CBG MEB

# PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

# Ebastine BB 10 mg orodispersible tablets Brown & Burk UK Ltd, United Kingdom

# ebastine

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/2308/001/DC**
**Registration number in the Netherlands: RVG 110051**

**Date of first publication: 23 November 2012**
**Last revision: 11 June 2014**

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|---|---|
| Pharmacotherapeutic group: | other antihistamines for systemic use |
| ATC code: | RO6AX22 |
| Route of administration: | oral |
| Therapeutic indication: | symptomatic treatment of seasonal and non-seasonal allergic rhinitis, with or without allergic conjunctivitis; urticaria |
| Prescription status: | prescription only |
| Date of authorisation in NL: | 12 July 2012 |
| Concerned Member States: | Decentralised procedure with ES, repeat-use with FR |
| Application type/legal basis: | Directive 2001/83/EC, Article 10(1) |

This report includes an annex, concerning the repeat-use procedure, on page 12.

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), package leaflet and labelling.

# I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Ebastine BB 10 mg orodispersible tablets from Brown & Burk UK Ltd. The date of authorisation was on 12 July 2012 in the Netherlands.

The product is indicated for:

- symptomatic treatment of seasonal and non-seasonal allergic rhinitis, with or without allergic conjunctivitis
- urticaria

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

*In vitro* and *in vivo* studies ebastine demonstrates great affinity for $H_1$ receptors, which are rapidly and selectively inhibited over a long period of time.
Impairment of central functions is only slight; the risk of occurrence of anticholinergic effects is low, but, on the basis of the studies available, cannot be completely ruled out. After oral administration, neither ebastine nor its active metabolite cross the blood-brain barrier. This characteristic is consistent with the low level of sedation determined in experimental studies on the effects of ebastine on the central nervous system.

This decentralised procedure concerns a generic application with reference to the innovator product Kestine 10 mg, film-coated tablets (NL License RVG 17708), which has been registered in the Netherlands by Almirall B.V. since 9 July 1996 (original product). Essential similarity is claimed with Kestine Smelt 10 mg, oral lypophilisate (NL License RVG 29927). In addition, reference is made to Kestine authorisations in the individual member states (reference product).

Following this DCP, a repeat-use procedure was finalized (see Annex I).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Kestinlyo 10 mg oral lyophilisate, registered in France. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

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.

# II SCIENTIFIC OVERVIEW AND DISCUSSION

## II.1 Quality aspects

**Compliance with Good Manufacturing Practice**
The MEB 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 authorisation.

**Active substance**
The active substance is ebastine, 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 polymorphic forms are known.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph. Eur. and the additional specifications as mentioned on the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for one batch.

Stability of drug substance
The active substance is stable for 2 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM. The MAH applies a retest period of 6 months.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

**Medicinal Product**

Composition
Ebastine BB 10 mg is a white to off white, circular, flat face beveled edge, uncoated tablet plain on both faces.

The orodispersible tablets are packed in Alu-Alu blisters, PVC/PE/PVdC-Aluminium blisters and HDPE containers with HDPE screw cap.

The excipients are: crospovidone (E1202), mannitol (E421), aspartame (E951), silicon dioxide (E551), magnesium stearate (E572), peppermint flavour (Powdarome peppermint premium), maltodextrine (maize), acacia gum (E141)/Arabic gum, pulegone.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. During development composition and process parameters were optimized until the final formulation was obtained. The composition of the batch used in the bioequivalence study is identical to the proposed final composition. Comparative dissolution profile data were provided on registration batches versus the innovator product in different media. In all cases rapid dissolution of more than 85% after 10 minutes was observed.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process involves dispensing, sifting, dissolving and spraying of the drug substance, drying, sifting, blending/lubrication and tableting. Process validation data on the product has been presented for three batches of the smallest commercial size. Process validation for full-scale batches will be performed post authorization.

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 product specification includes tests for appearance, identification, average mass, dissolution, disintegration, hardness, friability, uniformity of dosage units, assay, related substances, microbial test, residual solvents and water content. The release and end-of-shelf-life specifications are identical. The proposed limits for the various parameters are acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided for the three batches included in the validation study; all batches comply with the release specification.

Stability of drug product
Stability data on the product has been provided for three batches of the smallest commercial scale, stored at 25°C/60%RH (12 months), and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in all three of the proposed packaging types. For the tablets stored in the HDPE-container an in-use stability study was performed. No up or downward trends in any of the parameters examined were observed. Photostability of the drug product was adequately demonstrated.
On the basis of the available stability data the claimed shelf-life of 24 months was granted, without special storage conditions. After first opening of the tablet container, the shelf life is 6 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. Mannitol, magnesium stearate and Powdarome Peppermint Premium are of plant origin.

