Public Assessment Report –

Scientific discussion

Hydroxyzinhydrochlorid EQL Pharma
(Hydroxyzine hydrochloride)
Film-coated tablet, 25 mg

DK/H/2313/001/DC

Date: 04-06-2014

This module reflects the scientific discussion for the approval of Hydroxyzinhydrochlorid EQL Pharma. The procedure was finalised at 04-06-2014. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Hydroxyzinhydrochlorid EQL Pharma, film-coated tablet, 25 mg, from EQL Pharma.

The product is indicated for:
- Symptomatic treatment of urticaria and pruritus.
- Symptomatic treatment of anxiety in adults where no alternative medication is indicated.

Hydroxyzinhydrochlorid EQL Pharma is indicated in adults, adolescents and children of 5 years and above. A comprehensive description of the indications and posology is given in the SmPC.

Hydroxyzine, a piperazine derivative, is a sedating antihistamine with antimuscarinic and significant sedative properties; it is also an entiemiatic. Its main uses are as an anxiolytic, as a sedative pre- and postoperative medication, and in the management of pruritus and urticaria.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

Essential similarity is claimed to the product Atarax filmovertrukne tabletter fra UCG Nordic A/S, approved in DK in May 1957. To prove essential similarity to the brand leader a bioequivalence study has been performed with Atarax 25 mg film-coated tablets, UCB Nordic A/S approved in FR.

In agreement with the pharmacovigilance legislation (Directive 2010/84/EC) a risk management plan and summary of pharmacovigilance system master file have been submitted.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h).

II. QUALITY ASPECTS

II.1 Introduction
The finished product is Hydroxazine 25 mg scored off white oblong, biconvex film coated tablets with score line on both sides, to be marketed in thermoformed blisters made of aluminium and clear PVC and PVC/PDVC.

Compliance with Good Manufacturing Practice
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorization.
II.2 Drug Substance

**Drug substance**

Hydroxyzine Hydrochloride is monographed in the European Pharmacopoeia. The documentation is presented in an European drug master file in CTD format.

**Physico-chemical characterisation**

Description: A white or almost white, hygroscopic, crystalline powder

Solubility: Freely soluble in Water and in ethanol (96%), very slightly soluble in acetone.

Polymorphisme: The product does not exhibit polymorphism

Isomerisme: Racemic mixture of the two enantiomers

The synthesis in the ASMF is described; Selection of 4-chloro benzophenone (PCB) as starting material is considered acceptable.

The specification limits and control methods employed are aligned with those described in the Ph.Eur. monograph for Hydroxyzine Hydrochloride. The analytical methods are adequately validated.

The applicant’s specification has been compiled taking into consideration the information in both ASMF and the Ph.Eur. monograph requirements for Hydroxyzine Hydrochloride (1786).

The retest period proposed is 36 months when stored at 25°C and packed in the primary packaging material (white polyethylene bags).

II.3 Medicinal Product

The product development has been satisfactorily performed and explained and the chosen excipients are well-known and commonly employed.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on three batches. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of 30 months when not stored according to any special requirements is based on extrapolation beyond the presented data. However, the presented data indicate the final drug product is stable.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of Hydroxyzine Hydrochloride are well known. As Hydroxyzine Hydrochloride is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate

III.1 Environmental risk assessment (ERA)
Since Hydroxyzinhydrochlorid EQL Pharma is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

For this generic application a clinical overview on clinical pharmacology, efficacy and safety is presented and to support the application, the applicant has submitted one bioequivalence study, where the 25 mg film coated tablets has been compared with the same strength of the reference product under fasting conditions.

IV.2 Pharmacokinetics

Bioequivalence studies
To support the application, the applicant has submitted one bioequivalence study, where the 25 mg film coated tablets has been compared with the same strength of the reference product under fasting conditions.

The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting with a wash out period of 8 days between the two administrations. 25 mg was administered in each period.

The study was conducted in compliance with GCP, the principles of GLP, local regulatory requirements and the principles of the Declaration of Helsinki.

