Public Assessment Report

Oroeze/Benzydamine 0.15% w/v Mouthwash

(benzydamine hydrochloride)

PL 20046/0048

Focus Pharmaceuticals Ltd

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY
Oroeze/Benzydamine 0.15% w/v Mouthwash (benzydamine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Oroeze/Benzydamine 0.15% w/v Mouthwash (PL 20046/0048). It explains how Oroeze/Benzydamine 0.15% w/v Mouthwash was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Oroeze/Benzydamine 0.15% w/v Mouthwash.

For practical information about using Oroeze/Benzydamine 0.15% w/v Mouthwash, patients should read the package leaflet or contact their doctor or pharmacist.

What is Oroeze/Benzydamine 0.15% w/v Mouthwash and what is it used for?
Oroeze/Benzydamine 0.15% w/v Mouthwash is a 'hybrid generic medicine'. This means that it is similar to a reference medicine (Difflam™ Oral Rinse, Valeant Pharmaceuticals Ltd) containing the same active substance, but differs in the choice of the flavourings used.

Oroeze/Benzydamine 0.15% w/v Mouthwash used to treat many painful conditions affecting the throat or mouth, including sore throat, sore tongue or gums, mouth ulcers, discomfort caused by dentures and pain after dental surgery.

How does Oroeze/Benzydamine 0.15% w/v Mouthwash work?
Oroeze/Benzydamine 0.15% w/v Mouthwash contains a substance called benzydamine hydrochloride which belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). This medicine works by stopping the formation of prostaglandins. Prostaglandins are natural substances made by the body when it is injured or has an infection, and causes an increase in the blood supply to the area of injury or infection.

How is Oroeze/Benzydamine 0.15% w/v Mouthwash used?
Oroeze/Benzydamine 0.15% w/v Mouthwash is for use in the throat or mouth.

The usual dose in adults including the elderly is 15 ml every 1½ to 3 hours. This mouthwash is not recommended for use in children aged 12 years or under.

Oroeze/Benzydamine 0.15% w/v Mouthwash can be obtained from a pharmacy.

For further information on how Oroeze/Benzydamine 0.15% w/v Mouthwash is used, please see the Summary of Product Characteristics or the package leaflet available on the MHRA website.

What benefits of Oroeze/Benzydamine 0.15% w/v Mouthwash have been shown in studies?
Because Oroeze/Benzydamine 0.15% w/v Mouthwash is a hybrid application and is considered to be therapeutically equivalent, to the reference product (Difflam™ Oral

Rinse, Valeant Pharmaceuticals Ltd), its benefits and risks are taken as being the same as those of the reference medicine (Difflam™ Oral Rinse).

What are the possible side effects from Oroeze/Benzydamine 0.15% w/v Mouthwash?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Oroeze/Benzydamine 0.15% w/v Mouthwash, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why is Oroeze/Benzydamine 0.15% w/v Mouthwash approved?
It was considered that the benefits of using Oroeze/Benzydamine 0.15% w/v Mouthwash to treat many painful conditions affecting the throat or mouth, outweighs the risks; and the grant of a Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Oroeze/Benzydamine 0.15% w/v Mouthwash?
A satisfactory pharmacovigilance system has been provided to monitor the safety of this product. The safety information has been included in the Summary of Product Characteristics and the package leaflet for Oroeze/Benzydamine 0.15% w/v Mouthwash, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Oroeze/Benzydamine 0.15% w/v Mouthwash
A Marketing Authorisation was granted in the UK on 19th June 2012.
For more information about using Oroeze/Benzydamine 0.15% w/v Mouthwash, read the package leaflet, or contact your doctor or pharmacist.

The full PAR for Oroeze/Benzydamine 0.15% w/v Mouthwash follows this summary.

This summary was last updated in February 2015.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Focus Pharmaceuticals Limited a Marketing Authorisation for the medicinal product, Oroeze/Benzydamine 0.15% w/v Mouthwash (PL 20046/0048) on 19 June 2012. The product is a pharmacy (P) licensed medicine.

This is an abridged application for Oroeze/Benzydamine 0.15% w/v Mouthwash, submitted under Article 10(3) of Directive 2001/83 EC, as amended. This hybrid application makes reference to the UK product, Difflam™ Oral Rinse (PL 19166/0071), authorised to Valeant Pharmaceuticals Ltd on 13 October 2007. The cross-referenced product was originally licensed to 3M Health Care Limited (PL 00068/0096) on 11 June 1981; this Marketing Authorisation underwent a Change of Ownership (CoA) procedure to the current Valeant Pharmaceuticals Ltd licence. The reference product has been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired.