## II.2 Non-clinical aspects

This product is a generic formulation of Kestine, which is available on the European market. 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.

**Environmental risk assessment**
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of ebastine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

## II.3 Clinical aspects

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 a bioequivalence study in which the pharmacokinetic profile of the test product Ebastine BB 10 mg orodispersible tablets (Brown & Burk UK Ltd, United Kingdom) is compared with the pharmacokinetic profile of the reference product Kestinlyo 10 mg oral lyophilisate (Almirall, France).

*The choice of the reference product*
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

*Design*
A single-dose, randomised, three-period, three-treatment, three-sequence, crossover bioequivalence study was carried out under fasted conditions in 54 healthy adult subjects (46 males/8 females). After an overnight fast for at least 10 hours, just before dosing, 20 mL of water was provided to the subjects and the subjects were asked to wet the mouth by swallowing water directly before applying the orodispersible tablet on the tongue. According to randomization schedule, one tablet of test (in any one period) or reference (in any two periods) product was placed on the tongue. The subjects were then asked to move the tablet around the tongue and upper palate for 30 seconds without any attempt to chew or spit until it disintegrated completely. After complete disintegration of the tablet in the mouth, the subject was asked to swallow all the contents with saliva. There were 3 dosing periods, separated by a washout period of 11 days.

Blood samples were collected pre-dose and at 0.50, 1.00, 1.33, 1.67, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.33, 4.67, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 24.00, 48.00, 72.00 and 96.00 hours after administration of the products.

Elimination half-life of carebastine is estimated between 10 and 19 hours. Therefore, a washout period of 11 days is considered sufficient. Sufficient time points were taken to estimate rate of absorption accurately.

*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.

Bioequivalence is demonstrated based on the parameters of the active metabolite carebastine. The MAH adequately justified the use of carebastine as primary substance to demonstrate bioequivalence based on its high concentration, negligible contribution of parent to activity and high intrasubject variability in pharmacokinetics of ebastine. Carebastine plasma concentration (Cmax) values are 50 times higher than those of ebastine. Ebastine fulfills the criteria in which the parent compound exposure is low and variable and exposure to active metabolite is very much higher, therefore it is acceptable to demonstrate bioequivalence for the main active metabolite (CPMP/EWP/QWP/1401/98 Rev. 1, 2010).

*Results*
Two subjects did not report to the facility for period 2 and 3 check-in and these subjects were considered as drop-outs. Fifty-two subjects were eligible for pharmacokinetic analysis.

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

| Treatment N=52 | $AUC_{0-t}$ ng.h/ml | $AUC_{0-\infty}$ ng.h/ml | $C_{max}$ ng/ml | $t_{max}$ h | $t_{1/2}$ h |
|---|---|---|---|---|---|
| **Test** | 4464 ± 960 | 4817 ± 987 | 171 ± 46 | 4.33 (3.5-12) | 18.7 ± 2.9 |
| **Reference** | 4677 ± 1137 | 4821 ± 1168 | 175 ± 52 | 4.33 (2.25-12.0) | 18.5 ± 2.5 |
| ***Ratio (90% CI)** | 1.01 (0.97 - 1.05) | 1.01 (0.97 -1.05) | 0.99 (0.93 - 1.05) | -- | -- |
| **CV (%)** | 14.6 | 14.3 | 21.9 | -- | -- |

**$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity
**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum concentration
**$t_{1/2}$** half-life

**ln-transformed values*

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

| Treatment N=52 | $AUC_{0-t}$ ng.h/ml | $AUC_{0-\infty}$ ng.h/ml | $C_{max}$ ng/ml | $t_{max}$ h | $t_{1/2}$ h |
|---|---|---|---|---|---|
| **Test** | 10.6 ± 6.6 | 11.4 ± 6.6 | 4.7 ± 2.7 | 1.67 (0.5-4.0) | 4.2 ± 1.3 |
| **Reference** | 9.9 ± 8.9 | 10.4 ± 9.0 | 4.2 ± 2.7 | 1.67 (0.5-4.67) | 4.1 ± 1.9 |
| ***Ratio (90% CI)** | 1.13 | 1.11 | 1.13 | -- | -- |
| **CV (%)** | 52 | 49 | 40 | -- | -- |

**$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity
**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum concentration
**$t_{1/2}$** half-life

**ln-transformed values*

The 90% confidence intervals calculated for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of carebastine under fasted conditions, it can be concluded that Ebastine BB 10 mg orodispersible tablets and Kestinlyo 10 mg oral lyophilisate are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

According to the SmPC, Ebastine BB 10 mg orodispersible tablets can be taken without any regard to food intake as the action of ebastine tablets is not affected by food intake. This is in agreement with the SmPC of the innovator in the Netherlands. As under fasted conditions the variability in general is less than under fed conditions, the study performed under fasted conditions is considered acceptable.

