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Public Assessment Report

Scientific discussion

IOSBENC 3MG LOZENGES LEMON FLAVOUR (Benzydamine hydrochloride)

ES/H/0504/001/DC

Date: 21/04/2025

This module reflects the scientific discussion for the approval of Iosbenc 3 mg lemon flavour. The procedure was finalised at 29/08/2018. For information on changes after this date, please refer to the module ôUpdateô.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Iosbenc 3 mg lozenges lemon flavour, from Geiser Pharma S.L.
The product is indicated for*: the treatment of symptomatic local treatment of acute sore throat in adults and children over 6 years of age.*
A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC (well-established use application).

II. QUALITY ASPECTS

The product Benzydamine hydrochloride 3 mg lemon lozenges consists on round yellow lozenges, with a diameter of 19±1 mm, containing 3 mg of benzydamine hydrochloride, equivalent to 2.68 mg of benzydamine and with lemon flavour.
The maximum daily dose is 9 mg of Benzydamine hydrochloride.
Benzydamine hydrochloride 3 mg lemon flavoured lozenges are packaged in PVC-PVDC/Aluminium blisters.

Drug substance

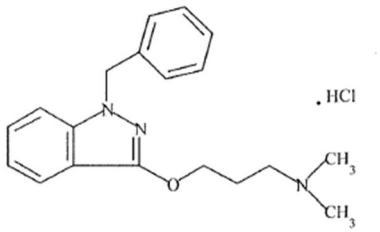
The CEP procedure is used to support the quality of the drug substance.

General Information

Nomenclature:

INN: Benzydamine Hydrochloride
Chemical name: 3-[(1-Benzyl-1*H*-indazol-3-yl)oxy]-*N*,*N*-dimethylpropan-1-amine hydrochloride
CAS Benzydamine base: 642-72-8
CAS Hydrochloride salt: 132-69-4

Chemical structure:



Molecular formula: $C_{19}H_{23}N_3O.HCl$
Molecular weight: 345.9

General Properties:

White or almost white, hygroscopic, crystalline powder. Very soluble in water, freely soluble in ethanol (96%) and in methylene chloride, slightly soluble in acetone, practically insoluble in heptane.

Manufacture, process controls and characterisation

As CEP procedure is used, information on manufacture, process controls and characterisation of the active substance has been assessed by EDQM.

Specification, analytical procedures, batch analysis

Active substance specifications are in accordance with Ph. Eur. monograph and additional relevant tests are included.

Container closure system
As CEP procedure is used, information on packaging material of active substance has been assessed by EDQM.

Stability

Re-test period is included in the CEP. Stability studies have been assessed by EDQM.

Drug Product

Description of the product

The drug product is a round yellow lozenge, with 19±1 mm of diameter containing 3 mg of benzydamine hydrochloride, equivalent to 2.68 mg of benzydamine and with lemon flavour.
The qualitative composition of the finished product is as follows:
Benzydamine hydrochloride
Isomalt (E-953)
Citric acid monohydrate
Aspartame (E-951)
Quinoleine yellow (E-104)
Lemon flavour: (Butylated Hydroxyanisole (BHA) E 320, Ethanol)
Peppermint oil

The packaging material intended for the commercial use consists in PVC-PVDC/Aluminium blisters.

Pharmaceutical Development

The development of the product has been described, the choice of excipients is justified and their functions explained.
The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.

Manufacture of the product

The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.

Sufficient validation data are provided.

Excipients

Excipients used are well known and of appropriate quality.
None of the excipients is of animal origin.

Product specification, analytical procedures, batch analysis

The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.

Container closure system

The finished product is packaged in PVC-PVDC/Aluminium blisters. The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed .

Stability

Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Shelf-life: 3 years

Storage conditions: This medicinal product does not require any special storage conditions.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of benzydamine hydrochloride are well known. The applicant has provided an overview based on literature review which is considered appropriate. Additional studies are not required.

III.1 Pharmacology

The Applicant has shown a variety of effects on benzydamine on different *in vitro* and *in vivo* models. These actions including anti-inflammatory and membrane stabilization effects, and antibacterial activity.

The lack of secondary and safety pharmacology studies, and pharmacodynamic drug interactions information from animal studies is considered acceptable. Under a nonclinical point of view, the publications and the post-marketing experience accumulated during these years support its pharmacological actions.

III.2 Pharmacokinetics

Minimal information related to biodistribution studies is available in the scientific literature. However, considering the extended post marketing experience, additional pharmacokinetic investigations are considered not necessary.

III.3 Toxicology

Data compiled include studies in mice, rats, rabbits and dogs receiving oral administration of doses up to 150, 500, 20 and 30 mg/kg/day, respectively, for 6 months. Several deaths were reported in rats administered with high oral doses (500 mg/Kg/day), which resulted from acute pharmacodynamic effects of benzydamine rather from pathologic changes in target organs. In the studies in mice and rats, an increase in liver weight was reported. These effects could be interpreted as the macroscopic expression of a biochemical reaction rather than a pathologic change. Since the enlargement of the liver occurred in mice and rats after higher doses and a good dose-response relationship exist, and furthermore, it was not observed in rabbits and dogs, it is reasonable to assume that this change may not occur in human after therapeutic doses of benzydamine.

