Public Assessment Report

Decentralised Procedure

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

Procedure No: UK/H/6230/001/DC

UK Licence No: PL 04569/1649

Generics [UK] Limited (trading as Mylan).
LAY SUMMARY
Benzydamine hydrochloride 0.15% w/v Oromucosal Spray
(Benzydamine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Benzydamine hydrochloride 0.15% w/v Oromucosal Spray (PL 04569/1649; UK/H/6230/001/DC). It explains how Benzydamine hydrochloride 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 hydrochloride 0.15% w/v Oromucosal Spray.

The product will be referred to as Benzydamine hydrochloride Spray throughout the remainder of this PAR.

For practical information about using Benzydamine hydrochloride Spray, patients should read the package leaflet or contact their doctor or pharmacist.

What is Benzydamine hydrochloride Spray and what is it used for?
Benzydamine hydrochloride Spray is a ‘hybrid generic medicine’. This means that Benzydamine hydrochloride Spray contains the same active substance as, and is similar to, a reference medicine already authorised in the UK called Difflam 0.15% w/v Spray (Meda Pharmaceuticals Ltd, UK).

Benzydamine hydrochloride Spray is used to treat painful conditions of the mouth or throat:

- Mouth ulcers
- Teething
- Sore throat
- Sore tongue or gums
- Discomfort associated with dentures.
- Upon the doctor’s recommendation, it is also used for relief of discomfort associated with dental work.

How does Benzydamine hydrochloride Spray work?
This medicine contains the active ingredient 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 hydrochloride Spray used?
Benzydamine hydrochloride Spray is sprayed onto the sore area of the mouth or throat.

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

Benzydamine hydrochloride Spray should not be used for more than 7 days except under medical supervision.

How much Benzydamine hydrochloride Spray should be used?
Recommended dosage:
Adults, adolescents and the elderly:
4 to 8 puffs to the sore area every 1½ to 3 hours.

Children aged 6 to 12 years:
4 puffs to the sore area 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, to the sore area every 1½ to 3 hours.

**Do not use in children who are unable to hold their breath during spraying.**

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.

This medicine can be obtained without a prescription.

**What benefits of Benzydamine hydrochloride Spray have been shown in studies?**
No additional studies were needed as Benzydamine hydrochloride Spray is a ‘hybrid generic medicine’ that is locally applied, locally acting and contains the same active substance as the reference medicine Difflam 0.15% w/v Spray (Meda Pharmaceuticals Ltd, UK).

**What are the possible side effects of Benzydamine hydrochloride Spray?**
Because Benzydamine hydrochloride Spray is a ‘hybrid generic medicine’, its 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 hydrochloride Spray, see section 4 of the package leaflet available on the MHRA website.

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

**Why was Benzydamine hydrochloride Spray approved?**
The MHRA decided that the benefits of Benzydamine hydrochloride Spray outweigh the identified risks and it was recommended that it be approved for use.

**What measures are being taken to ensure the safe and effective use Benzydamine hydrochloride Spray?**
A risk management plan (RMP) has been developed to ensure that Benzydamine hydrochloride 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 hydrochloride Spray including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.
Other information about Benzydamine hydrochloride Spray
The Czech Republic, Germany, Italy, Poland and the UK agreed to grant a Marketing Authorisation for Benzydamine hydrochloride Spray on 03 November 2017. A Marketing Authorisation was granted in the UK on 23 November 2017.

The full PAR for Benzydamine hydrochloride Spray follows this summary.

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

This summary was last updated in January 2018.
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I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Benzydamine hydrochloride Spray (PL 04569/1649; UK/H/6230/001/DC) could be approved. The product is a Pharmacy (P) medicine indicated as a locally acting analgesic and anti-inflammatory treatment for the throat and mouth.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and the Czech Republic, Germany, Italy and Poland as Concerned Member States (CMS). 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 Difflam 0.15% w/v Spray (PL 15142/0046; Meda Pharmaceuticals Ltd, 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.

The indazole analogue benzydamine hydrochloride has physicochemical properties and pharmacological activities which differ from those of the aspirin-like NSAIDs. Unlike aspirin-like NSAIDs which are acids or metabolised to acids, benzydamine hydrochloride is a weak base. In further contrast, benzydamine hydrochloride is a weak inhibitor of the prostaglandin synthesis. Only at concentration of 1mM and above benzydamine hydrochloride effectively inhibits cyclooxygenase and lipoxygenase enzyme activity. It mostly exerts its effects through inhibition of the synthesis of proinflammatory cytokines including tumour necrosis factor-alpha (TNF-α) and Interleukin-1β (IL-1β) without significantly affecting other pro-inflammatory (IL-6 and 8) or anti-inflammatory cytokines (IL-10, IL-1 receptor antagonist). Further mechanisms of action are hypothesised including the inhibition of the oxidative burst of neutrophils as well as membrane stabilisation as demonstrated by the inhibition of granule release from neutrophils and the stabilisation of lysosomes. The local anaesthetic activity of the compound has been related to an interaction with cationic channels.

