Public Assessment Report

Scientific discussion

Hydroxyzine Substipharm
(hydroxyzine hydrochloride)

Asp no : 2013-1411

This module reflects the scientific discussion for the approval of Hydroxyzine Substipharm. The procedure was finalised at 2014-09-18. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

The application for Hydroxyzine Substipharm, 25 mg, film-coated tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Substipharm Développement, applies for a marketing authorisation in Sweden through the National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is ATARAX, 25 mg, film-coated tablet, authorised in Sweden since 1957, with UCB Nordic A/S as marketing authorisation holder.

The reference product used in the bioequivalence study is ATARAX, 25 mg film-coated tablet from France with UCB Nordic A/S as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Hydroxyzine Substipharm is presented in the form of film-coated tablets containing 25 mg of hydroxyzine hydrochloride. The excipients are lactose anhydrous, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate and Opadry white OY-58900 (containing hypromellose, titanium dioxide and macrogol). The tablets are packed in thermoformed blisters made of aluminium and clear PVC and PVC/PDVC.

II.2 Drug Substance

Hydroxyzine hydrochloride has a monograph in the Ph Eur.

Hydroxyzine hydrochloride is a white or almost white, crystalline powder which is freely soluble in water. The structure of hydroxyzine hydrochloride has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism, chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Hydroxyzine Substipharm film-coated tablet, 25 mg, is formulated using excipients described in the current Ph Eur, except for Opadry white OY-58900 which is controlled according to acceptable in house specifications. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NiG on Minimising the risk of
transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

From a quality view, there are no objections to approval of Hydroxyzine Substipharm.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

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 SPC of the originator. The terminal half-life is hydroxyzine is approximately 14 hours (7-20 h).

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 26 healthy volunteers, comparing Hydroxyzine hydrochloride, 25 mg, film-coated tablets, manufactured by Medreich Limited, India with Atarax, 25 mg, film-coated tablets under fasting conditions. The study was conducted at Micro Therapeutic Research Labs Private Limited, Chennai, India between 26th October and 7th November 2012. Blood samples were collected pre-dose and up to 72 hours post-dose. The study design is considered acceptable. Plasma concentrations of hydroxyzine were determined with a validated achiral LC/MS/MS method. Hydroxyzine is a racemic drug, but the use of an achiral method was considered justified. For AUC₀₋τ and Cₘₐₓ the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.
IV.2 Pharmacodynamics/Clinical Efficacy/Clinical safety

Hydroxyzine, a piperazine derivative, is a sedating antihistamine with antimuscarinic and significant sedative properties; it is also an antiemetic. Its main uses are as an anxiolytic, as a sedative pre- and postoperative medication and in the management of pruritus and urticaria. No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted.

IV.3 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Hydroxyzine EQL Pharma 25 mg, DK/H/2313/001/DC. The bridging report submitted by the applicant has been found acceptable.

Hydroxyzine is a well-known substance available on the EU market for several years. This current application (Hydroxyzine Substipharm) is a generic application bridging to the reference product Atarax. Bioequivalence between the test and reference product has been adequately demonstrated.

The quality of the product, Hydroxyzine Substipharm, is found adequate. There are no objections to approval of Hydroxyzine Substipharm, from a non-clinical and clinical point of view. The product information is acceptable. The application is therefore recommended for approval.

The risk/benefit ratio is considered positive and Hydroxyzine Substipharm, 25 mg, film-coated tablet is recommended for approval.

VI. APPROVAL

Hydroxyzine Substipharm was approved in the national procedure on 2014-09-18.
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