LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bilastin Teva

(bilastine)

SE/H/2034/01/DC
2019-1316

This module reflects the scientific discussion for the approval of Bilastin Teva. The procedure was finalised on 2021-03-18. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The applications for Bilastin Teva, 20 mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Alfred E Tiefenbacher GmbH & Co. KG, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BG, ES, FR, HU, PL and PT as concerned member states (CMS). IT was initially CMS as well, but the applicant withdrew the MAA in this MS during the clock-off period.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Bilaxten, 20 mg, tablet authorised in IS since 2010, with Menarini International Operations Luxembourg S.A. as marketing authorisation holder.

The reference product used in the bioequivalence study is BITOSEN, 20 mg, tablet, from DE with Menarini International Operations Luxembourg S.A. as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

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 have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

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

To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Bilastin Teva with the reference product BITOSEN.

Pharmacokinetic properties of the active substance

Absorption: Bilastine is rapidly absorbed after oral administration with a time to maximum plasma concentration of around 1.3 hours. No accumulation was observed. The mean value of bilastine oral bioavailability is 61%.

The SmPC of the reference product recommends administration one hour before or two hours after intake of food or fruit juice.

Linearity: Bilastine presents linear pharmacokinetics in the dose range studied (5 to 220 mg), with a low interindividual variability.

Elimination: The mean elimination half-life calculated in healthy volunteers was 14.5 h.

Study 0153-18

Methods

This was a single-dose, two-way crossover study conducted in 62 healthy volunteers (60 completed), comparing Bilastin Teva, 20 mg, tablet with BITOSEN, 20 mg, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of bilastine were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 25 July 2019 and 05 August 2019.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for bilastine, n=60.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1553.8 ± 474.2**	**261.5 ± 107.8**	**1.500 (0.500 -6.017)**
Reference	**1588.0 ± 499.2**	**264.7 ± 113.7**	**1.333 (0.667 -6.000)**
***Ratio (90% CI)**	**98.6 (93.69 -103.72)**	**99.9 (91.43 -109.23)**	**-**

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 plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Bilastin Teva is considered bioequivalent with BITOSEN.

IV.2 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.

IV.3 Risk Management Plan

The MAHs have submitted a risk management plan, Bilastin Teva, RMP v.1.0 (18 January 2021), 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 the applied product containing bilastine.

Safety specification

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• Use in pregnancy and breastfeeding • Use in children below 12 years of age

The table of Summary of safety concerns in the submitted RMP is acceptable.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. 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. Layout: making reference to Capecitabin Tiefenbacher DCP, FR/H/0589/001-002/DC (former BE/H/0196/01-02/DC). Content: BILAXTEN NAP, PL 16239/0034.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Bilastin Teva is found adequate. There are no objections to approval of Bilastin Teva from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Bilastin Teva was positively finalised on 2021-03-18.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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