Public Assessment Report

UK PAR

Hydroxyzine hydrochloride 25 mg film-coated tablets

(Hydroxyzine hydrochloride)

UK Licence No: PL 21880/0192

Medreich PLC
LAY SUMMARY

Hydroxyzine hydrochloride 25 mg film-coated tablets

(Hydroxyzine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Hydroxyzine hydrochloride 25 mg film-coated tablets (PL 21880/0192). It explains how the application for Hydroxyzine hydrochloride 25 mg film-coated tablets was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Hydroxyzine hydrochloride 25 mg film coated tablets.

For practical information about using Hydroxyzine hydrochloride 25 mg film-coated tablets, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Hydroxyzine hydrochloride tablets’ in this Lay summary.

What are Hydroxyzine hydrochloride tablets and what are they used for?

Hydroxyzine hydrochloride tablets are a generic medicine. This means that Hydroxyzine hydrochloride tablets are similar to a ‘reference medicine’ already authorised in the EU called Atarax 25 mg film-coated tablets (UCB Pharma S.A, France). The corresponding reference medicine in the UK is Ucerax 25 mg film-coated tablets (UCB Pharma Limited, UK).

Hydroxyzine hydrochloride tablets are used to treat:
- anxiety in adults
- itching (pruritus) caused by allergic reactions in adults and children over 6 years of age.

How do Hydroxyzine hydrochloride tablets work?

Hydroxyzine hydrochloride tablets contain the active ingredient, hydroxyzine hydrochloride, which belongs to a group of medicines called sedating antihistamines. Hydroxyzine hydrochloride is thought to work by inhibit some activity in the brain.

How are Hydroxyzine hydrochloride tablets used?

Hydroxyzine hydrochloride film-coated tablets are taken by mouth.

The patient should always take Hydroxyzine hydrochloride tablets exactly as his/her doctor has advised. The patient should check with his/her doctor or pharmacist if unsure.

The patient’s doctor will choose the dose that is right for the patient.

Other presentations of hydroxyzine are available for doses that cannot be achieved with this product.

This medicine can only be obtained with a prescription.

What benefits of Hydroxyzine hydrochloride tablets have been shown in studies?

Studies in patients have been limited to tests to determine that Hydroxyzine hydrochloride tablets are bioequivalent to the reference product Atarax 25 mg film-coated tablets (UCB Pharma SA, France). 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 tablets?
As Hydroxyzine hydrochloride tablets are a generic medicine, the possible side effects are taken as being the same as those of the reference medicine, Atarax 25 mg film-coated tablets (UCB Pharma SA, France).

For the full list of all side effects reported with Hydroxyzine hydrochloride tablets, see Section 4 of the package leaflet.

Also, for the full list of restrictions, see the package leaflet.

Why are Hydroxyzine hydrochloride tablets approved?
In accordance with the EU requirements, Hydroxyzine hydrochloride tablets have been shown to have comparable quality and to be bioequivalent to the reference product Atarax 25 mg film-coated tablets (UCB Pharma SA, France). Based on this evaluation, the MHRA concluded that the benefits of Hydroxyzine hydrochloride tablets outweigh the identified risks and recommended Hydroxyzine hydrochloride tablets for approval.

What measures are being taken to ensure the safe and effective use of Hydroxyzine hydrochloride tablets?
A Risk Management Plan has been developed to ensure that Hydroxyzine hydrochloride tablets are used as safely as possible. The relevant safety information has been included in the Summary of Product Characteristics and the package leaflet for Hydroxyzine hydrochloride tablets, 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 / reviewed continuously.

Other information about Hydroxyzine hydrochloride tablets
A Marketing Authorisation was granted in the UK to Medreich PLC on 27 October 2016.

The full PAR for Hydroxyzine hydrochloride tablets follows this summary.

