CBG MEB

Public Assessment Report

Scientific discussion

Notaxo 10 mg and 20 mg, orodispersible tablets

(ebastine)

NL/H/3189/001-002/DC

Date: 28 July 2016

This module reflects the scientific discussion for the approval of Notaxo 10 mg and 20 mg, orodispersible tablets. The procedure was finalised on 16 June 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Notaxo 10 mg and 20 mg, orodispersible tablets from Stada Arzneimittel AG.

The product is indicated for the symptomatic treatment of seasonal and perennial allergic rhinitis, in conjunction with or without allergic conjunctivitis in adults and adolescents aged 12 years and older. The 10 mg tablet is also indicated for the treatment of urticaria in adults aged 18 years and older.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application with reference to the innovator product Kestine 10 mg and 20 mg, tablets (NL License RVG 17708 and 27500) which has been registered in the Netherlands by Almirall B.V. since 9 July 1996 and 1 June 2004. Essential similarity is claimed with Kestine smelt 10 and 20 mg, oral lyophilisate (NL License 29927-29928) registered since 5 April 2005.

The concerned member states (CMS) involved in this procedure were Italy and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Notaxo 10 mg are white to off white, round shaped, flat faced, bevel edged orodispersible tablets debossed with '10' on one side and plain on the other side. One orodispersible tablet contains 10 mg of the active substance ebastine.
Notaxo 20 mg are white to off white, round shaped, flat faced bevel edged orodispersible tablets debossed with '20' on one side and plain on the other side. One orodispersible tablet contains 20 mg of the active substance ebastine.

The orodispersible tablets are packed in OPA/Alu/PVC – Paper/PET/Alu peel-off blisters.

The excipients are: hypromellose (E464), povidone (E1201), poloxamer, gelatin, carmellose calcium, crospovidone (E1202), mannitol (E421), microcrystalline cellulose (E460), croscarmellose sodium (E468), colloidal hydrated silica (E551), trusil peppermint special (composition: natural flavouring, nature identical flavouring, acacia gum (E414), maltodextrin, sodium benzoate (E211), butylated hydroxyanisole (E320)), neotame (E961), magnesium stearate (E572).

The composition of the two strengths is dose proportional.

II.2 Drug Substance

The active substance, ebastine, is an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, crystalline powder, which is practically insoluble in water, very soluble in methylene chloride and sparingly soluble in methanol. Ebastine contains no chiral centres and no other polymorphic forms are known.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the

complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The active substance is manufactured by one supplier. The manufacturing process consists of a five step synthesis. The active substance is adequately characterised. Sufficient data have been provided.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with additional specifications for residual solvents and particle size. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 24 months (stored at 25°C/60% RH) and 6 months (stored at 40°C/75% RH). Based on the data submitted, a retest period could be granted of 36 months without any specific storage conditions.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. During development composition and process parameter were optimised until the final formulation was obtained.
To support this generic application, the MAH has submitted a cross-over bioequivalence study with the 20 mg strength. A biowaiver is requested for the 10 mg strength. The dissolution profiles of the two Notaxo strengths at three different buffers without surfactant are considered comparable. The composition of the batch used in the bioequivalence study is identical to the proposed final composition. Comparative dissolution profiles between test and reference biobatches at three different buffers without the use of surfactant have been provided. The products are almost comparable at low pH and not comparable at pH 4.5 and 6.8. However, the results of the pharmacokinetic study, demonstrating bioequivalence, were found to be sufficient.

Manufacturing process
The manufacturing process involves dispensing, sifting, dry mixing, granulation, prelubrication, blending/lubrication and tabletting and has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three industrial scaled batches.

Control of excipients
The excipients comply with Ph. Eur. Requirements, except for the peppermint aroma, which is tested by use of in-house specifications consisting of standard tests. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average mass, dissolution, disintegration, hardness, uniformity of dosage units assay, related substances, microbial test and water content. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three industrial scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three industrial scaled batches of each tablet strength in accordance with applicable European guidelines. The data cover 24 months stored at 25°C/60%RH and 6 months stored at 40°C/75%RH in the registered blisters. No up or downward

trends in any of the parameters examined was observed. On basis of the data submitted, a shelf life was granted of 3 years without additional temperature restrictions.
Results of a formal photostability in accordance with the Note for Guidance on the Photostability testing of new Active substances and Medicinal Products are included in the validation of the assay method. Direct exposed tablet powder is showing a very slight degradation in sun-light and little degradation in UV-light. The finished product does not need protection from light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product except for gelatin. Scientific data and a Certificate of suitability for gelatin issued by the EDQM has been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Notaxo 10 mg and 20 mg, orodispersible tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Notaxo 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.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Kestine which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ebastine is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study for the 20 mg strength which is discussed below. For the 10 mg strength the MAH requested a biowaiver.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Notaxo 20 mg, orodispersible tablet (Stada Arzneimittel AG, Germany) is compared with the pharmacokinetic profile of the reference product Ebastel Forte Flas 20 mg oral lyophilisate (Almirall S.A., Spain).