A published study on the genotoxic potential of benzydamine reveals a positive result at the highest dose (1.5 mg/mL); however, this finding has not been confirmed by additional studies.

No toxicological information regarding the carcinogenicity potential is available in the scientific literature. This is not a concern considering the wide clinical knowledge of benzydamine.

No deleterious effects on reproductive toxicity have been reported in the literature for benzydamine.

Minimal local irritating effect was observed form the dose level of 0.25 %. Benzydamine also showed to have phototoxic properties *in vitro* and to cause both, phototoxicity and photoallergy. In addition, bencydamine has been shown to have cytotoxic effects when present in mouth wash/rinses formulation in oromucosal related cells. In these studies, some cytotoxic effects were observed, but benzydamine showed the lowest cytotoxic potential compared to other oral mouth rinses. However, the safety profile of benzydamine hydrochloride can be considered as well known, since medicinal products containing the same active principle and dose have been marketed during more than 10 years (well-established use). Its use in clinical practice has not revealed any toxicity with a favourable benefit/risk balance.

On other hand, the excipients used in the final formulation of the test product are well known for their use in the manufacture of pharmaceutical products and are not expected to modify the performance nor the safety and efficacy profiles of the active, at the low concentrations included in the Applicantõs formulation.

III.4 Ecotoxicity/environmental risk assessment (ERA)

An ERA phase I, Estimation of Exposure has been provided. A log Kow values have been experimentally calculated and submitted from bibliographic references. A refined PEC value, considering the prevalence of the disease has been submitted. Values were calculated in agreement with the ñGuideline on the Environmental Risk Assessment of Medicinal Products for Human Useò (EMEA/CHMP/SWP/4447/00 corr* 2). The PEC calculated using the refined Fpen is below the threshold set in the aforementioned guideline. Consequently, Phase II is not required.

Summary of main study results

Substance (INN/Invented Name): Benzydamine hydrochloride			
CAS-number (if available): 642-72-8			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	RI detector: 3.75 UV detector: 3.82	Potential PBT N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	RI detector: 3.75 UV detector: 3.82	not B
Persistence	DT50 or ready biodegradability	ND	ND
Toxicity	NOEC or CMR	ND	ND
PBT-statement:	The compound is not considered as PBT nor vPvB		

Conclusions on studies:
Benzydamine is not a PBT substance.
Considering the above data, benzydamine is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Pharmacokinetic (PK) parameters of benzydamine were determinated after intravenous, oral and topical administration, including mouthwash, topical, vaginal or rectal formulations in several studies. Benzydamine has a relatively low systemic clearance approximately 160 ml min-1, but high volume of distribution (å110 L); the apparent terminal half-life in plasma was å 8 h.

The absorption through the mucosa of the mouth and pharynx was demonstrated by the presence of measurable quantities of benzydamine in the human plasma. About 2 hours after the 3 mg lozenge administration, benzydamine peak plasma values of 37.8 ng/ml with an AUC of 367 ng/ml*h were observed.

When locally applied, benzydamine has been shown to accumulate in inflamed tissues where it reaches effective concentrations because of its capacity to penetrate the epithelial lining.
The excretion occurs mainly in the urine and mostly in the form of inactive metabolites or conjugation products. Several inactive oxidized metabolites are formed and excreted in urine.

Biowaiver
Not applicable

Bioequivalence studies
Not applicable

Conclusion on bioequivalence studies:
N/A

IV.2 Clinical efficacy

Benzydamine is a NSAID with analgesic and local anaesthetic properties, which is indicated for the treatment of several oral inflammatory and painful conditions, including, but not limited to, sore throat, oropharyngeal mucositis, musculoskeletal injuries and gynaecological inflammations.

❖ Efficacy of Benzydamine in the treatment of Sore throat

In the treatment of acute sore throats, the efficacy of lozenges, mouthwash and spray formulations were evaluated since the earlies 1980ôs. Those studies included-placebo controlled and comparatives with other sore throat treatments. In some studies, the efficacy of benzydamine was accessed when associate with other drugs. Also systematic reviews evaluated the efficacy of benzydamine for sore throat relief.

Mouthwash, oral spray and lozenges are oropharyngeal formulations intended to exert local effects in the oral cavity and/ or throat, and drug plasma levels reported after topical administrations are probably related to absorption through the oral mucosa (Benzydamine, Angelini, 2015). Notably, all the three abovementioned formulations lead to similar rate and

extent of exposure, even when different doses are given, due to the differences in the transient time of contact for each formulation (see Table 9 and Figure 9). It is important to mention that the differences in the total doses given in each one of the oropharyngeal formulations are driven by the estimated time of contact with the local site. For instance, mouthwash formulation needs higher doses to attain the desired local absorption since it offers only a transient exposure to the drug, while spray and lozenges remain in contact with the oropharyngeal mucosa for a longer period, therefore lower doses suffice the intended local absorption and effect.

