Public Assessment Report

National Procedure

Benzydamine 0.15% w/v Oromucosal Spray
(Benzydamine hydrochloride)

UK Licence No: PL 35104/0019

Phoenix Labs
LAY SUMMARY

Benzydamine 0.15% w/v Oromucosal Spray
(Benzydamine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Benzydamine 0.15% w/v Oromucosal Spray (PL 35104/0019). It explains how Benzydamine 0.15% w/v Oromucosal Spray 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 Benzydamine 0.15% w/v Oromucosal Spray.

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

The product may be referred to as ‘Benzydamine Oromucosal Spray’ in this Lay summary.

What is Benzydamine Oromucosal Spray and what is it used for?
Benzydamine Oromucosal Spray is a 'hybrid' medicine. This means that Benzydamine Oromucosal Spray contains the same active substance as, and is similar to, a reference medicine already authorised in the European Union (EU) called Tantum Verde, 1.5mg/ml Oromucosal Spray (Aziende Chimiche Riunite Angelini Francesco, ACRAF, S.p.A), which was approved in Poland on 13 October 1993. The corresponding reference product in the UK is Difflam 0.15% Spray (PL 15142/0046; Meda Pharmaceutical Limited, UK), which was approved in the UK on 23 March 2010 following a series of Change of Ownership (COA) Procedures of Difflam Spray (PL 00068/0112; 3M Health Care Limited), which was approved in the UK on 30 November 1984.

Benzydamine Oromucosal Spray is used to relieve the symptoms of painful conditions affecting the throat or mouth including:
- sore throat
- sore tongue or gums
- mouth ulcers
- discomfort caused by dentures or after dental work.

How does Benzydamine Oromucosal Spray work?
Benzydamine Oromucosal Spray contains the active substance, benzydamine hydrochloride, which belongs to a group of medicines called non-steroidal anti-inflammatory drugs or NSAIDS. Benzydamine hydrochloride works by stopping pain and swelling (inflammation).

How is Benzydamine Oromucosal Spray used?
Benzydamine Oromucosal Spray is sprayed onto the sore area of the mouth or throat.

The patient should always use Benzydamine Oromucosal Spray exactly as described in the package leaflet or as instructed by his/her doctor. The patient should check with his/her doctor or pharmacist if unsure.

The patient should avoid contact with the eyes. If any spray gets in the eyes, the eyes should be washed immediately with cold water.
How much Benzydamine Oromucosal Spray should be used?
**Recommended dosage:**
Adults including the elderly (and children over 12 years):
4 to 8 puffs every 1½ to 3 hours.

Children aged 6 to 12 years:
4 puffs every 1½ to 3 hours.

Children under 6 years of age:
1 puff for every 4 kilograms of body weight, up to maximum of 4 puffs, every 1½ to 3 hours.

Please read section 3 of the package leaflet for detailed information on how to use the spray, dosing recommendations, the route of administration, and the duration of treatment.

Benzydamine Oromucosal Spray can be obtained without a prescription.

**What benefits of Benzydamine Oromucosal Spray have been shown in studies?**
As Benzydamine Oromucosal Spray is a hybrid medicine, studies have been limited to tests to determine that it is therapeutically equivalent to the reference medicine, Tantum Verde, 1.5mg/ml Oromucosal Spray (Aziende Chimiche Riunite Angelini Francesco, ACRAF, S.p.A). Two medicines are therapeutically equivalent when they produce the same measure of therapeutic effect in the body.

**What are the benefits and risks of Benzydamine Oromucosal Spray?**
Because Benzydamine Oromucosal Spray is a hybrid medicine and is considered therapeutically equivalent to the reference medicine, its benefits and risks are taken as being the same as those of the reference medicine.

**What are the possible side effects from Benzydamine Oromucosal Spray?**
Like all medicines, Benzydamine Oromucosal Spray can cause side effects, although not everybody gets them.

Since Benzydamine Oromucosal Spray is a generic hybrid medicine, the benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of all side effects reported with Benzydamine Oromucosal Spray, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Benzydamine Oromucosal Spray.

**Why is Benzydamine Oromucosal Spray approved?**
It was concluded that, in accordance with EU requirements, Benzydamine Oromucosal Spray has been shown to have comparable quality and to be therapeutically equivalent to Tantum Verde, 1.5mg/ml Oromucosal Spray (Aziende Chimiche Riunite Angelini Francesco, ACRAF, S.p.A), and that the benefit outweighs the identified risk.

