a

long mean serum elimination half-life value, a large volume of distribution and a prolonged pharmacodynamics effect (suppressive effect on wheal and flare response to histamine) in the elderly.

In the elderly a number of age-related biological and physiological changes may have an effect on the pharmacology of hydroxyzine and its metabolite, cetirizine. These changes may impact upon the pharmacologic functions of absorption, distribution, metabolism, excretion, and receptor sensitivity.
Dosage reduction may be appropriate in elderly patients.

Paediatric patients
The pharmacokinetics and antipruritic effects of hydroxyzine hydrochloride was studied in 12 children aged 1 to 14 years (mean age 6.1 +/- 4.6 years) with severe atopic dermatitis. The children were given a single orally administered dose of 0.7 mg/kg hydroxyzine. The mean peak serum concentration of 47.4 +/- 17.3 ng/ml occurred at a mean time of 2.0 +/- 0.9 hours. Terminal elimination half life was shorter in children than in adults, at a mean of 7.1+/- 2.3 hours. This resulted from a larger clearance rate in children of 32.08 +/- 11.05 ml/min/kg. The elimination half-life values increased with increasing age. Half-life values were approximately 4 hours in the 1 year old patients and 11 hours in the 14 year old patient.
Dosage should be adjusted in the paediatric population.

Hepatic impairment
The pharmacokinetics and pharmacodynamics of hydroxyzine were studied in eight patients (mean age 53.4 +/- SD11.2 years) with primary biliary cirrhosis, given a single dose of 0.7 mg/kg (mean dose 43.9 +/- 6.6mg) hydroxyzine. All patients had abnormal liver biochemistry tests, all had biopsies compatible with primary biliary cirrhosis, and seven of eight had positive tests for antimitochondrial antibodies.
Hydroxyzine elimination was found to be impaired in patients with primary biliary cirrhosis. Mean peak hydroxyzine levels occurring at 2.3 +/- 0.7 hours were found to be 116.5 +/- 60.6 ng/ml, which was significantly higher than in other patient groups studied previously. Mean serum elimination half-life of hydroxyzine was 36.6 +/- 13.1 hours, which was significantly longer than in patients with normal hepatic function studied previously.

Dosage should be adjusted in patients with hepatic impairment.

Renal impairment
The pharmacokinetics of hydroxyzine and of its active metabolite cetirizine were studied in patients with reduced kidney function. Eight healthy volunteers and eight patients with renal insufficiency received a single peroral dose of 50 mg hydroxyzine.
With regards to hydroxyzine, results showed moderate elevation of the average terminal half-life in the patients group (t1/2 14 vs. 23 h). The areas under the concentration-time curves (AUC) were 996 ng·h·ml-1 in the healthy volunteers group and 1621 ng·h·ml-1 in the patients group. For cetirizine, AUC measured 6036 ng·h·ml-1 in the healthy volunteers group and 31635 ng·h·ml-1 in the patients group. The study concluded that the reduced renal clearance of cetirizine may be of clinical importance in patients with renal failure.

Dosage should be adjusted in patients with renal impairment.

IV.3 Pharmacodynamics
Mechanism of action
Hydroxyzine is a first generation antihistamine, a piperazine derivative, with antimuscarinic and sedative properties.
Antihistamines act as competitive antagonists of histamine at H1 histamine receptors, thus inhibiting H1 receptor-mediated reactions, such as vasodilation, flare and itch reactions and sneezing.
First-generation H1 antagonists easily cross the blood-brain barrier, consequently producing well-documented sedative and anticholinergic effects.
First-generation antihistamines also have affinity for 5-HT receptors, alpha-adrenoreceptors, and muscarinic receptors. They also reduce cyclic GMP concentrations, increase atrioventricular nodal conduction, and inhibit activation of airway vagal afferent nerves.

Pharmacodynamic effects
Hydroxyzine has CNS depressant, anticholinergic, antispasmodic, and local anaesthetic activity, in addition to antihistaminic effects. The drug also has sedative, antiemetic and primary skeletal muscle relaxant activity.
An onset of sedative action of hydroxyzine is usually noted within 15 to 30 minutes after oral administration. Sedative effects persist for 4-6 hours following administration of a single dose.

Hydroxyzine suppresses the inflammatory response (wheal and flare reaction) and pruritus for up to 4 days after intradermal skin tests with allergens and histamine.
The therapeutic range for plasma hydroxyzine concentrations and the relationship of plasma concentration to clinical response or toxicity have not been established.
Hydroxyzine does not appear to increase gastric secretions or acidity, and usually has mild antisecretory effects.

It induces a calming effect in anxious tense adults. It is not a cortical depressant, but its action may be due to a suppression of activity in certain key regions of the subcortical area of the central nervous system.

Paediatric population
The pharmacokinetics and antipruritic effects of hydroxyzine were studied in 12 children (mean age 6.1 +/- 4.6 years) with severe atopic dermatitis, each given a single 0.7 mg/kg oral dose. Pruritis was significantly suppressed from 1 to 24 hours after the administration of the dose, with greater than 85% suppression from 2 to 12 hours. The potent antipruritic effect persists even when serum concentrations of the drug are low (only 10% of the maximum levels achieved). In children, the biologic effects of hydroxyzine appear to be much more prolonged than would be predicted from the half-life values.

Pharmacovigilance System
The marketing authorisation holder (MAH) submitted a summary of the Pharmacovigilance System, including confirmation of the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

Risk Management Plan (version 2.0 Date: 14 June 2016)
Summary of safety concerns:

Important identified risks

- Cardiac dysrhythmias/ QT prolongation
- Convulsions
- Anticholinergic effect
- Interaction with alcohol
- Use in patients with moderate or severe renal impairment
- Use in patients with hepatic impairment
- Use in the elderly
- Use in children
- Use in patients with electrolyte imbalances
- Hypersensitivity

Important potential risks:

- Cerebrovascular events in patient with risk of stroke

Missing information:

- None

Assessor comment:
Routine pharmacovigilance measures and routine risk minimisation activities are considered acceptable.

The schedule for Periodic Safety Update Reports (PSUR) submission should be addressed.

IV.6 Discussion on the clinical aspects
Overall and through the information provided, the applicant has adequately demonstrated the equivalence of the product in terms of efficacy and safety with that of the reference.

V. OVERALL CONCLUSIONS

Hydroxyzine hydrochloride 25mg film-coated tablets, from Brillpharma (Ireland) Limited is a generic form of Atarax 25mg film-coated tablets. Atarax is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Hydroxyzine hydrochloride 25mg film-coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
New National	N/A	SmPC Section 1 to 9	2nd December 2022	1st December 2027