IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Benylin Sore Throat Relief Berry Flavour 8 mg Compressed Lozenge
Benzocaine
PA0330/058/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Benylin Sore Throat Relief Berry Flavour 8 mg Compressed Lozenge, from Johnson & Johnson (Ireland) Ltd. on 8th April 2022 for the treatment of short-term symptomatic relief of pain and discomfort in acute sore throat. The product is indicated for use in adults and patients over the age of 16 years.

This is a decentralised application for a Marketing Authorisation for Benylin Sore Throat Relief 8mg Compressed Lozenge, submitted under Article 8.3 'mixed application' of Directive 2001/83/EC, as amended.

With IE acting as RMS in this Decentralised Procedure, Johnson & Johnson Consumer Service EAME Limited is applying for the Marketing Authorisation for Benylin Sore Throat Relief 8mg Compressed Lozenge in FI MT SE and UK(NI).

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Benylin Sore Throat Relief Berry Flavour 8 mg Compressed Lozenge
Name(s) of the active substance(s) (INN)	Benzocaine
Pharmacotherapeutic classification (ATC code)	R02AD01
Pharmaceutical form and strength(s)	Compressed Lozenge
Marketing Authorisation Number(s) in Ireland (PA)	PA0330/058/002
Marketing Authorisation Holder	Johnson & Johnson (Ireland) Limited
MRP/DCP No.	IE/H/0935/002/DC
Reference Member State	IE
Concerned Member State	FI MT SE XI

II. QUALITY ASPECTS

II.1. Introduction

This application is for Benylin Sore Throat Relief Berry Flavour 8mg Compressed Lozenge

II.2 Drug substance

The active substance is benzocaine, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The medicinal product contains 8 mg of benzocaine.
The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Benylin Sore Throat Relief Berry Flavour 8mg Compressed Lozenge.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Benylin Painful Sore Throat Relief Berry is a compressed lozenge formulation containing 8 mg benzocaine. The applicant has provided a mixed dossier for this well-known active substance consisting of bibliographic nonclinical data, which is acceptable. In general, the GLP status of published studies referenced in support of this application cannot be verified.

III.2 Pharmacology

In vitro studies on the pharmacodynamics (PD) of benzocaine are reported from a number of literature sources. Voltage clamp experiments conducted in the 1980s first demonstrated the mechanism of action of benzocaine via the inactivation of sodium channels. The applicant also referenced studies using burn models to demonstrate the anaesthetic activity of locally-applied benzocaine in rabbits and guinea pigs. Although brief, the primary PD section is considered adequate as the clinical pharmacology of benzocaine is well-established. No safety pharmacology studies have been conducted with the product. This is acceptable due to the well-established clinical profile.

The applicant has presented a literature overview of the known pharmacology of benzocaine. While the data on local administration in the throat is not available, and safety pharmacology assessment is lacking, the well-established clinical data with benzocaine supersedes nonclinical data and further nonclinical investigation would not be beneficial to this application. This is acceptable in line with the *Guideline on the Non-clinical Documentation for Mixed Marketing Authorisation Applications* (CPMP/SWP/799/95).

III.3 Pharmacokinetics

The applicant has presented a limited literature overview of the pharmacokinetics of benzocaine in nonclinical species. Studies with oral administration are most relevant to the proposed clinical administration. Benzocaine appears to be rapidly absorbed and eliminated following oral administration. No metabolic studies of benzocaine have been reported. Although the pharmacokinetic assessment in nonclinical species is lacking, the well-established clinical use of oral benzocaine negates the need for further nonclinical investigation in line with the *Guideline on the Non-clinical Documentation for Mixed Marketing Authorisation Applications* (CPMP/SWP/799/95).