Unlike other locally applied drugs, benzydamine can be accurately measured in plasma after oropharyngeal application and in this case, PK could serve as a surrogate to suggest therapeutic equivalence. Indeed, having similar PK parameters been obtained with different oropharyngeal formulations should be an indicative that the active substance followed the same fate; as concerns release, dissolution in the buccal cavity, proportion of the dose absorbed via the oral mucosa and swallowed/absorbed through the gastrointestinal tract, etc. In this sense, the amount of benzydamine interacting with the local area where the intended effect is exerted (i.e. the oral and pharyngeal mucosa) as well as the duration of the contact could be assumed to be equal; thus the observed clinical outcomes of each one of those formulations can be considered interchangeable.

There is a perfect fitting of lozenges Cmax and AUC within the range of other current oropharyngeal formulations (mouthwash and spray) parameters, indicating that plasma levels attained after absorption in the oral mucosa are consistent between formulations, corroborating the ability of PK as a predictor/surrogate of efficacy and safety for those formulations. The Applicantôs formulation has similar *in vitro* profiles when compared with Tantum Verde lozenges and the excipients employed in their formulations are not expected to lead to changes in any ADME process. In such situation, it can be assumed that similar release will lead to similar local effects and similar magnitudes for Cmax and AUC for the proposed benzydamine HCl lozenges. Therefore, the clinical outcomes (efficacy and safety) could be assumed as equivalent not only between these two lozenges formulations, but also endorsed by the efficacy reported for other benzydamine oropharyngeal formulations and corroborated by the well-established use in clinical practice since its first approval more 4 decades ago.

Efficacy of benzydamine oral rinse/mouthwash for sore throat was evaluated against placebo over 52 patients suffering from presumed viral pharyngeal infection or tonsillitis. They received either benzydamine or placebo oral rinse as a gargle at 3-hourly intervals in a randomized double-blind study. Faster resolution of pain and dysphagia were observed in the group receiving benzydamine. After 7 days 88% of the patients were symptom-free compared with 38% on placebo, as can be seen in Table 10 (Whiteside 1982).

Table 10: Overall and disclosed symptoms before and after treatment with benzydamine (From Whiteside, 1982)

Observer's assessment of severity of symptoms before and after treatment

Treatment	No. patients	Total score		Mean score	
		On entry	Day 7	On entry	Day 7
Benzydamine	25	62	3	2.48	0.12
Placebo	26	55	20	2.11	0.77

Patients' assessment of severity of symptoms before and after treatment

Treatment	Pain		Dysphagia	
	Total score	Mean score	Total score	Mean score
Benzydamine (n=25)				
Day 1	63	2.52	62	2.48
Day 2	60	2.40	59	2.36
Day 3	36	1.44*	34	1.36*
Day 4	25	1.00	21	0.84
Day 5	12	0.48	11	0.44
Day 6	2	0.08	2	0.08
Day 7	2	0.08	2	0.08
Placebo (n=26)				
Day 1	56	2.15	55	2.12
Day 2	55	2.11	54	2.11
Day 3	55	2.11	53	2.08
Day 4	49	1.88	45	1.73
Day 5	32	1.23*	30	1.15*
Day 6	26	1.00	24	0.92
Day 7	20	0.77	17	0.65

*p<0.001

A small review from 1986 reported the efficacy of the benzydamine as an oral rinse in two other studies. In one study, benzydamine gargle relieved the symptoms of sore throat more effectively than placebo in a trial (41 patients) in general practice. In the other pump spray administration of benzydamine half an hour before meals improved sore throat and dysphagia but not ear pain in children, after tonsillectomy procedure (Difflam Bulletin, 1986).

Raj and Wickham (1986) studied in a double-blind study the efficacy of this benzydamine in the control of post-tonsillectomy symptoms. All patients were randomly allocated to treatment with either benzydamine (0.15 % W/V) or a matching placebo spray. The 'spray' consisted of an aerosol canister containing 30 mL of the liquid and on each activation delivered 160 ε L ('one puff'). Patients were divided into adults and children groups. The study has shown that benzydamine was effective as a local agent in alleviating symptoms of dysphagia and sore throat (but not the earache) and thus reducing requirement of analgesic medication in the adult post-tonsillectomy patient. From children patients with only pharyngeal symptoms only, 77 % improved with benzydamine and 56% improved with the placebo. The spray was therefore presumed to be effective in these patients. The spray was difficult to use in the younger child (4-8 years) and as a result had an indeterminate effect in this sub-group.