Oroeze/Benzydamine 0.15% w/v Mouthwash is indicated in adults and children aged 13 years and over. It is a locally acting analgesic and anti-inflammatory treatment for the relief of painful inflammatory conditions of the mouth and throat including:

- Traumatic conditions: pharyngitis following tonsillectomy or the use of a naso-gastric tube.
- Inflammatory conditions: pharyngitis, aphthous ulcers and oral ulceration due to radiation therapy.
- Dentistry: for use after dental operations.

Benzydamine exerts an anti-inflammatory and analgesic action by stabilising the cellular membrane and inhibiting prostaglandin synthesis.

Oral doses of benzydamine are well absorbed and plasma drug concentrations reach a peak fairly rapidly and then decline with a half-life of about 13 hours. Less than 20% of the drug is bound to plasma proteins.

No new non-clinical or clinical efficacy studies were conducted for this application, which is acceptable given that the application cross-refers to a product that has been licensed for over 10 years. Bioequivalence studies are not necessary to support this application for a locally-acting mouthwash solution.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

The MHRA considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a detailed Risk Management Plan (RMP). As the application refers to an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well-established.

II QUALITY ASPECTS

II.1 Introduction

Oroeze/Benzydamine 0.15% w/v Mouthwash is presented as a clear green solution with an odour of peppermint. Each 15 ml dose contains 22.5 mg of benzydamine hydrochloride.

Other ingredients consist of pharmaceutical excipients, namely glycerol, ethanol (96%), methyl parahydroxybenzoate, saccharin sodium, polysorbate 20, quinoline yellow (E104), patent blue V (E131), peppermint flavour (contains propylene glycol), aniseed flavour (contains ethanol 95%) and purified water. Appropriate justification for the inclusion of each excipient has been provided.

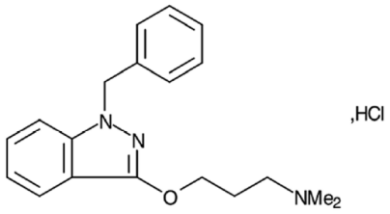
All excipients comply with their respective European Pharmacopoeia (Ph. Eur) monographs with the exception of peppermint flavour and aniseed flavour, which comply with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product. None of the excipients are sourced from genetically modified organisms. There were no novel excipients used.

II.2 Drug Substance

INN:	Benzydamine hydrochloride
Chemical names:	3-(1-benzylindazol-3-yloxy)propyldimethylamine hydrochloride

Structure:



Molecular formula:	$C_{19}H_{23}N_3O$, HCl
Molecular weight:	345.9 g/mol
CAS No:	132-69-4
Physical form:	A white crystalline powder
Solubility:	Very soluble in water; freely soluble in ethanol (96%); practically insoluble in ether

The active substance, benzydamine hydrochloride, is the subject of a British Pharmacopoeia (BP) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by Certificates of Analysis.

Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analyses data are provided that comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph. Eur. requirements and satisfies Directive 2002/72/EC (as amended); it is suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and an appropriate retest period has been applied.

II.3 Medicinal Product

Pharmaceutical development

Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The aim was to develop a stable medicinal product containing benzydamine hydrochloride 0.15% w/v, pharmaceutically equivalent to the reference product, Difflam™ Oral Rinse (Valeant Pharmaceuticals Ltd).

Manufacture

A description and flow-chart of the manufacturing method have been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies were conducted and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process. A commitment has been made by the Marketing Authorisation holder (MAH) that full process validation will be conducted on commercial scale batches in accordance with the process validation protocol.

Finished product specification

Finished product specifications are provided for release and shelf-life that are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. The test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

Oroeze/Benzydamine 0.15% w/v Mouthwash is supplied in clear, type III, glass bottles with child-resistant, tamper-evident caps, containing 300 ml of mouthwash. The bottles are packaged, with a measuring cup and product information leaflet, into cardboard outer cartons.

Specifications and Certificates of Analysis for all packaging components used have been provided and are satisfactory. The bottles satisfy Directive 2002/72/EC (as amended), and are suitable for contact with oral preparations.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support the applied shelf-life of 3 years, with the storage instruction 'Do not store above 25°C'. The mouthwash should be used within 6 months of opening the bottle.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The proposed product has been shown to be equivalent to the reference product, Difflam™ Oral Rinse (Valeant Pharmaceuticals Ltd), with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test product is pharmaceutically equivalent to the reference product, which has been licensed in the EU for over 10 years.

