



Public Assessment Report

National Procedure

**Hydroxyzine Hydrochloride 10 mg film-coated
tablets**

**Hydroxyzine Hydrochloride 25 mg film-coated
tablets**

Hydroxyzine hydrochloride

PL 28278/0031 - 0032

Ipca Laboratories UK Limited

LAY SUMMARY

Hydroxyzine hydrochloride 10 mg film-coated tablets **Hydroxyzine hydrochloride 25 mg film-coated tablets** **Hydroxyzine hydrochloride**

This is a summary of the Public Assessment Report (PAR) for Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about using Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets and what are they used for?

These applications are for generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised in the European Union (EU) called Atarax 10 mg and 25 mg Tablets.

Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets are used in adults and children to reduce itching caused by urticaria (nettle rash) and dermatitis (eczema).

They are also used to treat anxiety in adults.

How do Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets work?

These medicines contain the active ingredient hydroxyzine hydrochloride, which belongs to a group of medicines called antihistamines (used to treat allergic reactions). They work by blocking the effects of a substance called histamine in the body.

How are Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets used?

The pharmaceutical form of these medicines is a film-coated tablet and the route of administration is oral (by mouth).

For treating itching in adults

The starting dose is 25 mg at night. A doctor may increase the dose up to 25 mg three or four times daily.

For treating itching in children

In children up to 40 kg in weight, the maximum daily dose is 2 mg/kg/day.

Children aged 6 months to 6 years

The dose is 5 mg to 15 mg daily taken throughout the day. A doctor may change this depending on the child's weight.

Children over 6 years

The dose is 15 mg to 25 mg daily which a doctor may increase up to 50 mg – 100 mg daily, taken throughout the day. The doctor may change this depending on the child's weight.

For treating anxiety in adults

The dose is 50 mg to 100 mg daily, taken throughout the day.

For patients with liver disease

A doctor will reduce the dose by about one third if the patient has liver disease. Hydroxyzine hydrochloride is not suitable for patients with severe liver disease or liver failure.

For patients with kidney disease

A doctor will reduce the dose by about half if the patient has kidney disease.

For elderly patients

In the elderly, the maximum daily dose is 50 mg per day.

For further information on how Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets have been shown in studies?

Because Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicines. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets?

For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicines. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of these medicines.

Because Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets are generic medicines and are bioequivalent to the reference medicines, its benefits and possible side effects are considered to be the same as the reference medicines.

Why were Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets approved?

It was concluded that Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets have been shown to be comparable to and to be bioequivalent to the reference medicines. Therefore, the MHRA decided that, as for the reference medicines, the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets?

A Risk Management Plan (RMP) has been developed to ensure that Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets

Marketing Authorisations for Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets were granted in the United Kingdom (UK) on 16 November 2021.

The full PAR for Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets follows this summary.

This summary was last updated in December 2021.

TABLE OF CONTENTS

I	INTRODUCTION	6
II	QUALITY ASPECTS	7
III	NON-CLINICAL ASPECTS	8
IV	CLINICAL ASPECTS	9
V	USER CONSULTATION.....	11
VI	OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION	12
	TABLE OF CONTENT OF THE PAR UPDATE	12

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Hydroxyzine hydrochloride 10 mg and 25 mg film-coated tablets (PL 28278/0031 - 0032) could be approved.

The products are approved for the following indications:

- To assist in the management of anxiety in adults.
- For the management of pruritus associated with acute and chronic urticaria, including cholinergic and physical types, and atopic and contact dermatitis in adults and children.

Hydroxyzine hydrochloride 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.

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Atarax 10 mg and 25 mg tablets, that have been licensed within the EU for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products.

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the application is for generic medicinal products of suitable reference products. The bioequivalence studies were conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

National marketing authorisations were granted in the United Kingdom (UK) on 16 November 2021.

II QUALITY ASPECTS

II.1 Introduction

These products consist of film-coated tablets containing 10 mg or 25 mg hydroxyzine hydrochloride.

In addition to hydroxyzine hydrochloride, these products also contain the following excipients:

Core

Lactose monohydrate, calcium phosphate, pregelatinized starch, sodium lauryl sulphate, colloidal anhydrous silica, magnesium stearate.