III.4 Toxicology

The toxicology package presented by the applicant is entirely supported by bibliographic data. In general, the GLP compliance of referenced studies cannot be established. Single dose toxicity indicates that oral exposure in rodents is associated with moderate toxicity at doses significantly in access of the proposed clinical dose. Methemoglobinemia has been identified in nonclinical species and humans, which is noted in relevant sections of the SmPC. Repeat-dose studies with benzocaine administration are lacking in the literature. PABA, a significant metabolite of benzocaine was investigated in repeat-dose studies and toxicity was limited to doses far in excess of clinical exposure. In terms of genotoxicity, a published study on GLP-compliant *in vitro* and *in vivo* studies with benzocaine did not reveal any genotoxic potential. No carcinogenicity studies were available for benzocaine and considered not necessary due to the well-established clinical use, absence of carcinogenic signal clinically and the short-use duration of benzocaine lozenges. This is supported. The carcinogenic potential of PABA was investigated in mice with no evidence of carcinogenic potential. Data on reproductive and developmental toxicity with benzocaine is lacking. Again, the applicant considers the absence of this data is justified in the context of well-established clinical use, and rapid elimination kinetics. This is supported. Direct PABA exposure was associated with higher foetal resorption in one rat study. However, this was noted at doses in excess of the clinical dose and thus considered to be of no clinical relevance. A review of local tolerance studies was provided, including oral mucosal irritation. Immunotoxicity is unlikely in the proposed indication. A review of excipients was also provided and no safety issues are likely when the product is used as directed.

In summary, the toxicology package is considered adequate to support this application in line with the *Guideline on the Non-clinical Documentation for Mixed Marketing Authorisation Applications* (CPMP/SWP/799/95).

III.5 Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (INN/Invented Name): Benzocaine					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	Empirical	1.86			Potential PBT – No on basis of reported logkow
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surface\ water}$, default Fpen	0.24	mg/L			> 0.01 threshold Y
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					

Study type	Test protocol	Results			Remarks
Adsorption-Desorption	Empirical evidence	K_{oc} =3.2-3.6			Values for methyl and propyl esters of p-aminobenzoic acid-- expected similar behaviour to the ethyl ester benzocaine
Ready Biodegradability Test	Empirical evidence	No empirical data of benzocaine biodegradability in nature			Alkyl esters of p-aminobenzoic acid biodegrade rapidly in presence of microorganisms, benzocaine expected to react similarly
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = no data $DT_{50, sediment}$ = no data $DT_{50, whole\ system}$ = no data % shifting to sediment =			No empirical data however likely benzocaine is readily biodegradable, thus test not necessary.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	QSAR- ECOSAR	NOEC	3.65	mg/L	Lowest toxicity value in chronic studies (no species specified) range 3.65-18.26 (n=3)
Daphnia sp. Reproduction Test	QSAR- ECOSAR	NOEC	0.022	mg/L	Lowest toxicity value in chronic studies (no species specified) range 0.022-40.05
Fish, Early Life Stage Toxicity Test/*Species*	QSAR-ECOSAR	NOEC	0.158	mg/L	Lowest toxicity value in chronic studies (no species specified) range 0.158-17.45 (n=4)
Activated Sludge, Respiration Inhibition Test	Empirical data	NOEC	10	mg/L	
Phase IIb Studies					
Sediment dwelling organism		NOEC	0.12	mg/kg	A screening-level assessment conducted to characterize potential risk as water sediment study not available

Considering the above data, benzocaine is not expected to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects

Benzocaine is a widely used and well-known active substance and its pharmacodynamic, pharmacokinetic and toxicological properties are established. The information provided by the applicant is sufficient to support this MAA from a nonclinical perspective.

IV. CLINICAL ASPECTS

IV.1 Introduction

Benzocaine has been in clinical use as a local anaesthetic for many years.
Benzocaine is considered to be a well-known active substance with established efficacy and tolerability.

Benzocaine, ATC code:R02AD0, the active substance, is an ester-derived topical aesthetic, which produces local pain relief by blocking sodium channels on terminal nerve endings present on epithelial surfaces. It reversibly blocks the generation and transmission of impulses along nerve fibres and at nerve endings. It decreases flux of sodium and potassium ions through their channels in the axonal membranes, thereby preventing depolarization and propagation of nerve impulses.

