

# **Public Assessment Report**

## **Scientific discussion**

**Nefoxef film-coated tablets 120 mg and 180 mg  
Fexofenadine hydrochloride**

**DK/H/1106/001-002/MR**

**This module reflects the scientific discussion for the approval of Nefoxef. The procedure was finalised at 6 November 2007. For information on changes after this date please refer to the module 'Update'.**

## **I. INTRODUCTION**

This assessment report concerns a generic application for fexofenadine hydrochloride film-coated tablets 120mg and 180mg approved through MRP (DK/H/1106/001-002/MR) on 6 November 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 these 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 application is 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 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 chronic idiopathic urticaria.

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, active metabolite of terfenadine, is a histamine H<sub>1</sub>-receptor antagonist indicated for the treatment of seasonal allergic rhinitis and for chronic idiopathic urticaria. For rhinitis, the recommended dose is 120mg once daily and for urticaria, 180mg once daily. Doses are to be taken before a meal.

Fexofenadine is active as is and is rapidly absorbed following oral administration. Linear kinetics are exhibited for oral administration in the range 10-800 mg. Maximum plasma concentrations are reached within 2.6 hours post-dose. Fexofenadine is 60 – 70 % bound to plasma proteins, primarily albumin and  $\alpha_1$ -acid glycoprotein.

Approximately 5 % of the total oral dose is metabolised. Renal and faecal excretion of fexofenadine is 11% and 80% respectively. The mean elimination half-life of fexofenadine is approx. 14.4 hours. It is not known whether the faecal excretion represents unabsorbed drug or is the result of biliary excretion.

Fexofenadine pharmacokinetics are altered in the aged and renally impaired. In geriatric subjects ( $\geq 65$  years old) peak plasma levels 99 % higher than in normal volunteers may be observed with mean elimination half-life similar to normal volunteers. With mild to severe renal impairment, peak plasma levels are 87% to 111% greater than normal and elimination half-lives 59% and 72% longer than normal. Dialysis patients show 82% higher plasma levels and 31% longer elimination half-life than their normal counterparts. Hepatic impairment does not affect the kinetics. Gender differences are not observed.

The pharmacokinetics of adolescents (12-16 years of age) are similar to those of healthy adults.

Food ingestion 30 minutes before administration has no clinically significant effect on the rate or extent of absorption of fexofenadine tablets or capsules in volunteers.

### **Bioequivalence**

To support the application, the applicant has submitted one 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  $t_{1/2}$  of about 14½ hours. Blood sampling points are appropriate to allow an accurate measurement of  $T_{max}$ . 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 is 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 ( $\alpha=0.05$ ) 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  $AUC_{0-inf}$ ,  $AUC_{0-t}$  and  $C_{max}$ .

Secondary analysis parameters were  $T_{max}$ ,  $T_{1/2}$  and  $K_{el}$

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  $AUC_{0-inf}$ ,  $AUC_{0-t}$  and  $C_{max}$  and included sequence, formulation and period as fixed effects and subject nested within sequence as a random effect. Details for the secondary parameters  $T_{max}$ ,  $T_{1/2}$  and  $K_{el}$  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  $AUC_{0-t}$ ,  $AUC_{0-inf}$  and  $C_{max}$  lie within 80-125% required to demonstrate bioequivalence with the reference product. There were no significant differences between treatments for  $T_{max}$  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 Nefoxef film-coated tablets 120mg and 180mg 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.

*Commitments*

The following commitments have been made by the applicant:

- The active substance will be tested for compliance with the active substance specification on Impurity A immediately prior to use in the manufacture of Fexofenadine film-coated tablets.
- Prospective validation will be performed for each of the proposed batch sizes prior to placing on the market.
- Commitment has been given to forward the validation reports of the manufacturing process on the first three maximum commercial batch sizes for the EU prior to marketing. Furthermore, process validation will be conducted on all batch sizes and the RMS informed should any problems be identified during the process validation studies.
- Certificates of analysis on the first three batches of the maximum batch size of each strength will be forwarded to the Danish Medicines Agency, when available.
- The applicant commits to placing the first three production scale batches of the new maximum batch sizes on stability and to test the batches according to the stability protocol for long-term testing and accelerated testing as presented in section P.8.1.