Public Assessment Report

Scientific discussion

Alterfast
Clarifast
Histafast
Fexofenadinhydrochlorid ”IVAX”
Fexofenadinhydrochlorid ”Copyfarm”

Fexofenadine hydrochloride

DK/H/1087/001-002/MR
DK/H/1088/001-002/MR
DK/H/1089/001-002/MR
DK/H/1090/001-002/MR
DK/H/1091/001-002/MR

This module reflects the scientific discussion for the approval of Alterfast, Clarifast, Histafast, Fexofenadinhydrochlorid “IVAX” and Fexofenadinhydrochlorid “Copyfarm”. The procedures were finalised on 18 July 2007. For information on changes after this date please refer to the module ‘Update’.

I. INTRODUCTION

This assessment report concerns a range of generic applications for fexofenadine hydrochloride film-coated tablets 120mg and 180mg approved through MRP (DK/H/1087-1091/001-002/MR) on 18 July 2007 with Denmark acting as RMS.

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for this range of generic fexofenadine 120 and 180mg film-coated tablets, indicated for the relief of symptoms in seasonal allergic rhinitis (120mg strength) and chronic idiopathic urticaria (180mg strength), could be approved. A national marketing authorisation was granted on 12 July 2006.

The applications are submitted according to Article 10 (1) of the European Directive 2001/83/EC as amended.
Essential similarity is claimed with the innovator product Telfast 120mg and 180mg film-coated tablets, Aventis Pharma Ltd. which was first authorised in the United Kingdom on March 11, 1996.

Fexofenadine, the active metabolite of terfenadine, is a non-sedating well-established H1 antihistamine agent used for the relief of symptoms associated with seasonal allergic rhinitis (120mg strength) and chronic idiopathic urticaria (180mg strength). The efficacy and safety of fexofenadine in these indications have been extensively demonstrated in clinical trials and postmarketing use, which also support the recommendations of the proposed Summary of Product Characteristics.
The recommended dose for adults and children over 12 years is 120mg once daily for the relief of symptoms associated with seasonal allergic rhinitis and 180mg once daily for the relief of symptoms associated with chronica idiopathic urticaria. These same indications, using the same dosage, are also claimed for this present aplication.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all of the sites responsible for the manufacture and assembly of this product prior to granting its National authorisation.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For the manufacturing sites outside the Community, the RMS has accepted copy of current GMP Certificates or satisfactory inspection summary reports, ”close-out letters” or ”exchange of information” issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The PSUR cycle has been harmonised with the fexofenadine EU HBD and hence follows the PSUR cycle agreed for fexofenadine. PSURs should be submitted in 3-yearly intervals (next DLP 200903).

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as film-coated tablets in the strength of 120mg and 180mg packed in PVC/PVDC/Aluminium blisters.

The excipients in the tablet core are: Microcrystalline cellulose, croscarmellose sodium, maize starch, povidone and magnesium stearate.

The excipients in the coating are: Hypromellose, titanium dioxide, macrogol 400, macrogol 4000, iron oxide, yellow and iron oxide, red (for 120mg only).

II.2 Drug Substance

The active substance is fexofenadine hydrochloride. The EDMF procedure has been followed and appropriate letters of access have been included.
The control tests and specifications for the drug substance are adequately drawn up. Validation of the analytical methods have been presented.
Stability studies have been performed with the drug substance. The proposed re-test period 1 year applied for by the applicant is justified.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 3 and 4 batches, respectively, of the 120mg and 180mg strength. The batch analysis results show that the finished product meets the specifications proposed.
Stability studies have been conducted on both strengths of the drug product. The conditions used in the stability studies are according to the ICH stability guidelines. The proposed shelf-life of 2 years with no special requirements for storage is considered acceptable.
The Quality documentation in relation to the concerned products is of sufficient quality.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of fexofenadine hydrochloride are well known. As fexofenadine hydrochloride is a widely used, well-known active substance and the application is submitted in accordance with Article 10 (1) of Directive 2001/83/EEC as amended no further studies are required and the applicant provides none.
The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

No specific clinical studies have been performed, as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EEC as amended.
The clinical overview on the clinical pharmacology, efficacy and safety is adequate.
A bioequivalence study has been conducted demonstrating bioequivalence with the innovator product Telfast 180mg film-coated tablets, Aventis Pharma.
The application contains an adequate review of published clinical data and bioequivalence has been shown.

IV.2 Pharmacokinetics

General description

Fexofenadine hydrochloride is rapidly absorbed following oral administration. T_{max} is reached approx. 1-3 hours post-dose. Mean value for C_{max} was approx. 427 ng/ml after administration of 120mg once daily and 494 ng/ml after administration of 180mg once daily.

Fexofenadine is 60% to 70% bound to plasma proteins. Fexofenadine is only metabolised to a limited degree (hepatic or non-hepatic) and was the only major compound found in urine and faeces in animals and humans. The profile for the plasma concentration of fexofenadine follows a bi-exponential decline with a terminal half-life of 11-15 hours after multiple dosing. Single or multiple dose pharmacokinetics for fexofenadine are linear for oral doses of up to 120mg twice daily. At a dose of 240mg given twice

daily a slightly larger increase was observed (8.8 %) than the proportional increase for the steady state area under the curve, which could indicate that the pharmacokinetics for fexofenadine is linear at doses of 40-240mg daily. The major route of elimination is presumed to be through biliary excretion, while up to 10% of the administered dose is excreted unchanged through the urine.