An acceptable risk management plan has been agreed during the procedure. This describes the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Benylin Sore Throat Relief 8 mg Compressed Lozenge.
Routine pharmacovigilance and routine risk minimisation activities are considered sufficient.

With regard to Periodic Safety Update Report (PSUR) submission, PSURs will be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

The content of the SmPC approved during the decentralised procedure is considered to be generally in accordance with that accepted for the active substance benzocaine in the European market and reflects the data submitted with this application.

One pivotal clinical study was submitted in support of this application.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the clinical study which was conducted and submitted in support of this application.

IV.2 Pharmacokinetics

No new pharmacokinetic studies have been provided with this application.

Absorption
Benzocaine is well absorbed from mucous membranes but poorly absorbed through intact skin.

Distribution
There is no information available regarding the distribution of benzocaine in humans.

Biotransformation
Benzocaine is metabolized in the liver by hepatic and plasma cholinesterase.

Elimination
Benzocaine and its main metabolite, para-aminobenzoic acid, are mainly excreted in the urine. A small amount of benzocaine is excreted unchanged by the kidneys.

IV.3 Pharmacodynamics

No new pharmacodynamic studies have been provided with this application.
The pharmacodynamic profile of benzocaine is well known; therefore, no new data have been submitted. This is accepted.

IV.4 Clinical Efficacy

The toxicology, pharmacokinetic and pharmacodynamic properties, efficacy and safety profiles of benzocaine are well established over many years of use in the acute sore throat indication in adults.

In the context of this 'mixed' application, (Article 8(3) of Directive 2001/83/EC as amended), the Applicant has provided one new placebo-controlled clinical study which was conducted in n=260 adults with acute sore throat due to upper respiratory tract infection, across 18 sites in Russia in 2018.

This was a multi-centre, double-blind, randomized, parallel-group, placebo-controlled study to determine the efficacy and safety of an 8 mg film-coated compressed benzocaine lozenge for symptomatic treatment of sore throat caused by acute upper respiratory tract infection in adults.

The purpose of this study was to support the efficacy and safety of benzocaine 8 mg lozenge for a planned Marketing Authorisation Application (MAA) for symptomatic treatment of sore throat caused by acute upper respiratory tract infection in adults.

In order to provide data on the proposed benzocaine 8mg lozenge, efficacy data was collected over a 3-hour period after a single dose of investigational product in over 200 patients under observation.
Clinical data was also collected over the following 4 days while the dosing of investigational product was continued by the patient at home.
Safety data was also generated from the clinical study and no new safety concerns were identified.

From a clinical efficacy perspective the overall assessment of data provided from the pivotal clinical study of Benylin Sore Throat Relief Berry Flavour 8 mg Compressed Lozenge in the treatment of acute sore throat in adults is favourable.

By way of supporting data, the Applicant also discussed the established safety and efficacy profile of benzocaine lozenges in the treatment of acute sore throat from the available literature or bibliographic data.

The Applicant also presented preliminary dissolution data relating to the proposed product and an authorised EU product, which has been authorised for more than 10 years in the EU.
The product used in the dissolution studies provided in support of this application is Anaesthesin-Pastillen, 8 mg lozenge, Novartis Consumer Health GmbH, München (ERP, DE 6001844.00.00), licensed in Germany since 1961. The product is not currently licensed in the RMS.

From a clinical efficacy perspective, the totality of the data provided with this application is acceptable and the overall efficacy assessment of Benylin Sore Throat Relief Berry Flavour 8 mg Compressed Lozenge is favourable.

The agreed indication wording and the posology recommendations provided in the product information reflect the available data submitted with the application.

The agreed indication for use of Benylin Sore Throat Relief Berry Flavour 8 mg Compressed Lozenge is outlined as follows:
This medicine is indicated for the short-term symptomatic relief of pain and discomfort in acute sore throat. It is indicated in adults and adolescents 16 years and over.

Posology and method of administration for Benylin Sore Throat Relief Berry Flavour 8 mg Compressed Lozenge

Adults and Children 16 years and over:

1 lozenge to be dissolved slowly in the mouth no more frequently than every two hours.
Do not exceed 6 lozenges in 24 hours.