**What measures are being taken to ensure the safe and effective use of Benzydamine Oromucosal Spray?**
A Risk Management Plan has been developed to ensure that Benzydamine Oromucosal Spray is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Benzydamine Oromucosal Spray, including the appropriate precautions to be followed by healthcare professionals and patients.
Other information about Benzydamine Oromucosal Spray
A Marketing Authorisation was granted in the UK on 15 May 2017.

The full PAR for Benzydamine Oromucosal Spray follows this summary.

For more information about treatment with Benzydamine Oromucosal Spray, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2017.
SCIENTIFIC DISCUSSION

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Scientific discussion

I. INTRODUCTION
The Medicines and Healthcare products Regulatory Agency (MHRA) granted Phoenix Labs a Marketing Authorisation for the medicinal product Benzydamine 0.15% w/v Oromucosal Spray (PL 35104/0019) on 15 May 2017. The product will be referred to as Benzydamine Oromucosal Spray in this scientific discussion. The product is a Pharmacy (P) medicine indicated as an adjunct in the symptomatic relief of painful inflammatory conditions of the throat and mouth.

The application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. The reference medicinal product for this application is Tantum Verde, 1.5mg/ml Oromucosal Spray (Aziende Chimiche Riunite Angelini Francesco, ACRAF, S.p.A), which was approved in Poland on 13 October 1993. The corresponding reference product in the UK is Difflam 0.15% Spray (PL 15142/0046; Meda Pharmaceutical Limited, UK), which was approved in the UK on 23 March 2010 following a series of Change of Ownership (COA) Procedures of Difflam Spray (PL 00068/0112; 3M Health Care Limited), which was approved in the UK on 30 November 1984.

Benzydamine 0.15% w/v Oromucosal Spray contains the active ingredient, benzydamine hydrochloride, which is is a local analgesic and anti-inflammatory agent.

To support the application, the applicant submitted bibliographic data and a clinical comparative study, which is acceptable given that the application was based on the product being a hybrid application of an originator product that has been in clinical use for over 10 years.

With the exception of the clinical comparative study no new clinical data have been submitted and none are required for this type of application. In accordance with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), a bioequivalence study was not required to support this application for a locally-acting oromucosal aqueous product, containing the same active substance as the reference product.

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

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of Benzydamine Oromucosal Spray outweigh the risks and a Marketing Authorisation was granted.

II. QUALITY ASPECTS

II.1 Introduction
The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is an oromucosal spray presented as a metered dose pump spray solution.

Each 1 ml of the solution contains 1.5mg of benzydamine hydrochloride. Each puff (0.17 ml) contains 255 micrograms of benzydamine hydrochloride (0.15% w/v).
The product also contains pharmaceutical excipients namely glycerol, sodium saccharin, ethanol (96 per cent), sodium hydrogen carbonate, polysorbate 20, methyl parahydroxybenzoate (E218), fresh peppermint mouthwash flavour and purified water. Appropriate justification for the inclusion of each excipient has been provided.

Benzydamine 0.15% w/v Oromucosal Spray is presented in a box containing a 30 ml high density polyethylene (HDPE) bottle with a spray pump.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with foodstuff.

II.2 Drug substance

INN: Benzydamine hydrochloride
Chemical Name: 3-(1-benzylindazol-3-yl)oxy)propyl dimethylamine hydrochloride

Molecular formula: \( \text{C}_{19}\text{H}_{23}\text{N}_3\text{O},\text{HCl} \)

Structure:

Molecular mass: 345.9
Appearance: A white crystalline powder
Solubility: Very soluble in water, freely soluble in ethanol (96%), practically insoluble in ether.

Benzydamine hydrochloride is the subject of a European Pharmacopoeia 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 specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is 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 specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the pharmaceutical development programme was to produce a safe, efficacious oromucosal spray that was comparable in performance to the originator product, Tantum Verde, 1.5mg/ml Oromucosal Spray (Aziende Chimiche Riunite Angelini Francesco, ACRAF, S.p.A). Suitable pharmaceutical development data have been provided for this application.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of fresh peppermint mouthwash flavour, which is controlled to a suitable in-house specification. Certificates of Analysis have been provided for all excipients, showing compliance with their respective specifications.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full production-scale batches that have shown satisfactory results.

Control of Finished Product
The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data have been provided, which comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years for the unopened product and 6 months after first opening the container. The special storage instructions for the product are ‘Do not store above 25°C. Store in the original package.’

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section IV, Clinical Aspects.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for this application, from a quality point of view.

III. NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of benzydamine hydrochloride are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

### III.3 Pharmacokinetics
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

### III.4 Toxicology
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

### III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of already authorised product, it is not expected that environmental exposure of benzydamine hydrochloride will increase following approval of the Marketing Authorisation for the proposed product.

### III.6 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted, from a non-clinical point of view.

### IV. CLINICAL ASPECTS

#### IV.1 Introduction.
The clinical pharmacology of benzydamine hydrochloride is well-known. The proposed drug product is a locally acting oromucosal spray. Due to limited systemic bioavailability, bioequivalence is not considered suitable to show therapeutic equivalence for the proposed and the reference products. The applicant submitted bibliographic data and a comparative clinical study for the evaluation of efficacy and safety of the proposed product versus the reference product Tantum Verde, 1.5mg/ml Oromucosal Spray (Aziende Chimiche Riunite Angelini Francesco, ACRAF, S.p.A).

With the exception of data from the comparative study, no new clinical data are provided or required for this application.

#### IV.2 Pharmacokinetics
The clinical pharmacokinetic properties of benzydamine hydrochloride are well-known. No new pharmacokinetic data were submitted and none are required for this type of application.

#### IV.3 Pharmacodynamics
The clinical pharmacodynamic properties of benzydamine hydrochloride are well-known. No new pharmacodynamic data were submitted and none are required for this type of application.

#### IV.4 Efficacy
The efficacy of benzydamine hydrochloride is well-known. With the exception of the efficacy data generated during the comparative study, no efficacy data were submitted and none are required for this type of application.

#### IV.5 Safety
With the exception of the safety data generated during the comparative study, no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues arose during the comparative study.
IV.6 Risk Management Plan
The MAH has submitted a Risk Management Plan (RMP), 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 Benzydamine 0.15% w/v Oromucosal Spray.

A summary of safety concerns is listed in the table below:

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<th>Summary of safety concerns</th>
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<tr>
<td>Important identified risk</td>
<td>• Hypersensitivity reactions including bronchospasm, anaphylaxis, angioedema, pruritus, urticaria, photosensitivity reaction and rash</td>
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<td>Important potential risk</td>
<td>• Effects of long term exposure to low levels of alcohol in adults, during pregnancy and breastfeeding, and in children</td>
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<tr>
<td>Missing information</td>
<td>• None</td>
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Routine pharmacovigilance and risk minimisation activities are planned for all safety concerns which are considered acceptable.

IV.7 Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted, from a clinical point of view.

V. USER CONSULTATION
A package leaflet (Patient Information Leaflet and Information for Use) 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 language used for the purpose of user testing the pack leaflet 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, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
QUALITY
The important quality characteristics of Benzydamine Oromucosal Spray are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of benzydamine hydrochloride are well-known, no additional data were required.

EFFICACY
With the exception of the efficacy data generated during the comparative study, no efficacy data were submitted and none are required for this type of application.

SAFETY
With the exception of the safety data generated from the efficacy study, no new data were submitted and none are required for this type of application. As the safety profile of benzydamine hydrochloride is
well known, no additional safety data were required. No new or unexpected safety concerns arose from the comparative clinical study.

**PRODUCT LITERATURE**
The SmPC, PIL and labelling text is satisfactory and consistent with that for the reference product, where appropriate and in line with current guidance.

**BENEFIT/RISK ASSESSMENT**
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with benzydamine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.
In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:
Benzydamine 0.15% w/v Oromucosal Spray

For relief of pain and inflammation in the mouth and throat
30 ml

Keep out of the sight and reach of children. Avoid contact with the eyes. Do not store above 25°C. Use within 6 months after opening. Spray onto the sore area of the mouth or throat.

Usage:
- Adults: 4 to 8 puffs, 1½ - 3 hourly.
- Children (aged 6 to 12): 4 puffs, 1½ - 3 hourly.
- Children (under 6): 1 puff for every 4 kg of body weight, up to a maximum of 4 puffs, 1½ - 3 hourly.

Each puff (0.17 ml) contains 255 micrograms of benzydamine hydrochloride (0.15% w/v). Other ingredients: Glycerol, Sodium saccharin, Ethanol (96%), Sodium hydrogen carbonate, Polysorbate 20, Methyl-parahydroxybenzoate (E218). Fresh peppermint mouthwash flavour and Purified Water.

Benzydamine 0.15% w/v Oromucosal Spray
(Benzydamine hydrochloride)

PL 35104/0019

STEPS TAKEN AFTER AUTHORISATION-SUMMARY

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