All pharmaceutical issues have been resolved and the quality of this application is considered adequate. There are no objections to approval of Oroeze/Benzydamine 0.15% w/v Mouthwash from a pharmaceutical point of view.

The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

This application, submitted under Article 10(3) of Directive 2001/83/EC, as amended, is for Oroeze/Benzydamine 0.15% w/v Mouthwash, claiming to be equivalent to the UK reference product, Difflam™ Oral Rinse (Valeant Pharmaceuticals Ltd).

No new non-clinical data have been supplied with this application and none are required for applications of this type.

A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the expert has been supplied.

III.2 Pharmacology

No new data have been submitted and none are required for applications of this type.

III.3 Pharmacokinetics

No new data have been submitted and none are required for applications of this type.

III.4 Toxicology

No new data have been submitted and none are required for applications of this type.

III.5 Ecotoxicity/environmental risk assessment (ERA)

The MAH has provided adequate justification for not submitting a detailed Environmental Risk Assessment (ERA). The reference product, Difflam™ Oral Rinse, and other benzydamine hydrochloride based products, have been available on the European market for over 20 years. There is no reason to conclude that marketing of this product will change the overall use pattern of the existing market. The excipients used in the product formulation are commonly used pharmaceutical ingredients. There are no environmental concerns associated with the method of manufacture or formulation of the product.

III.6 Discussion on the non-clinical aspects

There are no objections to approval of Oroeze/Benzydamine 0.15% w/v Mouthwash from a non-clinical point of view.

IV CLINICAL ASPECTS

IV.1 Introduction

Benzydamine hydrochloride is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic, antipyretic and local anaesthetic activity. It is used both topically and systemically for the treatment of primary or more active types of inflammation.

IV.2 Pharmacology

The clinical pharmacology of benzydamine hydrochloride is well-known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application.

Benzydamine hydrochloride is poorly absorbed through non-specialised mucosa, thereby limiting systemic exposure to the drug when applied topically. Despite this, the clinical efficacy of benzydamine has been clearly demonstrated in patients with oral inflammation and pain. In the mouth, benzydamine adheres to the papillae of the tongue, the folds between the teeth, the surfaces under the tongue and to other oral tissues. It is then released over time from these locations into the saliva, rather than being systemically absorbed.

Pharmacokinetic conclusions

The proposed and reference formulations are oral solutions containing the same active ingredient concentrations, and a very similar excipient profile, differing qualitatively only in the choice of flavourings used. Furthermore these excipients are all widely used in pharmaceutical products and are not expected to have any pharmacological effects.

IV.3 Clinical efficacy

No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview. The efficacy of benzydamine hydrochloride is well-established from its extensive use in clinical practice.

Oroeze/Benzydamine 0.15% w/v Mouthwash is for local oromucosal use and contains the same active substance, in the same concentration, as the UK reference product, Difflam™ Oral Rinse (Valeant Pharmaceuticals Ltd). It does not contain excipients that may significantly affect gastrointestinal transit, absorption, *in vivo* solubility or *in vivo* stability of the active substance. For this mouthwash formulation, which isn't swallowed, activity arises directly from contact with the oral surfaces; there is no gastrointestinal transit aspect and no absorption step. Therefore, in accordance with the Bioequivalence Guideline (CPMP/EWP/QWP/1401/98 Rev 1**), the applicant is not required to submit a bioequivalence study.

IV.4 Clinical safety

No new data have been submitted and none are required for this type of application. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of benzydamine hydrochloride is well-known.

Publicly available spontaneous reporting data for benzydamine hydrochloride, incorporating all routes of administration, has been reviewed by the applicant, covering the period 1963 to 2009, that shows that benzydamine is well-tolerated.

CONCLUSION
Sufficient clinical information has been submitted to support this application. The benefit-risk of the product is considered favourable from a clinical perspective. The grant of a Marketing Authorisation was, therefore, recommended.

IV.5 Risk Management Plan (RMP)
The MAH has provided adequate justification for not submitting a detailed Risk Management Plan (RMP).

IV.6 Discussion on the clinical aspects
The grant of a Marketing Authorisation is recommended.