The ethology of postoperative sore throat (POST) is considered the result of damage to airway mucosa after insertion of a laryngeal mask airway device or endotracheal tube. Considering this concept, the effectiveness in alleviating postoperative sore throat (POST) of benzydamine HCL administration by spraying (5 puffs of 0.15%, total 0.75 mg) was studied, using different approaches to the endotracheal tube (ET) cuff or the oropharyngeal cavity, or both. A total of 380 patients were enrolled in this prospective and double-blind study. They were randomized into 4 groups: group A, oropharyngeal cavity spray benzydamine HCl, and distilled water on the ET cuff; group B, both the oropharyngeal cavity and the ET cuff received benzydamine HCL spray; group C, the ET cuff received benzydamine spray, and the oropharyngeal cavity received distilled water; and group D, distilled water sprayed on both the ET tube and into the oropharyngeal cavity. The patients were examined for sore throat 0, 2, 4, and 24 hours after extubation. In group D (all water application) the incidence of sore throat was 40.4%, against

23.2%, 13.8%, 14.7% in groups A, B, C. These difference were significant in groups B and C against D, but not between groups A and D. Moreover, no significant difference was found between groups B and C. The major finding was that spraying benzydamine HCl on the ET cuff may reduce the incidence and severity of POST up to 24 hours postoperatively compared with the application of distilled water (Huang et al., 2010).

The efficacy of benzydamine specifically for improving the recovery following tonsillectomy was evaluated in a meta-analysis published in the Cochrane library. Contradictory conclusions was found in terms of the effectiveness of pain relief with benzydamine treatment, however the authors pointed that pain is not the only post-tonsillectomy sequela and, although the complexities involved in assessing pain are acknowledged, the evaluation of the recognized anti-inflammatory properties of benzydamine and in particular its effects on accelerating the healing process would have been a valuable contribution to the overall completeness of the evidence base (Fedorowicz et al., 2013).

Recently, in 2014, another systematic review over randomized controlled trials that investigated the outcome of topical application of benzydamine vs non-application for POST in patients undergoing general anaesthesia was performed. Using a random effects model, the relative risks of the incidence of POST within 24 h following the surgical procedure were accessed. Five trials (824 patients) indicated that the incidence of POST was significantly reduced in the benzydamine group, with risk ratios (RRs) of 0.37 (95% confidence interval [CI]: 0.20 to 0.68) at zero to one hour, 0.39 (95% CI: 0.27 to 0.57) at one to two hours, 0.42 (95% CI: 0.22 to 0.81) at four to six hours, 0.29 (95% CI: 0.10 to 0.88) at six to 12 h, and 0.32 (95% CI: 0.18 to 0.56) at 12 to 24 h, compared with the control groups. The sum of results allows concluding that prophylactic benzydamine topical application to the oral cavity or airway devices con reduce the incidence of POST (Chen et al., 2014).

Besides the placebo controlled studies, comparative studies between benzydamine and other sore throat treatment were performed:

The efficacy of Difflam' Oral Rinse and soluble aspirin in the post-operative management of tonsillectomy in adult patients was compared. Benzydamine gargle (15ml 3-hourly) or soluble aspirin (600 mg four times daily) were given to 29 patients after tonsillectomy. Benzydamine acted at once and the effect lasted 2-3 hours; aspirin took half an hour to work, but the effect persisted for 6 hours. Whilst aspirin proved slightly more effective in relieving pain and discomfort of swallowing, 'Difflam' Oral Rinse was superior in the relief of earache, in promoting the healing of the tonsil bed and in the duration of necessity of treatment. It is therefore suggested that the two preparations might be taken concomitantly to provide quick, as well as long-lasting, pain relief (Irwin and Acharya, 1984).

A comparison of Benzydamine HCl spray and Salvia officinalis (SO) as adjuvant local treatments in controlling pain after tonsillectomy, adenoidectomy, or both, was performed in an open-label, single-blind, randomized clinical trial. The study included paediatric and adult patients that were randomized to receive benzydamine HCl spray or SO, in addition to ibuprofen 20 mg/kg/day (for children) or diclofenac 100 mg/day (for adults). The proportion of patients with mild or no pain on postoperative days 1, 2, 4, and 7 was evaluated. A significantly lower proportion of children in the benzydamine group presented moderate or severe pain than those treated with SO at each time point. Among the adults, a significantly lower number treated with benzydamine reported moderate or severe pain on days 1 and 2 following surgery than those treated with SO, however no difference was observed on days 4 and 7. In children, the

risk for postoperative infection was similar between benzydamine and SO groups, however, the risk was reduced in adults, concluding that benzydamine spray, as an adjuvant after tonsillectomy, adenoidectomy, or both surgeries, was more effective than SO in the control of pain and infection (Lalicevic et al., 2004).