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms.

Do not use for more than 3 days without seeking prior medical advice.

Children under 16 years

For use in adults and adolescents 16 years and over. Do not use in children under 16 years

IV.5 Clinical Safety

Benzocaine has been in clinical use as a local anaesthetic in the treatment of acute sore throat for many years.

The safety profile is considered to be well characterised and relevant warnings and precautions are reflected in the product information.

Overall, the content of the SmPC, PL and label approved during this decentralised procedure is considered to be generally in accordance with that accepted for the active substance benzocaine in the European market.

In addition, safety data was collected in the pivotal clinical trial submitted with the application.
Limited safety data was generated from the clinical study and no new safety concerns were identified.

The applicant will continue to monitor the safety of Benylin Sore Throat Relief 8 mg Compressed Lozenge through routine pharmacovigilance, which is endorsed.

Risk Management Plan
The applicant 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 Benylin Sore Throat Relief 8 mg Compressed Lozenge

The RMP (version 1.3, signed 10/12/2021) is acceptable. Routine pharmacovigilance and routine risk minimisation activities are considered sufficient.

The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	None
Missing Information	None

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

1. PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
2. For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
3. In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

This is a decentralised application for a Marketing Authorisation for Benylin Sore Throat Relief 8mg Compressed Lozenge, submitted under Article 8.3 'mixed application' of Directive 2001/83/EC, as amended.

Benylin Sore Throat Relief Berry Flavour 8 mg Compressed Lozenge, from Johnson & Johnson (Ireland) is indicated for the treatment of short-term symptomatic relief of pain and discomfort in acute sore throat.
The product is indicated for use in adults and patients over the age of 16 years.

Benzocaine is a widely used and well-known active substance with an established efficacy and safety profile.
The toxicology, pharmacokinetic and pharmacodynamic properties, efficacy and safety profiles of benzocaine are well established over many years of use in the acute sore throat indication in adults.

In support of this application, the Applicant submitted one pivotal clinical study.
This was a multi-centre, double-blind, randomized, parallel-group, placebo-controlled study to determine the efficacy and safety of an 8 mg film-coated compressed benzocaine lozenge for symptomatic treatment of sore throat caused by acute upper respiratory tract infection in adults.

The purpose of this study was to support the efficacy and safety of benzocaine 8 mg lozenge for a planned Marketing Authorisation Application (MAA) for symptomatic treatment of sore throat caused by acute upper respiratory tract infection in adults.

Additional supporting data was provided in a Clinical Overview which discussed the available bibliographic data to further support the established clinical efficacy and safety aspects of benzocaine lozenges. The submitted Clinical Overview includes a satisfactory review of relevant literature to discuss the pharmacodynamics, pharmacokinetics, efficacy and safety of Benzocaine.

Also in support of this application, the Applicant provided supporting data from the benzocaine lozenge development in the form of preliminary dissolution data against an approved EU benzocaine lozenge product (Anaesthesin-Pastillen authorised to Novartis Consumer Health GmbH).

The content of the SmPC and product labelling agreed during the decentralised procedure is considered to be generally in accordance with that accepted for the active substance benzocaine in the European market and reflects the available data.

The Applicant will continue to monitor the safety of Benylin Sore Throat Relief 8 mg Compressed Lozenge through routine pharmacovigilance, which is endorsed.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

A risk management plan has been provided which describes the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Benylin Sore Throat Relief 8 mg Compressed Lozenge.
Routine pharmacovigilance and routine risk minimisation activities are considered sufficient.

With regard to Periodic Safety Update Report (PSUR) submission, PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

From a clinical efficacy and safety perspective the overall assessment of Benylin Sore Throat Relief Berry Flavour 8 mg Compressed Lozenge is favourable.

V. OVERALL CONCLUSIONS

From a quality perspective the overall assessment of Benylin Sore Throat Relief Berry Flavour 8 mg Compressed Lozenge is favourable.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that Benylin Sore Throat Relief Berry Flavour 8 mg Compressed Lozenge demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

10.02.2027