V. User consultation
The package leaflet has been evaluated for Oroeze/Benzydamine 0.15% w/v Mouthwash via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the *guideline on the readability of the label and package leaflet of medicinal products for human use.*

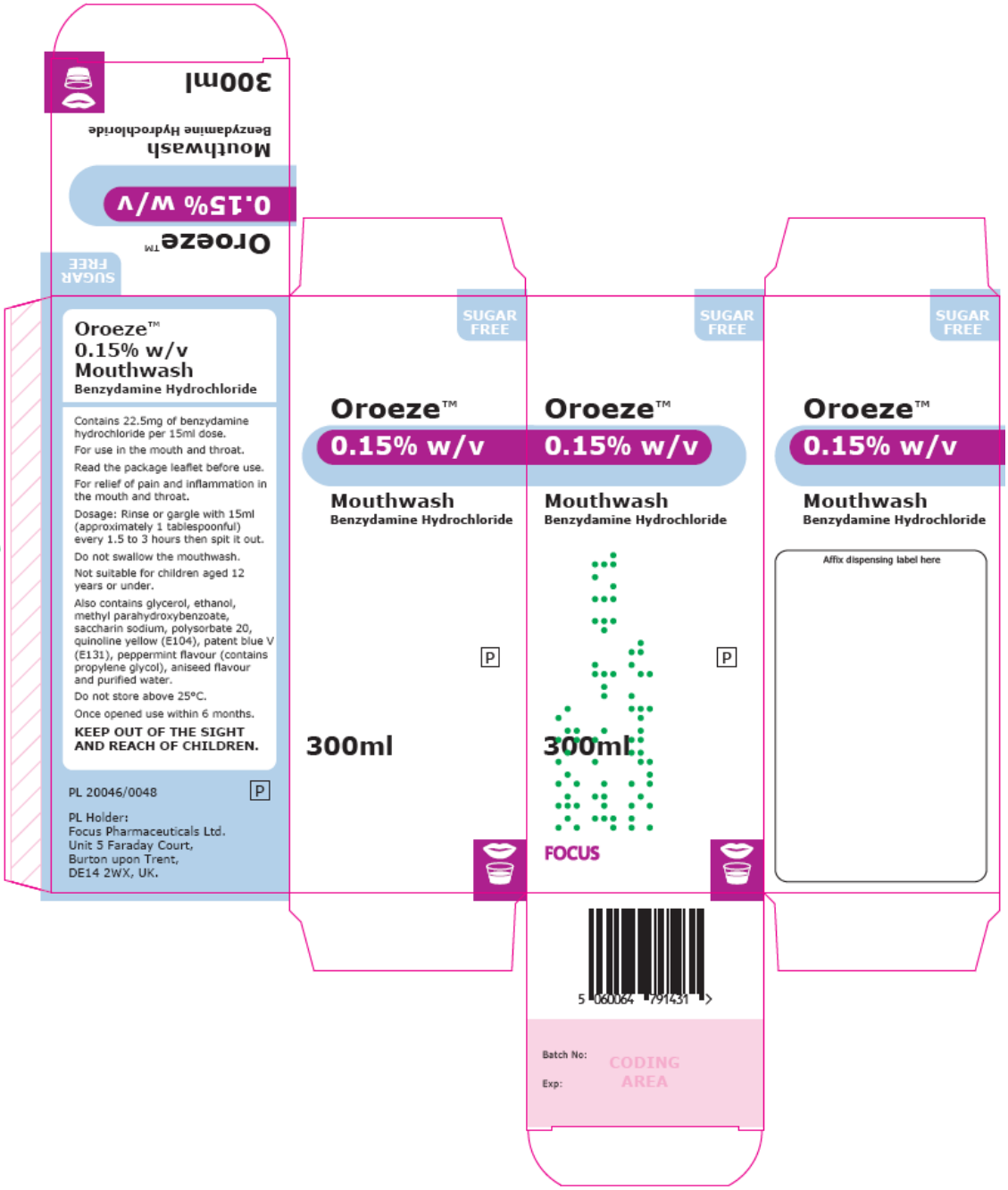
VI. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant's Oroeze/Benzydamine 0.15% w/v Mouthwash is a generic version of the reference product, Difflam™ Oral Rinse (Valeant Pharmaceuticals Ltd). Extensive clinical experience with benzydamine hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling

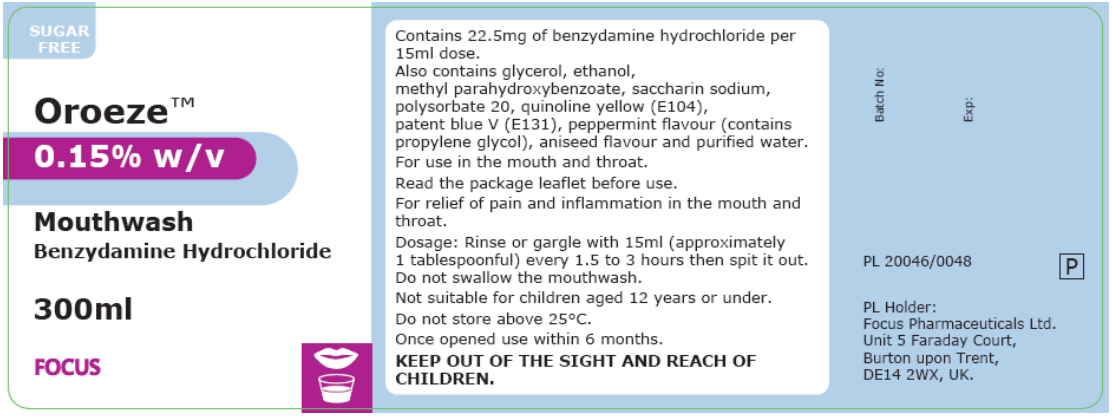
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

LABELLING

Brand labelling



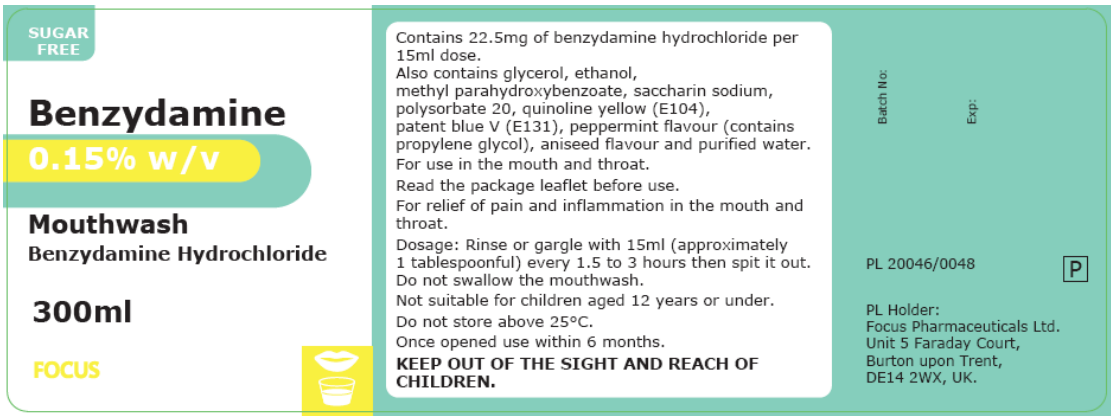
Bottle label



Braille

Generic labelling

Bottle label



Braille

Annex 1 - Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report

The following table lists some non-safety updates to the Marketing Authorisation for this product that has been approved by the MHRA since the product was first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

Date submitted	Application type	Scope	Outcome
02/12/2014	Type IB	To update the SmPC sections: 4.6, 4.8 and 4.9 for Oroeze/Benzydamine Mouthwash in line with the Brand Leader, Difflam Oral Rinse. As a consequence, the PIL has been updated.	Variation granted 15/01/2015

Reference: **PL 20046/0048 - application 0013**

Product: **Oroeze/Benzydamine 0.15% w/v Mouthwash**

MAH: **Focus Pharmaceuticals Limited**

Active Ingredient: **Benzydamine hydrochloride**

Reason:
To update the SmPC sections: 4.6, 4.8 and 4.9 for Oroeze/Benzydamine Mouthwash in line with the Brand Leader, Difflam Oral Rinse. As a consequence, the PIL has been updated.

Supporting evidence
The applicant has submitted updated sections of the SmPC and the leaflet.

Evaluation
The amended sections of the SmPC and the leaflet mock-up are satisfactory.

Conclusion
The variation was approved on 15th January 2015 and the updated SmPC fragments and the PIL have been incorporated into this Marketing Authorisation. The proposed changes are acceptable.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) Updated

Following approval of the variation on 15th January 2015 the SmPC was updated. In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

PATIENT INFORMATION LEAFLET (PIL) Updated

Following approval of the variation on 15th January 2015 the PIL was updated. In accordance with Directive 2010/84/EU the Patient Information Leaflet (PIL) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.