For more information about treatment with Hydroxyzine hydrochloride tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in December 2016.
SCIENTIFIC DISCUSSION

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I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Medreich PLC a Marketing Authorisation for the medicinal product Hydroxyzine hydrochloride 25 mg film-coated tablets (PL 21880/0192) on 27 October 2016. The product is a Prescription Only Medicine (POM) and is indicated to assist in the management of:

- anxiety in adults
- pruritus associated with acute and chronic urticaria, including cholinergic and physical types, and in atopic and contact dermatosis in adults and children over 6 years of age.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The application refers to the reference product Atarax 25 mg film-coated tablets (UCB Pharma SA, France), which was first granted a licence in France on 01 January 1962. The corresponding reference product in the UK is Ucerax 25 mg film-coated tablets (PL 00039/0538; UCB Pharma Limited, UK), which was first granted in the UK on 03 April 1991.

Hydroxyzine hydrochloride 25 mg film-coated tablets contain the active substance, hydroxyzine hydrochloride which is a member of the piperazine class of histamine (H1) receptors antagonist. Hydroxyzine hydrochloride is a strong antipruritic and anti-whealing agent. Hydroxyzine is a sedating antihistamine with antimuscarinic and significant sedative properties; it is also an antiemetic. It is a diphenylmethane derivative, chemically unrelated to the phenothiazines, reserpine, meprobamate or benzodiazepines.

No new non-clinical or clinical data were submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

A bioequivalence study was submitted to support this application comparing the applicant’s test product Hydroxyzine hydrochloride 25 mg Film-coated Tablets with the reference product Atarax (Hydroxyzine hydrochloride) 25 mg Film-coated Tablets (UCB Pharma S.A, Belgium) under fasting conditions. The applicant has stated that the bioequivalence study was conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) requirements and the Declaration of Helsinki.

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

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

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking the proposed doses of Hydroxyzine hydrochloride 25 mg film-coated tablets, in the listed conditions, outweigh the risks.

II QUALITY ASPECTS
II.1 Introduction
The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Hydroxyzine hydrochloride 25 mg film-coated tablets are off-white to white, oblong, biconvex, film-coated tablets, each with a score line on both sides and a diameter of 9.90 mm to 10.30 mm. The tablet can be divided in equal doses.

Each film-coated tablet contains 25 mg of hydroxyzine hydrochloride, as the active substance. The product also contains pharmaceutical excipients, namely anhydrous lactose, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate and Opadry white OY-58900 (which contains hypromellose, titanium dioxide (E171) and macrogol). Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in polyvinyl chloride/polyvinylidene chloride/aluminium blisters or polyvinylchloride/aluminium blisters, in pack sizes of 28, 30 and 84 film-coated tablets.

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

II.2 DRUG SUBSTANCE
Hydroxyzine hydrochloride

INN: Hydroxyzine hydrochloride
Chemical name: \((RS)-2-[2-\{4-[\text{4-Chlorophenyl}]\text{phenylmethyl}\}]\text{piperazin-1-yl}]\text{ethoxy}\)ethanol dihydrochloride

Structure:

\[
\text{Cl} \hspace{1cm} \text{N} \hspace{1cm} \text{N} \hspace{1cm} \text{O} \hspace{1cm} \text{OH} \hspace{1cm} \text{2 HCl}
\]

and enantiomer

Molecular formula: \(\text{C}_{21}\text{H}_{29}\text{Cl}_{3}\text{N}_{2}\text{O}_{2}\)
M\(_r\): 447.8
Appearance: A white or almost white, hygroscopic, crystalline powder.
Solubility: Freely soluble in water and in ethanol (96 per cent) and very slightly soluble in acetone.

Hydroxyzine hydrochloride is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification. Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, film-coated tablet that was bioequivalent to the reference product Atarax 25 mg film-coated tablets (UCB Pharma) from the French market. Suitable pharmaceutical development data have been provided for this application.

Comparative in-vitro dissolution and impurity profiles have been provided for this product and the reference product. The in-vitro dissolution and impurity profiles were satisfactory.