Coating

Opadry white Y-1-7000

The finished products are packaged in PVDC coated/PVC/aluminium blister packs in a pack size of 14, 25, 28, 56, 84 and 100 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

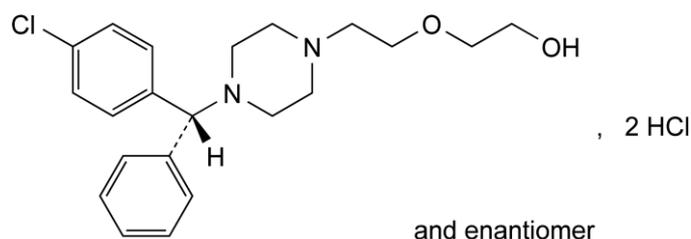
II.2 ACTIVE SUBSTANCE

rINN: Hydroxyzine hydrochloride

Chemical Name: (RS)-2-[2-[4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]ethanol dihydrochloride

Molecular Formula: C₂₁H₂₉Cl₃N₂O₂

Chemical Structure:



Molecular Weight: 447.8

Appearance: White or almost white, hygroscopic, crystalline powder

Solubility: Freely soluble in water and in ethanol (96 per cent), very slightly soluble in acetone.

Hydroxyzine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with no special storage conditions, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of hydroxyzine hydrochloride are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology

No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology

No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects

The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of hydroxyzine hydrochloride are well-known. With the exception of data from two bioequivalence studies, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of these studies is, thus, satisfactory.

IV.2 Pharmacokinetics

In support of the application, the applicant submitted the following bioequivalence studies.

Bioequivalence Study 1 - 10 mg strength

This study was a randomized, open-label, balanced, two-treatment, two-period, two-sequence, single dose, two-way crossover bioequivalence study comparing the test product Hydroxyzine hydrochloride 10 mg film-coated tablets, versus the reference product, Atarax 10 mg Tablets in healthy human adult male and/or female subjects under fasting conditions.

Subjects were administered test or reference product with 150 ml of water, after an overnight fast of at least 8 hours. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 7 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Pharmacokinetic parameters (non-transformed values)

Pharmacokinetic parameter	Arithmetic Means(\pm SD)	
	Test product	Reference Product
Hydroxyzine		
AUC(0-t)	192.840 (54.1840)	198.013 (56.4518)
AUC(0- ∞)	226.705 (84.6884)	226.638 (79.0786)
C _{max}	11.646 (3.5015)	12.016 (4.4184)
T _{max} ¹	2.385 (1.000, 5.000)	2.375 (1.250, 8.050)
Cetirizine		
AUC(0-t)	1663.875 (405.0355)	1694.073 (393.7525)
AUC(0- ∞)	1855.308 (417.7496)	1905.574 (458.6937)
C _{max}	56.699 (12.0677)	59.177 (13.0964)
T _{max} ¹	3.000 (1.250, 8.000)	4.000 (1.500, 4.100)

¹Median (Min, Max)

Bioequivalence evaluation

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV% ¹
Hydroxyzine			
AUC ² (0-t)	97.53	(93.74,101.48)	8.719
Cmax	98.83	(90.80,107.56)	18.741
Cetirizine			
AUC ² (0-t)	97.84	(95.10,100.66)	6.105
Cmax	96.13	(93.42, 98.92)	6.159

¹ Estimated from the Residual Mean Squares.

² In some cases AUC₍₀₋₇₂₎

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

Bioequivalence Study 2 - 25 mg strength

This study was a randomized, open-label, balanced, two-treatment, two-period, two-sequence, single dose, two-way crossover bioequivalence study comparing the test product Hydroxyzine hydrochloride 25 mg film-coated tablets, versus the reference product, Atarax 25 mg Film-coated Tablets in healthy human adult male and/or female subjects under fasting conditions.

Subjects were administered test or reference product with 150 ml of water, after an overnight fast of at least 8 hours. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 9 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Pharmacokinetic parameters (non-transformed values)

Pharmacokinetic parameter	Arithmetic Means(±SD)	
	Test product	Reference Product
Hydroxyzine		
AUC(0-t)	604.926 (197.6942)	617.717 (200.3134)
AUC(0-∞)	689.664 (237.4467)	699.099 (260.5142)
Cmax	41.093 (17.4273)	42.502 (14.2399)
Tmax ¹	2.000 (1.250, 4.000)	2.000 (1.250, 5.000)
Cetirizine		
AUC(0-t) ¹	4317.492 (1383.5501)	4359.066 (1169.8254)
AUC(0-∞) ²	5035.788 (1371.8625)	4927.383 (1464.0222)
Cmax	154.756 (48.1549)	153.148 (46.5853)
Tmax ³	4.000 (1.250, 12.000)	4.000 (1.500, 12.000)

¹ Median (Min, Max)

Bioequivalence evaluation

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV% ¹
Hydroxyzine			
AUC ^{0-t}	97.89	(92.13, 104.00)	13.349
C _{max}	95.41	(85.39, 106.59)	24.690
Cetirizine			
AUC ^{0-t}	97.44	(92.61, 102.52)	11.184
C _{max}	100.75	(98.27, 103.29)	5.467

¹ Estimated from the Residual Mean Squares.

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence studies, no new safety data were submitted with these applications.

The safety data from the bioequivalence studies showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL 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.