A total of 26 healthy subjects participated in the study and their mean age, height, weight and BMI were 27.92 years, 164.62 cm, 61.19 kg and 22.62 kg/m2, respectively. All subjects included in the study were Asians. A total of 21 males and 5 females were included in the study, 23 subjects completed the study.

Drop-outs: Three subjects. Subject ID (S13, S15 and S18). These subjects did not report to the facility for period II. According to the applicant the safety of these subjects were ensured over the telephone and there is no impact on the outcome of the study results.

Drug intake procedures: Oral administration with 240 ml of water. Overnight fasted

Blood samples were collected pre-dosing and at 0.00, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 7.00, 9.00, 12.00, 18.00, 24.00, 36.00, 48.00 and 72.00 hours post administration of a single-dose 25 mg Hydroxyzine (test or reference) with 240 ml of water for the analyses of Hydroxyzine Hydrochloride (parent compound).

Analytical methods
The hydroxyzine levels in the study plasma samples were measured by a validated LC/MS/MS method with an 8-point calibration curve covering the range 0.3100 ng/mL to 156.9080 ng/mL, with LLOQ of 0.3100 ng/mL.

The bioanalytical sample analysis was conducted according to GLP and the bioanalytical method was validated both pre-study start and during the analytical run (within run accuracy and precision).
According to current guide on bioanalytical method validation ISR and matrix effect are investigated. Ten percent of the samples were analyzed and 70.65 percent of the samples were within 20 percent of their mean, which comply with the guideline.

Method of assessment of pharmacokinetic parameters: WinNonlin® 5.3.

The parameters calculated were AUC0-t, AUC0-∞, Cmax, tmax, Kel and t½ el and trimary variables: AUC0-t and Cmax.

Statistical methods

ANOVA was performed on the ln-transformed Cmax and AUC0-t. The ANOVA model included sequence, period and treatment as fixed effects and subject nested within sequence as random effect.

Criteria for conclusion of bioequivalence: The 90% confidence interval for the ratio of the geometric least square mean for the log transformed pharmacokinetic parameters Cmax and AUC0-72 of Hydroxyzine of the test to reference product should be between 80.00% and 125.00%.

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median)

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>N</th>
<th>Untransformed Data (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Test Product (T)</td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>23</td>
<td>32.119 ± 9.2545</td>
</tr>
<tr>
<td>AUC0-72 (µg-hr/mL)</td>
<td>23</td>
<td>460.3215 ± 186.3062</td>
</tr>
<tr>
<td>*tmax (hr)</td>
<td>23</td>
<td>3.00(1.50-4.00)</td>
</tr>
<tr>
<td>Kel (hr⁻¹)</td>
<td>23</td>
<td>0.0415 ± 0.0123</td>
</tr>
<tr>
<td>t½ el (hr)</td>
<td>23</td>
<td>18.0653 ± 5.1257</td>
</tr>
</tbody>
</table>

* Median values are reported.

Table 11: Statistical Results of Test Product-T versus Reference Product-R for Hydroxyzine

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Geometric Mean</th>
<th>(TR) Ratio</th>
<th>90% Confidence Interval</th>
<th>Intra subject CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product (T)</td>
<td>Reference Product (R)</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>30.8468</td>
<td>30.7421</td>
<td>100.14%</td>
<td>92.97% to 100.29%</td>
</tr>
<tr>
<td>AUC0-72 (µg-hr/mL)</td>
<td>426.9332</td>
<td>456.4901</td>
<td>93.53%</td>
<td>88.82% to 100.75%</td>
</tr>
</tbody>
</table>

The mean
Safety evaluation:
There were no Adverse Event or Serious Adverse Events reported in this study. For all the subjects, who completed post-study procedures, there were no clinically significant changes in vital signs and in Laboratory parameters.

No predose Hydroxyzine levels were detected before start of treatment for the test and reference product, respectively.

Pharmacokinetic conclusion
The 90% confidence interval for the ratio between test and reference were within the acceptance criteria’s 80.00 – 125.00% for AUC0-72 and Cmax for the test product Hydroxyzine 25 mg tablets

Based on the submitted bioequivalence study Hydroxyzine 25 mg film coated tablets is considered bioequivalent with Atarax 25 mg.
IV.3 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 Hydroxyzinhydrochlorid EQL Pharma).