For postoperative sore throat (POST), a prospective, randomized, placebo-controlled, single-blind study in patients undergoing elective modified radical mastectomy under general anaesthesia compared mineral water, aspirin (tablet 350 mg) and benzydamine hydrochloride (0.15%, 15 mL). All the medications were made into 30 mL of solution for gargling during 30 s, 5 min before induction of anaesthesia. The evaluation of POST was done at 0, 2, 4, and 24 h postoperatively and the results are graphically displayed in Figure 12. POST was more severe in the control group at 0 and 2 h. Aspirin gargles reduced the incidence of POST for 4 h whereas benzydamine HCL gargles demonstrated superior efficacy being capable of reduce POST for 24 h (Agarwal et al., 2006)

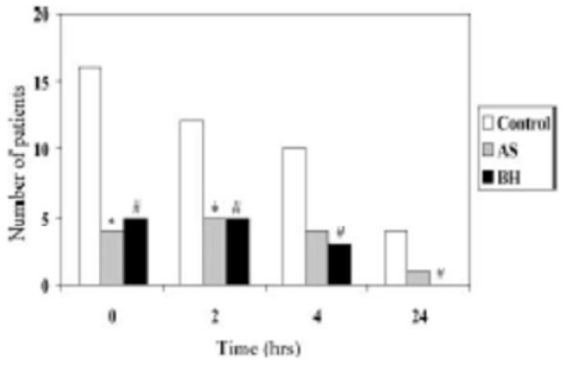


Figure 12: Incidence of postoperative sore throat (POST), data presented as number of patients. * P<0.05 during intergroup comparison between control (C) versus aspirin (AS) and # p<005 between control (C) and benzydamine (BH) (From Agarwal et al., 2006).

Another study compared the effectiveness of dexpanthenol pastille and benzydamine HCl spray on the prevention of a sore throat. Patients undergoing general anaesthesia were randomized to receive benzydamine HCl, dexpenthanol or water. The treatments were: benzydamine four puffs sprayed into the mouth initially 30 min before the operation and repeatedly 5 min before anaesthesia induction; two pastilles of dexpanthenol administered orally to be sucked 30 min before the operation or four puffs of distilled water were sprayed into the mouth initially 30 min before the operation.
Postoperatively, patients were evaluated for a sore throat during a period of 24 h. Starting from 10 min, within the first 6 h postoperatively, the incidence of POST was significantly lower in the patients that received dexpanthenol when compared with distilled water and benzydamine. Starting from 12 h, until the end of the evaluation period of 24 h, the incidence of POST was similar for the group with benzydamine and dexpanthenol, whereas the incidence of POST was significantly higher for those who received only water. The result demonstrated that treatment with dexpanthenol provided relief during the entire period of 24h, whereas benzydamine showed improvement in pain condition after 12 hours (Gulhas et al., 2007).

Comparison between mouthwash formulations of ketoprofen lysine salt (KLS) and benzydamine HCl in patients with acute inflammation of the pharyngeal cavity were performed. A randomized, multicentre, parallel-group, single-blind study, patients were blindly randomized to receive undiluted benzydamine HCl 15 mL (22.5 mg) (n=121) or KLS 10 mL (160 mg) (n=120) diluted in 100 mL of water. Both agents were gargled twice daily until pain remission or up to 7 days. The efficacy was accessed via physical examination of the oropharyngeal cavity, where severity of oedema and hyperaemia was evaluated after 3 days of

treatment and, if symptoms had not resolved, after pain remission. The differences between groups in the duration of analgesic effect after the first dose of drug and the time course of pain were found to be statistically significant (P = 0.006 and P = 0.017, respectively), favouring KLS (Passali et al, 2001).
The effectiveness on POST of spraying the endotracheal tube cuff with benzydamine hydrochloride, 10% lidocaine, and 2% lidocaine were compared. For that purpose, 372 patients were randomly allocated into 4 groups. The ET cuffs in each group were sprayed with benzydamine hydrochloride (10 puffs, ~ 1.5mg), 10% lidocaine hydrochloride, 2% lidocaine hydrochloride, or normal saline before endotracheal intubation. The patients were examined for sore throat (none, mild, moderate, or severe) at 1, 6, 12, and 24 hours after extubation. There was a significantly lower incidence of POST in the benzydamine group than 10% lidocaine, 2% lidocaine, and normal saline groups ($P < 0.05$) at each observation time point. At 6 hours after extubation, the incidence of POST was significantly lower in the benzydamine group (17.0%) compared with 10% lidocaine (53.7%), 2% lidocaine (37.0%), and normal saline (40.8%) groups ($P < 0.05$). The benzydamine group had significantly decreased severity of POST compared with the 10% lidocaine, 2% lidocaine, and normal saline groups ($P < 0.05$) at each observation time point (Hung et al., 2010). The better effectiveness of benzydamine hydrochloride when compared to local anaesthetics, could be attributed not only to its analgesic properties, but also its anti-inflammatory ones.