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).

Risk management plan

Ebastine was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ebastine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SmPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

**Product information**

SmPC

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Kestine.

Readability test

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 test consisted of two rounds with 10 participants each. The results show that the percentage of participants successfully finding the section and answering the questions correctly was within the acceptable percentage outlined in the protocol and was 90% or more. General comments on the format and layout of the leaflet were positive indicating that participants were able to find the required information and understand it. The format and layout were generally considered helpful. The readability test has been sufficiently performed.

## III OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

Ebastine BB 10 mg orodispersible tablets has a proven chemical-pharmaceutical quality and is a generic form of Kestine Smelt 10 mg, oral lypophilisate. Kestine is a well-known medicinal product 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 is consistent with that of the reference product. The SmPC, package leaflet and labelling are in the agreed templates.

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 Ebastine BB 10 mg orodispersible tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 22 May 2012. Ebastine BB 10 mg orodispersible tablets was authorised in the Netherlands on 12 July 2012.

The date for the first renewal will be: 25 May 2017.

There were no post-approval commitments made during the procedure.

## List of abbreviations

| | |
|---|---|
| ASMF | Active Substance Master File |
| ATC | Anatomical Therapeutic Chemical classification |
| AUC | Area Under the Curve |
| BP | British Pharmacopoeia |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence Interval |
| $C_{max}$ | Maximum plasma concentration |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CV | Coefficient of Variation |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EU | European Union |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| MEB | Medicines Evaluation Board in the Netherlands |
| OTC | Over The Counter (to be supplied without prescription) |
| PAR | Public Assessment Report |
| Ph.Eur. | European Pharmacopoeia |
| PIL | Package Leaflet |
| PSUR | Periodic Safety Update Report |
| SD | Standard Deviation |
| SmPC | Summary of Product Characteristics |
| $t_{½}$ | Half-life |
| $t_{max}$ | Time for maximum concentration |
| TSE | Transmissible Spongiform Encephalopathy |
| USP | Pharmacopoeia in the United States |

## 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 |
|---|---|---|---|---|---|---|
| Update of the Pharmacovigilance System in line with the new legislations. | NL/H/2308/ 001/IA/001 | IA | 15-3-2013 | 15-4-2014 | Approval | N |
| Repeat use procedure with FR. | NL/H/2308/ 001/E/001 | E | 4-4-2013 | 24-9-2013 | Approval | Y, Annex I |

## ANNEX I – Repeat use procedure (NL/H/2308/001/E/001)

The repeat use procedure for Ebastine BB 10 mg orodispersible tablets started on 4 April 2013, with France as the only CMS.

Agreement between the Reference and Concerned Member State could not be reached during the written procedure. A CMD(h) referral was initiated due to a different insight regarding acceptability of bioequivalence data for ebastine or the metabolite carebastine as a basis to demonstrate bioequivalence of an ebastine generic product with the innovator product.

CMD(h) outcome
The CMD(h) requested advice from the Pharmacokinetics Working Party (PKWP) on whether it is acceptable for a generic application for ebastine to demonstrate bioequivalence based on either the parent ebastine or on the active metabolite carebastine, provided proper justification in the study protocol has been provided. The PKWP group advised that in this case the fact that the MAH demonstrates bioequivalence based on the pharmacokinetics of the active metabolite carebastine is acceptable. After consideration of the MAH's responses to the list of questions and the PKWP advice, the CMD(h) concluded that bioequivalence thus has been demonstrated adequately, and that the application for Ebastine BB 10 mg orodispersible tablets is acceptable. The MAH *a priori* justified the use of carebastine as primary substance to demonstrate bioequivalence. The 90% CI for the rate and extent of absorption of carebastine were within the acceptance range. This final CMD(h) opinion is in line with the advice of the PKWP.

The repeat use procedure was finished with a positive outcome on 24 September 2013. The concerned member state agreed to grant a marketing authorisation.

The following post-approval commitments have been made during the repeat-use procedure:
- The MAH committed to submit a variation to remove the higher batch size.
- The MAH committed to submit a variation for harmonization of the SmPC.