Summary table of safety concerns as approved in RMP:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
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<tbody>
<tr>
<td>Important identified risks</td>
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<td></td>
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<tr>
<td>Important potential risks</td>
</tr>
<tr>
<td>Missing information</td>
</tr>
</tbody>
</table>

- Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac dysrhythmias/ QT prolongation</td>
<td>(Proposed) text in SmPC sections Contraindication (section 4.3), Special warnings and special precautions for use (section 4.4), Interaction with other medicinal products and other forms of interaction (section 4.5), and Undesirable effects (section 4.8).</td>
<td>NA</td>
</tr>
<tr>
<td>Convulsions</td>
<td>(Proposed) text in SmPC sections Special warnings and special precautions for use (section 4.4) and Undesirable effects (section 4.8).</td>
<td>NA</td>
</tr>
<tr>
<td>Anti-cholinergic effect</td>
<td>(Proposed) text in SmPC sections Special warnings and special precautions for use (section 4.4), Interaction with other medicinal products and other forms of interaction (section 4.5) and Undesirable effects (section 4.8).</td>
<td>NA</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<tr>
<td>----------------------------------------------------</td>
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<tr>
<td>Interaction with alcohol</td>
<td>(Proposed) text in SmPC sections Special warnings and special precautions for use (section 4.4) and Interaction with other medicinal products and other forms of interaction (section 4.5).</td>
<td>NA</td>
</tr>
<tr>
<td>Use in patients with moderate or severe renal impairment</td>
<td>(Proposed) text in SmPC sections Posology and method of administration (section 4.2), Special warnings and special precautions for use (section 4.4), and Undesirable effects (section 4.8).</td>
<td></td>
</tr>
<tr>
<td>Use in patients with hepatic impairment</td>
<td>(Proposed) text in SmPC sections Posology and method of administration (section 4.2), Special warnings and special precautions for use (section 4.4), and Undesirable effects (section 4.8).</td>
<td></td>
</tr>
<tr>
<td>Use in elderly patients</td>
<td>(Proposed) text in SmPC sections Posology and method of administration (section 4.2), Special warnings and special precautions for use (section 4.4), and Undesirable effects (section 4.8).</td>
<td></td>
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<tr>
<td>Use in patients with electrolyte imbalances</td>
<td>(Proposed) text in SmPC sections Special warnings and special precautions for use (section 4.4), and Interaction with other medicinal products and other forms of interaction (section 4.5).</td>
<td></td>
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<tr>
<td>Hypersensitivity</td>
<td>(Proposed) text in SmPC sections Posology and method of administration (section 4.2), Special warnings and special precautions for use (section 4.4), and Undesirable effects (section 4.8).</td>
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<tr>
<td>Important potential risks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular events in patients with risk of stroke</td>
<td>(Proposed) text in SmPC sections Special warnings and special precautions for use (section 4.4).</td>
<td>NA</td>
</tr>
<tr>
<td>Missing information</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in children under 5 years of age</td>
<td>(Proposed) text in SmPC sections Posology and method of administration (section 4.2).</td>
<td></td>
</tr>
</tbody>
</table>
Pharmacovigilance System Master File (PSFM)
The applicant has provided a summary of the PSMF in which proof is provided that the applicant has at his disposal a qualified person responsible for pharmacovigilance. Information about the Member States in which the qualified person resides and carries out his/her tasks and the contact details of the qualified person is also included. A statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC as amended has been provided together with a reference to the location where the pharmacovigilance system master file for the medicinal product is kept.

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 PIL 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.