With the exception Opadry white OY-58900, which is controlled to a suitable in-house specifications, all the excipients (including the constituents of Opadry white OY-58900) comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of anhydrous lactose, none of the excipients contain materials of animal or human origin. The supplier of anhydrous lactose has confirmed that the milk used in the production of anhydrous lactose is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material, other than calf rennet, is used during the production of anhydrous lactose.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated with pilot-scale batches and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on the first three full-scale production batches.

Control of Finished Product

The finished product specification is acceptable. Test methods have been described and have been validated adequately. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with no special temperature storage conditions has been accepted.

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

Bioequivalence/Bioavailability

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies. The bioequivalence studies are discussed in Section IV, Clinical Aspects.
II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for the application for Hydroxyzine hydrochloride 25 mg film-coated tablets, from a quality point of view.

III NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of hydroxyzine hydrochloride are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

III.3 Pharmacokinetics
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

III.4 Toxicology
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the product is intended for generic substitution with a product that is already marketed, no increase in environmental exposure to hydroxyzine hydrochloride is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Hydroxyzine hydrochloride 25 mg film-coated tablets, from a non-clinical point of view.

IV. CLINICAL ASPECTS
IV.1 Introduction.
The clinical pharmacology of hydroxyzine hydrochloride is well-known. With the exception of data from the bioequivalence study detailed below, no new clinical data is provided or required for this application.

The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

In accordance with the regulatory requirements CPMP/EWP/QWP/1401/98 Rev 1/Corr**, Guideline on the Investigation of Bioequivalence, the Applicant submitted one bioequivalence study to support the application comparing the applicant’s test product Hydroxyzine hydrochloride 25 mg Film-coated Tablets with the reference product Atarax (Hydroxyzine hydrochloride) 25 mg Film-coated Tablets (UCB Pharma S.A, France) under fasting conditions.
Hydroxyzine hydrochloride 25 mg film-coated tablets

IV.2 Pharmacokinetics
The clinical pharmacokinetic properties of hydroxyzine hydrochloride are well-known. In support of the application, the applicant submitted the following bioequivalence study:

An open label, randomised, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence comparing the pharmacokinetics of the applicant’s test product Hydroxyzine hydrochloride 25 mg Film-coated Tablet (Medreich PLC) versus the reference product Atarax (Hydroxyzine hydrochloride) 25 mg Film-coated Tablets (UCB Pharma S.A, France) in healthy adult male and female subjects under fasting conditions.

The subjects were administered a single oral dose (one 25 mg tablet) of either treatment with 240 ml of water after at least an eight hour overnight fast. Blood samples were collected before, up to and including 72 hours after each administration. The washout period between the treatment phases was 8 days. The pharmacokinetic results are presented below.

Results

Summary of Pharmacokinetic Parameters of Test Product-T and Reference Product –R for Hydroxyzine (N=23)

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>N</th>
<th>Untransformed Data (Mean ± SD)</th>
<th>Test Product (T)</th>
<th>Reference product (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/mL)</td>
<td>23</td>
<td>32.1192 ± 9.2345</td>
<td>31.3709 ± 8.2831</td>
<td></td>
</tr>
<tr>
<td>AUC_{0-72} (ng.hr/mL)</td>
<td>23</td>
<td>460.3215 ± 186.3062</td>
<td>479.1738 ± 180.4712</td>
<td></td>
</tr>
</tbody>
</table>

Statistical results of Test product-T vs. Reference product-R for hydroxyzine

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Geometric Mean</th>
<th>(T/R) Ratio</th>
<th>90% Confidence Interval</th>
<th>Intra subject CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/mL)</td>
<td>30.8468</td>
<td>30.7421</td>
<td>100.34%</td>
<td>92.97% to 108.29%</td>
</tr>
<tr>
<td>AUC_{0-72} (ng.hr/mL)</td>
<td>426.9332</td>
<td>456.4901</td>
<td>93.53%</td>
<td>86.52% to 100.75%</td>
</tr>
</tbody>
</table>

Conclusion
The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**)’. Thus, these data support the claim that the applicant’s test product is bioequivalent to the reference product Atarax (Hydroxyzine hydrochloride) 25 mg Film-coated Tablet of UCB Pharma S A, France) under fasting conditions.