No new non-clinical or clinical data were submitted, which is acceptable given that the application was based on being a hybrid generic medicinal product of an originator product that has been in clinical use for over 10 years. 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 RMS 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.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and the CMS considered that the application could be approved at the end of procedure on 03 November 2017. After a subsequent national phase, a licence was granted in the UK on 23 November 2017.
II  QUALITY ASPECTS

II.1  Introduction
Each spray delivers benzydamine hydrochloride 0.15% w/v, approximately 270 micrograms per puff. Other ingredients consist of the pharmaceutical excipients polysorbate 20, ethanol (96 per cent), glycerol, saccharin sodium [E954], methyl parahydroxybenzoate [E218] and peppermint oil.

The finished product is presented in an amber glass bottle (Type III) and white cap fitted with stopper and POM/EVA/PP/PE-LD/stainless steel metering spray pump consisting of a dip tube and nozzle containing 30 ml liquid, packed in a cardboard box. Each 30 ml bottle contains 166 metered doses.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2.  Drug Substance
INN:  Benzydamine hydrochloride
Chemical Name:  3-(1-benzylindazol-3-yl oxy)propyldimethylamine hydrochloride

Molecular formula:  C₁₉H₂₃N₃O.HCl

Structure:

\[
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{OCH₂CH₂CH₂NCH₃} \\
\end{array}
\]

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 not the subject of a European Pharmacopoeia monograph but it is the subject of a British 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 for the active substance. 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 used.
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food. Appropriate stability data have been generated supporting 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, Difflam 0.15% w/v Spray (Meda Pharmaceuticals Ltd, UK). A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

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

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
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 at the commercial-scale batch size and shown satisfactory results.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that 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 bottle with the storage conditions ‘This medicinal product does not require any special storage conditions, do not freeze. Keep out of the reach of children.’

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

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS
III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of benzydamine hydrochloride are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.
The Marketing Authorisation Holder’s (MAH’s) non-clinical expert report 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
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Benzydamine hydrochloride Spray 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.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint.

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. According to the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), for locally applied, locally acting products containing known constituents ‘bio-equivalence generally is not a suitable way to show therapeutic equivalence since plasma levels are not relevant for local efficacy, although they may play a role with regard to safety’. The applicant has justified that their product is therapeutically equivalent to the reference product on the basis that both products are pharmaceutically equivalent topical oral solutions that produce the same concentrations at the site of action.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of benzydamine hydrochloride.

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 Clinical efficacy
The efficacy of benzydamine hydrochloride is well-known. No new efficacy data were submitted and none are required for this type of application.

IV.5 Clinical safety
No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP)
The marketing authorisation holder (MAH) has submitted a 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 hydrochloride Spray.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Summary of the safety concern</th>
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<td>Important identified risk</td>
<td>- Hypersensitivity reactions</td>
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<tr>
<td></td>
<td>- Laryngospasm or bronchospasm in patients with asthma</td>
</tr>
<tr>
<td>Important potential risks</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Missing information</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and risk minimisation measures are proposed and considered to be acceptable.

**IV.7 Discussion on the clinical aspects**

The grant of a marketing authorisation is recommended for this application from a clinical viewpoint.

**V User consultation**

The package leaflet 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 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, benefit/risk assessment and recommendation**

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.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The following text is the approved label text for this medicine. No label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained:
1. **NAME OF THE MEDICINAL PRODUCT**

Benzydamine hydrochloride 0.15% w/v Oromucosal Spray

2. **STATEMENT OF ACTIVE SUBSTANCE**

Each spray delivers benzydamine hydrochloride 0.15% w/v, approximately 270 micrograms per puff.

3. **LIST OF EXCipients**

Also contains: ethanol (96 per cent) and methylparahydroxybenzoate [E218].
See leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Oromucosal spray

30 ml
166 metered doses.

5. **METHOD AND ROUTE OF ADMINISTRATION**

For oromucosal use

Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNINGS, IF NECESSARY**

8. **EXPIRY DATE**

Expiry Date.

9. **SPECIAL STORAGE CONDITIONS**

Do not freeze.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mylan, Potters Bar, Herts, EN6 1TL, U.K.

12. MARKETING AUTHORISATION NUMBER

FL 04569/1649

13. BATCH NUMBER

Batch No.

14. GENERAL CLASSIFICATION FOR SUPPLY

P

15. INSTRUCTIONS ON USE

For the treatment of pain and inflammation of the mouth or throat:
- Mouth ulcers.
- Teething.
- Sore throat.
- Sore tongue or gums.
- Discomfort associated with dentures.

Dosage:
- Adults, adolescents (above 12 years of age) and elderly: 4 to 8 puffs every 1½-3 hours.
- Children (6-12 years of age): 4 puffs every 1½-3 hours.
- Children under 6 years of age: 1 puff for every 4 kilograms of bodyweight, up to a maximum of 4 puffs, every 1½ to 3 hours.

16. INFORMATION IN BRAILLE

Benzydamine hydrochloride 0.15% w/v Oromucosal Spray (on the outer packaging only)

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable.
Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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