COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Butylscopolamine bromide RIA 10 mg film-coated tablets (hyoscine butylbromide)

NL License RVG: 129760

Date: 3 April 2023

This module reflects the scientific discussion for the approval of Butylscopolamine bromide RIA 10 mg film-coated tablets. The procedure was finalised on 28 September 2022. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Butylscopolamine bromide RIA 10 mg film-coated tablets, from RIA Generics Limited.

The product is indicated for treatment of spasms of the gastrointestinal tract.

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

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this national procedure, essential similarity is proven between the new product and the innovator product Buscopan 10 mg, coated tablets (RVG 03834), registered in the Netherlands by the National Procedure (EU/1/11/699) on 20 May 1990 by Boehringer Ingelheim BV, the Netherlands. The current MAH of Buscopan is Genzyme Europe B.V., the Netherlands.

II. QUALITY ASPECTS

II.1 Introduction

Butylscopolamine bromide RIA is a white, round biconvex film-coated tablet, plain on both sides. Each tablet contains as active substance 10 mg of butylscopolamine bromide.

The excipients are:
Tablet core – lactose monohydrate, microcrystalline cellulose (E460), sodium starch glycollate (type A), magnesium stearate (E470b), talc (E553b) and tartaric acid (E344).
Tablet coating – Opadry II white (85F28751), consisting of polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol/PEG (E1521) and talc (E553b).

The tablets are packed in PVC/PVdC blisters with a backing of aluminium foil.

II.2 Drug Substance

The active substance is hyoscine butylbromide (also known as scopolamine butylbromide), an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder and is very soluble in water. The active substance has several chiral centres and a specification for specific optical rotation is added to the drug substance specification. The MAH demonstrated that the polymorphic form is stable during storage of the substance and product.

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 Ph.Eur.

Manufacturing process

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

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the CEP and of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for four batches; three were analysed by the supplier and one batch was analysed by the MAH.

Stability of drug substance

The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

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. Adequate information has been provided on the excipients and their compatibility with hyoscine butylbromide. No increase in impurities or decrease in assay were observed in the compatibility study. A bioequivalence study is performed. The production scaled batch used in this study was compared with the reference product and tested for dissolution at pH 1.0, 4.5 and 6.8. The difference in dissolution between the test and reference product is considered to be caused by the sugar-coating of the reference product while the test product is film-coated with an Opadry coating. As the drug product is an immediate release product, the difference in dissolution is not considered an issue since the test product dissolves faster than the reference product. The choice of packaging is justified in relation to the innovator.

Manufacturing process

The manufacturing process is a standard process and has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for one full scale and two pilot scale batches in accordance with the relevant European guidelines. Process validation for two additional full-scale batches will be performed post authorisation. The tablets are made by sifting of the raw materials, followed by co-sifting, blending, lubrication, compression, coating and packaging.

Control of excipients
The excipients (except the Opadry coating) comply with Ph.Eur. requirements with some additional functionality related characteristics. The in-house specification for the Opadry coating and the Ph.Eur. 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, uniformity of weight, water content, dissolution, related substances, assay, uniformity of dosage units and microbial limit. The release and shelf life limits are identical except for the related substances. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from one full scale and two pilot scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided on two pilot scale batches and one production scale batch stored at 25°C/60%RH (24 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 PVC/ PVDC blisters with a backing of aluminium foil. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. All test results are within the specification limits. The proposed shelf-life of 24 months and the storage condition “This medicinal product does not require any special storage conditions” are acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
TSE / BSE risk free certificates from the drug substance manufacturer and the excipient manufacturers have 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 MEB considers that Butylscopolamine bromide RIA has 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 Butylscopolamine bromide RIA 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 Buscopan, 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 MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Hyoscine butylbromide is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The MEB agreed that no further clinical studies are required, besides the two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Butylscopolamine bromide RIA 10 mg film-coated tablets, (RIA Generics Limited, Ireland) was compared with the pharmacokinetic profile of the reference product Buscopan 10 mg, coated tablets (Genzyme Europe B.V., the Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Bioequivalence studies

Study 1 – single dose, fed, 10 mg

This study was performed under fed conditions, whereas only a study under fasted conditions is needed according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), because hyoscine can be taken regardless of food intake. This study was considered to be supportive.

Study 2 – single dose, fasting, 20 mg

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 35 - 49 years. Each subject received a single dose (2 x 10 mg) of one of the two hyoscine butylbromide formulations. The dose used was 20 mg to facilitate precise measurements; in study 1 (10 mg) the maximum plasma concentrations were close to 10x the lower limit of measurement. Therefore the dose of 2 x 10 mg was considered appropriate. The tablets were orally administered with 240 mL water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.3, 1.7, 2, 2.3, 2.7, 3, 3.5, 4, 5, 6, 8, 10, 12, 24 and 48 hours after administration of the products.

The design of the study is acceptable. Hyoscine may be taken regardless of food intake.

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.

Results

Two subjects withdrew in the second period. A total of 26 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of hyoscine butylbromide, 20 mg, under fasted conditions.

Treatment N=26	**AUC_{0-t}** (pg.h/mL)	**$AUC_{0-\infty}$** (pg.h/mL)	**C_{max}** (pg/mL)	**t_{max}** (h)
Test	1299 ± 74.2	1479 ± 68.0	184.6 ± 60.8	3.5 (0.5 - 6.0)
Reference	1303 ± 77.2	1475 ± 70.0	193.2 ± 64.8	3.5 (0.5 - 6.0)
***Ratio (90% CI)**	1.00 (0.94 - 1.06)	1.00 0.95 - 1.06)	0.96 (0.90 - 1.02)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25 under both fasting and fed conditions. Based on the submitted bioequivalence studies, Butylscopolamine bromide RIA is considered bioequivalent with Buscopan.

The MEB has been assured that the bioequivalence studies have 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 Butylscopolamine bromide RIA.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The MEB 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 Buscopan. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Buscopan 10 mg tablets for content and Carbimazole 5 mg and 20 mg tablets for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Butylscopolamine bromide RIA 10 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Buscopan 10 mg tablets. Buscopan 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 Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Butylscopolamine bromide RIA with the reference product, and have therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 28 September 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-