The choice of the reference product in the bioequivalence studies is justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The MAH filed a biowaiver request for the 10 mg strength. Both formulations are identical in qualitative composition, have a proportional quantitative composition and are manufactured by the same manufacturer. The pharmacokinetics of ebastine are linear over the dosage range. Comparative dissolution has been investigated in different media (pH 1.2, pH 4,5 acetate buffer and pH 6.8 phosphate buffer). Based on the provided dissolution-time curves in which the dissolution data of the 2 x 10 mg tablets is compared to the 20 mg tablet of the test product at pH 6.8. Similarity has been demonstrated between the two strengths, meaning that there is no formulation effect between the two strengths at pH 6.8. Together with the similarity at pH 1.2 and 4.5, the dissolution of 10 mg strength is considered similar with the 20 mg strength at all three pH levels. The bioequivalence with the reference product tested with 20 mg tablets can be extrapolated to the lower strength of 10 mg. The biowaiver is therefore granted for the 10 mg tablet.

Bioequivalence study

Design

A single-dose, fully replicated, four-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 82 healthy male subjects of Indian origin, aged 22-44 years. Each subject received a single dose (20 mg) of one of the 2 ebastine formulations. Before administration the subjects swallowed 20 ml water in order to wet their mouth. The formulation was then placed on the tongue and swallowed only when the tablet was totally disintegrated in the buccal cavity. There were 4 dosing periods, separated with a wash-out of 7 days between each period.

Blood samples were collected pre-dose and at 0.33, 0.5, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 24, 32, 48 and 72 hours post-dose administration.

The design of the study is acceptable. The sampling period is adequate and the wash-out periods are long enough. The replicate design is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Ebastine is rapidly absorbed and undergoes extensive first pass metabolism following oral administration. Ebastine is almost totally converted to the pharmacologically active acid metabolite, carebastine. Both ebastine and carebastine are primary endpoints for demonstration of bioequivalence. For AUC0-t, the bioequivalence acceptance range should be 0.80-1.25. For Cmax, if the intra-subject CV would be higher than 30%, these acceptance criteria could be widened using schale-average-bioequivalence.

In the Questions & Answers: Positions on specific questions addressed to the pharmacokinetics working party (EMA/618604/2008 Rev. 9) it was concluded that demonstration of bioequivalence could be based on either ebastine or carebastine. In case both ebastine and carebastine are analysed, the analyte to be used for bioequivalence evaluation should be prospectively defined in the protocol.
The basis for bioequivalence is adequate and possible widening of the acceptance criteria for Cmax is in accordance with the Guideline.

Results

A total of 18 subjects withdrew from the study due to medical reasons, protocol violations and on their own accord. 64 subjects were still eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ebastine under fasted conditions.

Treatment N=64	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	21.8 ± 18.6	23.1 ± 19.5	4.15 ± 2.71	1.5 (0.5 - 8.0)
Reference	22.5 ± 19.1	23.9 ± 20.1	4.2 ± 2.5	2.0 (0.5 – 10.0)
***Ratio (90% CI)**	0.98 (0.89 – 1.07)	--	0.97 (0.90 – 1.05)	--

AUC0-t	Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$	Area under the plasma concentration curve extrapolated to infinite time.
C_{max}	Maximum plasma concentration
t_{max}	Time until Cmax is reached

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of carebastine under fasted conditions.

Treatment N=64	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg.h/ml	**t_{max}** µg.h/ml
Test	6.21 ± 1.29	7.13 ± 1.49	0.208 ± 0.054	6.5 (4.0 -12.0)
Reference	6.29 ± 1.42	7.19 ± 1.61	0.241 ± 0.058	6.5 (4.0 – 12.0)
***Ratio (90% CI)**	0.99 (0.96 – 1.02)	--	0.98 (0.94 – 1.02)	--

AUC0-t	Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$	Area under the plasma concentration curve extrapolated to infinite time.
C_{max}	Maximum plasma concentration
t_{max}	Time until Cmax is reached

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Notaxo is considered bioequivalent with Ebastel Forte Flas. Bioequivalence is demonstrated based on both ebastine and the active metabolite carebastine.

A total of 16 adverse events (AEs) were reported by 14 subjects during conduct of the study. There were no serious AEs during the conduct of the study. However, 11 AEs reported were considered to be significant. 9 AEs were reported in 7 subjects after administration of the test formulation and 7 AEs in 7 subjects after administration of the reference formulation. These results show no apparent differences between test and reference formulation.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Notaxo.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity reactions • Serious hepatobiliary disorders

Important potential risks	• Cardiac rhythm disorders • Agitation/anxiety, depression
Missing information	• Data in fertility, pregnancy and breastfeeding • Data in children <12 years old

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Kestine smelt 10 mg and 20 mg, tablets. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The MAH provided a bridging report to support the readability of the package leaflet (PL) for Notaxo 10 and 20 mg, orodispersible tablets. The leaflet was compared to the previously user tested PL of Notaxo 10 mg (version 2011). Small differences were found but deemed acceptable as it concerns no additional key safety messages that would warrant testing. The bridging report was found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Notaxo 10 mg and 20 mg, orodispersible tablets have a proven chemical-pharmaceutical quality and are generic forms of Kestine smelt 10 mg and 20 mg oral lyophilisate, well-known medicinal products with an established favourable efficacy and safety profile.

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

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Notaxo 10 mg and 20, orodispersible tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 16 June 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	NL/H/3189/ 1-2/IA/001	IA	13-10-2015	10-11-2015	Approved	N
Change in the (invented) name of the medicinal product; for Nationally Authorised Products (Italy)	NL/H/3189/ 1-2/IB/002	IB	21-10-2015	20-11-2015	Approved	N
Change in the (invented) name of the medicinal product; for Nationally Authorised Products (Spain)	NL/H/3189/ 1-2/IB/003	IB	07-12-2015	06-01-2016	Approved	N