❖ Clinical experience with lozenges:

The clinical experience with lozenges is limited to 3 unpublished clinical trials that served as basis for the aproval of Tantum verde in the EU:

-Technical Document on Benzydamine (Benzydamine, Angelini, 2015) reported two unpublised studies performed in 1981, demonstrating the therapeutic equivalence of benzydamine 3 mg lozenges with the mouthwash formulation for the treatment of oropharyngeal disease. Benzydamine 0.15% mouthwash was chosen as the reference product due to its proven effectiveness and extensive use in the topical treatment of oral inflammatory and painful conditions. Efficacy parameters were evaluated using a 4-point scale (from no to severe symptomatology). Results of these studies are shown in Figure 10 and Figure 11, in comparison with basal time score.
In the first study (Figure 10), it was observed a clear improvement/reduction of edema, hyperemia, dysphagia, burning sensation, swelling sensation and pain, with no statistically significant differences between the two benzydamine oropharyngeal dosage forms.

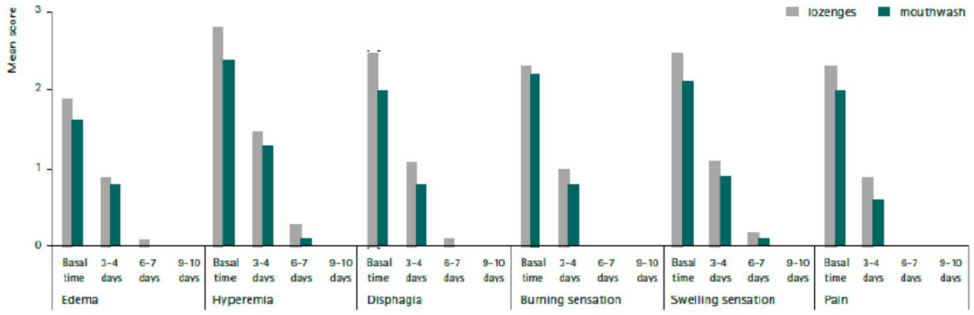


Figure 10: Mean score for the evaluated signs and symptoms of the oropharyngeal disease recorded at basal and subsequent observation times (Extracted from Benzydamine, Angelini, 2015).

In the second study (Figure 11) the symptoms of edema, hyperemia, spontaneous pain, evoked pain and dentin hypersensitivity had the scores reduced by both oropharyngeal formulations.

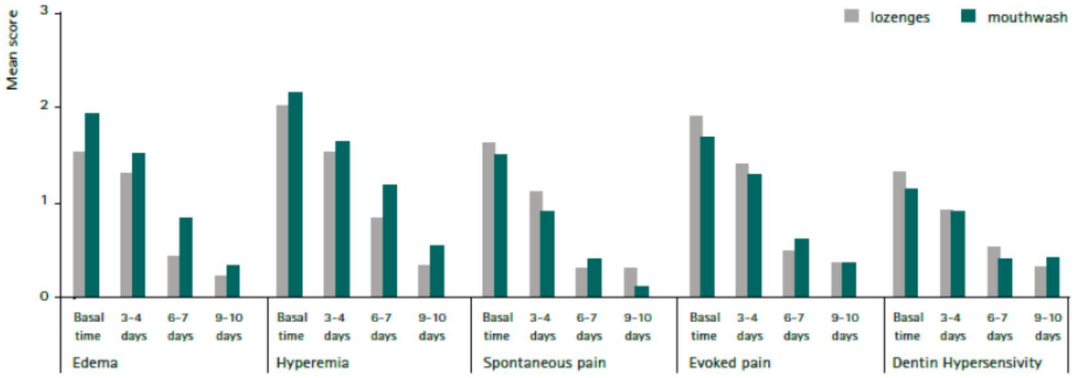


Figure 11 Mean score for the evaluated signs and symptoms of the oropharyngeal disease recorded at basal and subsequent observation times (extracted from Benzydamine, Angelini, 2015)

The Technical Document on Benzydamine (Benzydamine, Angelini, 2015) also reported a placebo-controlled clinical trial performed in 146 children (4 to 17 years) with sore throat from 1998. This study demonstrated the efficacy of benzydamine 0.15% mouthwash. One single 15 ml dose of benzydamine 0.15% mouthwash was significantly better ($p<0.05$) than placebo in all efficacy parameters (Figure 14). Efficacy evaluations were performed at 5-minute intervals over a 1-hour evaluation period. In same document, a report from 1985 demonstrated that benzydamine 0.15% oropharyngeal spray administered to children (age range 4-12years) with sore throat proved to be an effective, acceptable and trouble-free treatment for sore-throat in younger patients.