The test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Hydroxyzinhydrochlorid EQL Pharma, film-coated tablet, 25 mg have a proven chemical-pharmaceutical quality and are generic forms of Atarax. Hydroxyzinhydrochlorid is a well-known active substance with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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

The SmPC, package leaflet and labelling are in the agreed templates and in agreement with other hydroxyzine hydrochloride containing products.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Hydroxyzinhydrochlorid EQL Pharma with the reference product. The decentralised procedure was finalised on 04-06-2014.
Summary Public Assessment Report

Generics

Hydroxyzinhdrochlorid EQL Pharma
(Hydroxyzine hydrochloride)
Film-coated tablet, 25 mg

DK/H/2313/001/DC

Date: 04-06-2014
Summary Public Assessment Report

Generics

Hydroxyzinhydrochlorid EQL Pharma
Film-coated tablet, 25 mg

This is a summary of the public assessment report (PAR) for Hydroxyzinhydrochlorid EQL Pharma. It explains how Hydroxyzinhydrochlorid EQL Pharma was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Hydroxyzinhydrochlorid EQL Pharma.

For practical information about using Hydroxyzinhydrochlorid EQL Pharma, patients should read the package leaflet or contact their doctor or pharmacist.

What is Hydroxyzinhydrochlorid EQL Pharma and what is it used for?
Hydroxyzinhydrochlorid EQL Pharma is a ‘generic medicine’. This means that Hydroxyzinhydrochlorid EQL Pharma is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Atarax.

Hydroxyzinhydrochlorid EQL Pharma is used in the treatment of:
- anxiety in adults where no alternative medication is indicated,
- hives (urticaria) and itching (pruritus) caused by allergic reactions in adults, adolescents and children of 5 years and above.

How does Hydroxyzinhydrochlorid EQL Pharma work?
Hydroxyzinhydrochlorid EQL Pharma belongs to a group of medicines called sedating antihistamines. It suppresses certain functions in the brain without creating a habit. It also blocks histamine, a substance found in body tissues, which is responsible for allergic reactions.

How is Hydroxyzinhydrochlorid EQL Pharma used?
The pharmaceutical form of Hydroxyzinhydrochlorid EQL Pharma is film-coated tablets for oral administration.

The recommended dose is:

Hives and itchiness of the skin:
- **Adults and adolescents aged 12 and above:**
  - Starting dose is 1 tablet (25 mg) in the evening.
  - Normal dose might be increased to up to 4 tablets (100 mg).
- **Children aged 5-11 years:** 1-2 mg per kg body-weight per day divided into 2-3 doses.

Anxiety:
- **Adults:** normal dose is 2 tablets (50 mg) in divided single doses. In severe cases the dose can be increased up to 12 tablets (300 mg) daily.

Medical treatment of anxiety should always be a supportive measure. Treatment should be started, followed up and completed by the same physician.

Maximum dose:
In all cases, the maximum dose is 12 tablets (300 mg) per day. Never take more than 8 tablets (200 mg) at once.
Please read section 3 of the PL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

The medicine can only be obtained with a prescription.

**What benefits of Hydroxyzinhydrochlorid EQL Pharma have been shown in studies?**
Because Hydroxyzinhydrochlorid EQL Pharma is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Atarax. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Hydroxyzinhydrochlorid EQL Pharma?**
Because Hydroxyzinhydrochlorid EQL Pharma is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

**Why is Hydroxyzinhydrochlorid EQL Pharma approved?**
It was concluded that, in accordance with EU requirements, Hydroxyzinhydrochlorid EQL Pharma has been shown to have comparable quality and to be bioequivalent to reference medicine. Therefore, the Danish Health and Medicines Authority decided that, as for the reference medicine called Atarax, the benefits are greater than its risk and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Hydroxyzinhydrochlorid EQL Pharma?**
A risk management plan has been developed to ensure that Hydroxyzinhydrochlorid EQL Pharma is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Hydroxyzinhydrochlorid EQL Pharma, 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 as well.

**Other information about Hydroxyzinhydrochlorid EQL Pharma**
The marketing authorisation for Hydroxyzinhydrochlorid EQL Pharma was granted on 14-08-2014 in Denmark.

The full PAR for Hydroxyzinhydrochlorid EQL Pharma can be found on the website (MRIndex). For more information about treatment with Hydroxyzinhydrochlorid EQL Pharma, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in 20-08-2014.