Bioequivalence

To support the application, the applicant has submitted one 1 study using the 180mg strength.
The study was performed in accordance with GCP, GLP, local regulatory requirements and the Helsinki declaration.
From a clinical perspective the choice of 180mg over 120mg is acceptable and justified by the known linear kinetics of fexofenadine.

Study design

Open label, balanced, randomised, single dose, 2-treatment, 2-sequence, four-period (replicate design) crossover study, performed under fasting conditions. Treatment periods separated by a washout period of 8 days. Subjects were confined to the clinical research centre from at least 10.5 hours prior to drug administration until 24 hour post-dose blood collection in each period.
Subjects received one tablet (180mg) with 240ml water. Subjects remained seated upright or were ambulatory for 2 hours post dosing. Water was not allowed for one hour before or after dosing but was allowed *ad libitum* thereafter. Meals were standardised and foods and beverages containing caffeine or other xanthenes were not allowed throughout the housing period. Alcohol was banned from at least 48 hours prior to dosing and throughout the period of sample collection. Smoking was not allowed.

Methods of analysis

Blood sampling was performed predosing and at several time-points up to 72.0 hours post dose in each period. Samples were analysed by LC/MS/MS for fexofenadine.
The design of the study is considered adequate. The sampling period of 72 hours is sufficient to characterize the plasma concentration-time profile and to ensure measurements over a period of at least 5 half-lives based on an expected t½ of about 14½ hours. Blood sampling points are appropriate to allow an accurate measurement of Tmax. The wash-out period of 8 days is long enough to avoid any carry over effect to the second period. It is acceptable that the study is conducted under fasting conditions since literature indicates no problems with concomitant food intake and no recommendations are given in the SPC for administration of the drug in relation to food.

Test and reference products

Fexofenadine 180mg film-coated tablets have been tested against Telfast 180mg film-coated tablets, Aventis Pharma.
Satisfactory certificates of analysis of the test products are presented.
The size of the test batch is representative of commercial scale and therefore acceptable.

Population(s) studied

40 healthy volunteers (Dravidian, male, 18-36 years, 51-75 kg) were randomised to the study. 35 completed.
The sample size was based on experience from previous trials from the Sponsor, that intrasubject variability was 24%. 36 subjects were calculated as being needed to give an 80% power (α=0.05) to show bioequivalence within the limits required for the primary parameters.
The population chosen is satisfactory. No females were enrolled but this acceptable as literature reports no gender-related differences in fexofenadine pharmacokinetics. In addition, the BE guideline does not insist on both sexes being included in trials.

Analytical methods

Fexofenadine was extracted and analysed by LC/MS/MS.
A validation report has been provided in which the method is shown validated within a range of 25.855-1003.266ng/ml. Inter- and intra-assay variances have been satisfactorily determined. Fexofenadine has been shown to be stable in plasma samples following 3 freeze-thaw cycles, and for up to 6 hours at room temperature. Long term data are also presented showing that fexofenadine is stable for up to 445 days stored below -80°C.

A bioanalytical report has been provided.
The analytical method has been satisfactory validated (pre-study and within study) and the handling of samples is adequate. Plausible reasons are presented for analysis repetition, which in any case was relatively low and primarily necessitated as values were above the concentration curve range. Method validation included dilution integrity testing.
Adequate stability data are presented indicating that samples were stable by the end of the analysis period and that the results are therefore valid.

Pharmacokinetic variables
Primary analysis parameters were AUC0-inf, AUC0-t and Cmax.
Secondary analysis parameters were Tmax, T½ and Kel
Safety parameters were clinical examination, clinical chemistry, vital signs and AEs.
The pharmacokinetic variables evaluated are considered adequate.

Statistical methods
ANOVA was performed on ln-transformed AUC0-inf, AUC0-t and Cmax and included sequence, formulation and period as fixed effects and subject nested within sequence as a random effect. Details for the secondary parameters Tmax, T½ and Kel are not given. Safety was analysed descriptively.
The statistical methods have been adequately described and are acceptable. All statistical calculations were performed using SAS PROC MIXED procedures and WinNonLin. 35 subjects completed and data from all 35 were used for statistical analysis. The statistical requirements are met and the results are considered valid.
There were no major protocol deviations.

Results
The 90% CIs for AUC0-t, AUC0-inf and Cmax lie within 80-125% required to demonstrate bioequivalence with the reference product. There were no significant differences between treatments for Tmax and the residual areas were less than 20% for all treatments and analytes (apart from subject 12 (test)) indicating that the sampling period of 72 hours was adequate.

Safety evaluation
3 subjects experienced a total of 5 AEs, of which all were classified as remotely related to the investigational product. All AEs were mild and no serious or unexpected AE was reported. All AEs were resolved with full recovery. Overall, the test product was tolerated to at least the same extent as the reference.

Pharmacokinetic conclusion
Based on the submitted bioequivalence study these generic fexofenadine film-coated tablets are considered bioequivalent with Telfast film-coated tablets with respect to rate and extent of absorption of fexofenadine hydrochloride. Tolerability of the test product is acceptable and not significantly different from reference product.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that this generic product and the innovator are interchangeable. The benefit risk is, therefore, considered to be positive.

The applicant has committed to carrying out process validation prior to placing the product on the market. Process validation reports with Certificates of Analysis will be forwarded to the Danish Medicines Agency when available. Additional stability testing will be performed and the Danish Medicines Agency will be informed should any problems with stability of products arise during the stability studies.