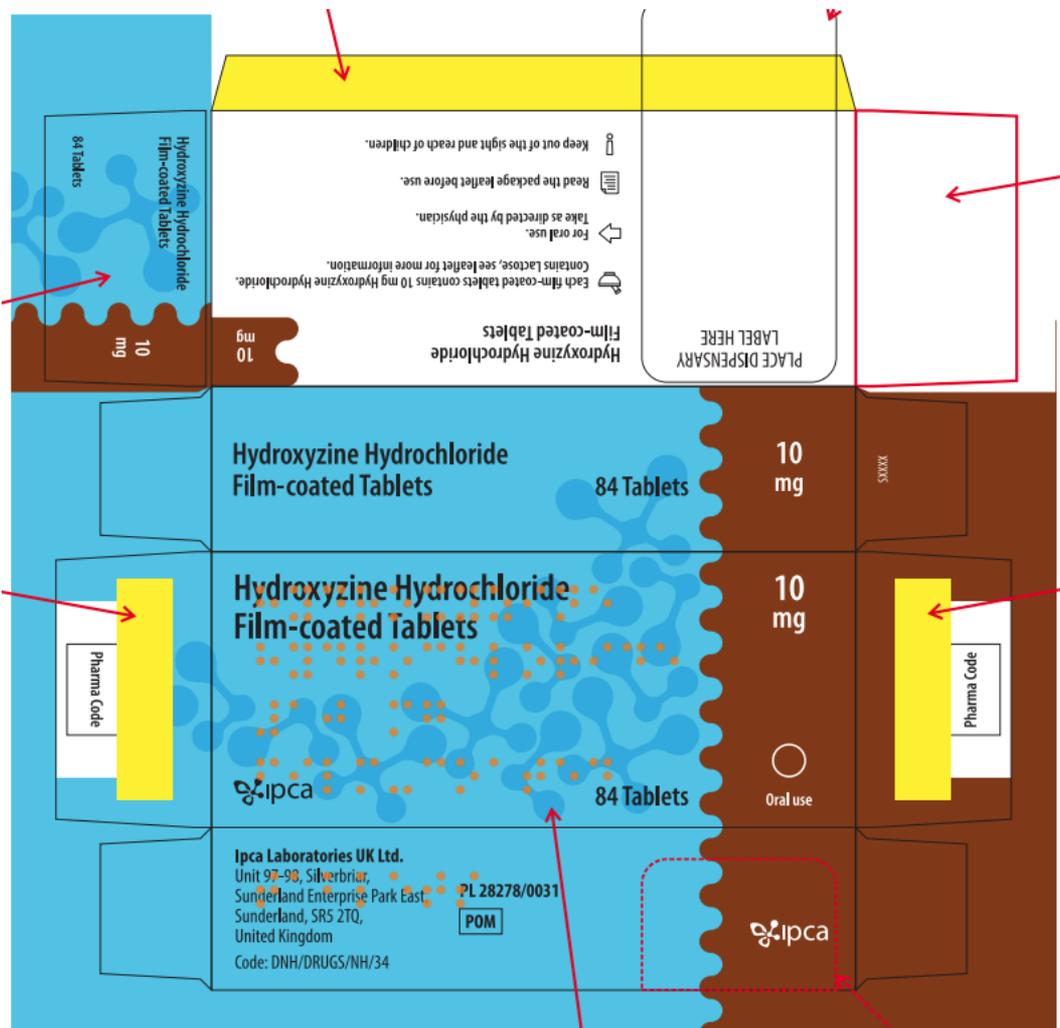
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with hydroxyzine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.



<p>Hydroxyzine Hydrochloride 25mg Film-coated Tablets Ipca Laboratories UK Ltd. Code: DNH/DRUGS/NH/34</p>	<p>Hydroxyzine Hydrochloride 25mg Film-coated Tablets Ipca Laboratories UK Ltd. Code: DNH/DRUGS/NH/34</p>	<p>Hydroxyzine Hydrochloride 25mg Film-coated Tablets Ipca Laboratories UK Ltd. Code: DNH/DRUGS/NH/34</p>	<p>↓Esp ↓BN XXXX</p>
<p>Hydroxyzine Hydrochloride 25mg Film-coated Tablets Ipca Laboratories UK Ltd. Code: DNH/DRUGS/NH/34</p>	<p>Hydroxyzine Hydrochloride 25mg Film-coated Tablets Ipca Laboratories UK Ltd. Code: DNH/DRUGS/NH/34</p>	<p>Hydroxyzine Hydrochloride 25mg Film-coated Tablets Ipca Laboratories UK Ltd. Code: DNH/DRUGS/NH/34</p>	
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Hydroxyzine Hydrochloride Film-coated Tablets

25 mg

Keep out of the sight and reach of children. The medicinal product does not require any special storage condition.

Code: DNH/DRUGS/NH/34

PL 28278/0032

POM

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TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N