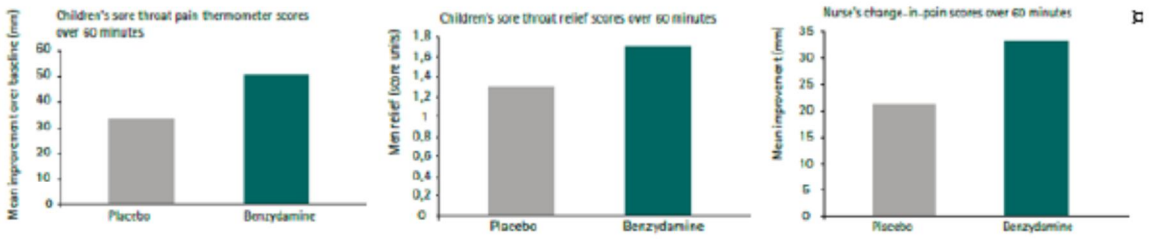


Figure 14: Efficacy assessment after treatment with a single 15 ml dose of benzydamine 0.15% mouthwash or placebo with Children's Sore Throat Pain Thermometer (VAS 0 to200 mm), Children's Sore Throat Relief Scale (Scale 0 to 4 units) and Nurse's Change-in-Pain Scale (VAS 0 to 100 mm) (extracted from Benzydamine, Angelini, 2015).

Another study from 1990 reported efficacy in younger patients. Benzydamine 0.15% oropharyngeal spray has proven efficacy in the post-operative course of children and

adolescents undergoing adenotonsillectomy. A significant reduction in the intensity of local pain (pharyngodynia) and/or of pain at swallowing, already 24 hours after surgery, was observed in young patients (aged 3 to 17 years) treated with benzydamine in comparison to placebo (4 nebulisations up to 8 times a day for 6 days). Improvement in symptoms of pharyngodynia, dysphagia, and if any can be seen in Figure 15 (Benzydamine, Angelini, 2015).

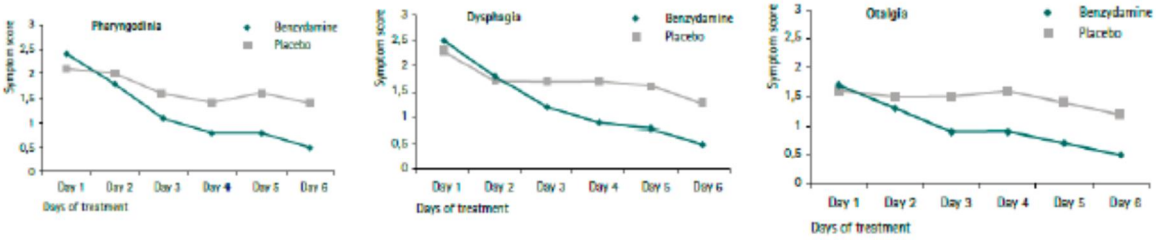


Figure 15: Symptom course during treatment (4 nebulisations in up to 8 times a day for 6 days) with benzydamine and placebo (extracted from Benzydamine, Angelini, 2015).

The use of benzydamine was also studied in association with chlorhexidine for viral and bacterial pharyngitis:

-The efficacy of benzydamine 3 mg lozenges associated or not with dextromethorphan 7.5 mg was studied in 120 patients with acute or chronic disorders of the respiratory tract characterized by cough and inflammatory symptoms of the oropharynx. Benzydamine 3 mg lozenges, dextromethorphan 7.5 mg lozenges and their combination were administered t.i.d for a period of 15 days. Benzydamine produced a progressive clinical improvement in symptoms and signs caused by the inflammatory process, with no effect on the cough symptom (Benzydamine, Angeline, 2015).

❖ Bridging strategy and scientific bases of bridging

The available literature is mainly referred to rinses, mouthwashes and sprays which can be considered supportive in the scope of this application. As far as the pharmaceutical form of lozenges is concerned, no published literature is available.

ñAs the Applicantôs product is similar to Tantum Verde regarding the in vitro release, the PK may also be assumed to be comparable; given that the PK of Tantum Verde is similar to that of other oropharyngeal formulations, the efficacy and safety reported for benzydamine lozenges, mouthwashes and sprays can then be applied to the proposed productò.

The bridging report includes a comparison of the qualitative/quantitative composition of the proposed Benzydamine versus tantum verde (lemon lozenges) as well as in-vitro dissolution tests:

The qualitative and quantitative composition in the main active ingredient (benzydamine) of the Applicantôs benzydamine HCl 3mg lemon taste lozenges is equal to other marketed benzydamine lemon taste lozenges. The Applicantôs and marketed formulations have a very similar excipients profile. The differences remain in the absolute amount of Isolmalt (sugar substitute for the hard candy preparation) corresponding to less than 20% of difference, and in the other ingredients responsible for the organoleptic characteristics of the lozenges: Peppermint Oil instead of mint flavour and the colorants employed.

The results of the first *in-vitro* dissolution test (fast and complete dissolution (<30 min) at pHs 1.2, 4.5 and 6.8 under acceptable conditions), concluded fin similarity for all the formulations under comparison and for all the batches tested.

The applicant also performed and additional in-vitro dissolution test intended to mimic saliva conditions in order to assess the release of active substance to the medium.
Test and reference products (lemon lozenges) were dissolved in simulated saliva (pH 6.2) at 37ºC (test medium destilled water 2.34g NaCL, 1.63g KH2PO4, 0.17g CaCL2 and fill up to 1L. Adjust to pH=6.2 with NaOH. According to USP).