IV.3 Clinical Efficacy
With the exception of the bioequivalence study, no new data were submitted and none are required for an application of this type.

Bioequivalence has been demonstrated between the applicant’s test product and the reference product, Atarax (Hydroxyzine hydrochloride) 25 mg Film-coated Tablets of UCB Pharma SA, France), under fasting conditions.

IV.4 Clinical Safety
The clinical safety of hydroxyzine hydrochloride is well-known. No new efficacy data are presented and none are required for this type of application.
IV.5 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 hydrochloride 25 mg film-coated tablets. A summary of safety concerns is listed in the table below:

**Table 1: Summary of safety concerns**

| Important Identified risks | • Use in patients with history of hypersensitivity to the active substance or to any of the excipients, to cetirizine, to other piperazine derivatives, to aminophylline or to ethylenediamine  
| • Use in patients suffering from porphyria  
| • Use in patients with predisposition to cardiac arrhythmia, including electrolyte imbalance (hypokalemia, hypomagnesaemia) and who have pre-existing heart disease  
| • History of QT interval prolongation and Torsade de Pointes  
| • Use in patients suffering from glaucoma, bladder outflow obstruction, decreased gastro-intestinal motility, myasthenia gravis or dementia  
| • Use in patients with increased potential for Convulsions  
| • Potentiation of the effects of hydroxyzine on concomitant use with alcohol  
| • Antagonism of the effects of anticholinesterase drugs and betahistine on concomitant use  
| • Use in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption  
| • Counteraction of epinephrine pressor action on concomitant use  
| • Concomitant use with monoamine oxidase inhibitors (MAOIs)  
| • Increase in serum concentration of hydroxyzine with concomitant use of cimetidine (600 mg bid [bis in die])  
| • Use in pregnancy Hypotonia, movement disorders including extrapyramidal disorders, clonic movements |
### Important potential risks

- Use in patients with hepatic impairment
- Use in patients with moderate or severe renal impairment
- Potentiation of the effects of CNS depressants or drugs having anticholinergic properties on concomitant use
- Impaired ability to react and to concentrate
- Increase in hydroxyzine blood concentration on concomitant use with other drugs known to be potent inhibitors of liver enzymes
- Drug-drug interactions with CYP2D6 substrates at high doses
- Interference with allergy testing or methacholine bronchial challenge

### Missing Information

- None

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

### IV.6 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for Hydroxyzine hydrochloride 25 mg film-coated tablets, from a clinical point of view.

### V. USER CONSULTATION

A 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 pack leaflet 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

**QUALITY**

The important quality characteristics of are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.
NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type. As the pharmacokinetics, pharmacodynamics and toxicology of hydroxyzine hydrochloride are well-known, no additional data were required.

CLINICAL EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for an application of this type.

Bioequivalence has been demonstrated between the applicant’s test product and the reference product, Atarax (Hydroxyzine hydrochloride) 25 mg Film-coated Tablet of UCB Pharma S A, France) under fasting conditions.

CLINICAL SAFETY
No new data were submitted and none are required for this application. As the safety profile of hydroxyzine hydrochloride is well known, no additional safety data were required. No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product 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 product is bioequivalent to the reference product. The benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.
In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:
Hydroxyzine hydrochloride 25 mg film-coated tablets

INGREDIENTS
Each tablet contains 25 mg Hydroxyzine hydrochloride. Also contains lactose.

DOSSAGE
For oral use. Use as directed by the physician.

WARNING
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
Hydroxyzine hydrochloride 25 mg film-coated tablets
**Hydroxyzine hydrochloride 25 mg film-coated tablets**

*(Hydroxyzine hydrochloride)*

**PL 21880/0192**

**STEPS TAKEN AFTER AUTHORISATION-SUMMARY**

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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