The results obtained let us conclude that for each flavor tested the dissolution profiles of benzydamine when released from both test and reference formulations are similar provided that the similarity factors (f2) obtained are among the established values to consider the formulations similar.

The similarity is a strong indicator that in vivo benzydamine will be in like manner released from the two formulations into the oral cavity, thus suggesting that in vivo benzydamine fate (e.g., proportion of the dose absorbed through the oral mucosa and the gastrointestinal tract) is expected to be the same.

Expected similar release rate of benzydamine in vivo will lead to comparable amount of active substance interacting with the local area where the intended effect is exerted (i.e. the oral and pharyngeal mucosa). Therefore, the dissolution profiles could serve as a bridge to link the proposed formulations not only to the pharmacokinetics of the currently approved benzydamine lozenges (Tantum Verde) but also to the well-established efficacy and safety profile of oropharyngeal benzydamine.

On the basis of the published literature submitted in support of this application together with the bridging report,it can be concluded that Applicantôs benzydamine HCl 3 mg lozenges is efficacious, safe and well tolerated for the short-term treatment of acute uncomplicated sore throat.

IV.3 Clinical safety

Benzydamine lozenges is a product for topical use, and serious adverse events are not expected. Benzydamine shows a very good safety profile.

The first marketing authorization for 3 mg benzydamine lozenges was granted in Italy in 1982.

In 2000 a Marketing Authorization in eleven EU Countries was granted according to a Mutual Recognition Procedure.

As benzydamine is a NSAID and a large number of patients present hypersensitivity to this class of drugs, the use of benzydamine is not advisable in patients with hypersensitivity to salicylic acid or other NSAIDs.

All the studies and isolated reported cases are in accordance and corroborate the undesirable effects that can be found in the Summary of Product Characteristics from the already marketed benzydamine HCl 3mg lozenges,such as the Difflam lozenges and Tantum Verde lozenges (Difflam lozenges (Angelini) SmPC, 2008; Tantum Verde lozenges (Angelini) FT, 2013), which are:

Gastrointestinal disorders:

-Rare (>1/10000, <1/1000): Burning mouth, Dry mouth
-Not known: hypoaesthesia oral

Immune system disorders:
-Rare (>1/10000, <1/1000): Hypersensibility reaction
-Not known: anaphylactic reaction

Respiratory, thoracic, and mediastinal disorders:
- Very rare (<1/10000): Laryngospasm

Skin and subcutaneous tissue disorders:
-Uncommon (>1/1000, <1/100): Photosensitivity
-Very rare (<1/10000): Angiodema

Furthermore, the safety profile of benzydamine is largely corroborated by the elevated number of patients treated with 3 mg lozenges. During Jan-2005 and Aug-2008, according with the Periodic Safety Update Report (PSUR) of TANTUM VERDE Benzydamine Lozenges, more than 7 million patients were treated with benzydamine lozenges, having a total of 20 adverse events reported (all non-serious) (Benzydamine, Angelini, 2015).

Most of the references used in this clinical overview have been identified by a search performed within the clinical databases in January 2018. This database search has demonstrated that a broad experience exists on the clinical use of benzydamine HCl when administered topically in the form of lozenges aimed to provide symptomatic relief of sore throat.

IV.4 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 Iosbenc 3 mg lozenges.
There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Iosbenc 3 mg lozenges.

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

❖ **Benefit risk assessment**

Benzydamine preparations have been available in the EU for many years. Its use can be considered well established. They have recognised efficacy and acceptable safety.

The efficacy and safety of benzydamine was initially supported by the submission of several studies from the literature mainly related orally administered products other than lozenges (rinses, mouthwashes and sprays) some of them under circumstances not directly comparable to the indication sought. In this light, although the submitted literature is not directly transferable to the proposed medicinal product, it can be considered at least partially supportive of the oropharingeal use of the active substance in sore throat.
As far as the pharmaceutical form of lozenges is concerned, the applicant referred to 3 clinical trials that demonstrated the therapeutic activity and safety of Benzydamine Hydrochloride lozenges in the symptomatic treatment for the relief of pain and irritation of mouth and throat. It is worth highlighting that these clinical trials, though unpublished, served as basis for the approval of tantum verde lozenges in several member states in the EU (IT/H/0103/001-004).

Despite strictly speaking there is scarce evidence from the literature in support of the pharmaceutical form of lozenges, it appears reasonable to accept the efficacious and safe use of the proposed benzydamine lozenges based on the *in-vitro* similarity of the proposed product and Tantum verde and the minor differences in terms of non-active ingredients of both formulations. Moreover, the extensive experience with oropharingeal formulations in the treatment of sore throat of different aetiologies can be considered supportive.

Overall, the published literature presented in support of this application together with the bridging report submitted as part of the day 106 response document is considered enough to positively conclude on the benefit/risk balance of *Benzydamine hydrochloride* 3 mg lozenges.