17 October 2019
EMA/589361/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 29(4) of Directive 2001/83/EC

Flurbiprofen Geiser 8,75 mg oromucosal spray, solution

INN/active substance: flurbiprofen

Procedure number: EMEA/H/A-29(4)/1487

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background Information

An application under Article 10(3) of Directive 2001/83/EC was submitted under the decentralised procedure for Flurbiprofen Geiser 8,75 mg oromucosal spray, solution and associated names, on 17/04/2018.

The application was submitted to the reference Member State (RMS): Spain and the concerned Member States (CMS): Czech Republic, the Netherlands, Portugal and Slovakia.

The decentralised procedure ES/H/0552/001/DC started on 17/05/2018.

On day 210, major issues on bioequivalence, raised by the Netherlands, remained unresolved; hence the procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), under Article 29, paragraph 1 of Directive 2001/83/EC, by Spain on 14/03/2019. The CMDh 60 day procedure was initiated on 08/04/2019.

Day 60 of the CMDh procedure was on 07/06/2019 and as no agreement could be reached the matter was referred to the CHMP.

On 10/06/2019 the RMS Spain therefore triggered a referral under Article 29(4) of Directive 2001/83/EC. The Netherlands raised objections on the demonstrated bioequivalence between the reference and the test medicinal products that were considered to be a potential serious risk to public health.

2. Scientific discussion

2.1. Introduction

The applicant Geiser Pharma S.L. submitted an application under the decentralised procedure for Flurbiprofen Geiser 8,75 mg oromucosal spray, solution and associated names (ES/H/0552/001/DC). The application was submitted under Article 10(3) of Directive 2001/83/EC. The reference medicinal product was Strefen Direct 8,75 mg Oromucosal spray (UK/H/5072/001). The application for Strefen Direct 8,75 mg Oromucosal spray was made under Article 8(3) of Directive 2001/83/EC.

The proposed indication is 'pain relief of mild to moderate symptoms of acute sore throat'.

The originator product is Strepflam 8.75 Lozenges by Crookes Healthcare/Reckitt Benckiser Healthcare, which has been registered since June 2001.

Flurbiprofen belongs to the non-steroidal anti-inflammatory class of medicines (NSAID) which have analgesic, antipyretic, and anti-inflammatory properties. The drug inhibits the synthesis of prostaglandins by mixed inhibition of the enzymes COX-1/COX-2 with some selectivity towards COX-1.

According to the Guideline on the equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract (CPMP/EWP/239/95 Rev.1) pre-clinical and clinical trials are considered necessary in order to bridge the test to the reference medicinal product in case the definition of a generic medicinal product is not met.

Differences with respect to the reference medicinal product are possible in the context of a hybrid application, as long as these differences do not affect the therapeutic equivalence between the reference and the test products.

For this application, in order to demonstrate therapeutic equivalence, the applicant has submitted *in-vitro* studies. No clinical studies have been contacted and instead the applicant requested a biowaiver.

Based on the *in-vitro* tests, equivalence has been shown between the reference and the test products with respect to the following quality attributes: amount of active substance in each dose, the particle size, the plume geometry and the spray pattern. However, there are some quantitative and qualitative differences among the products which concern:

i) the concentration: 17.16 mg/ml in the test medicinal product versus 16.20 mg/ml in the reference product;

ii) the amount of cyclodextrins: the amount of cyclodextrins is lower in the test product compared to this of the reference medicinal product;

iii) the flavours: in the test product one flavour is employed (cherry) instead of two flavours employed in the reference medicinal product (cherry and mint)

During the decentralised procedure (DCP) and the CMDh procedure, the RMS (ES) considered that the above mentioned differences were minor and without a clinical impact on the efficacy and safety of the test product. On the other hand, the waiver of clinical studies supporting equivalent efficacy and safety has been questioned by one of the CMS (NL) because of the difference in concentration of the active substance, the qualitative difference in flavours and the quantitative difference in cyclodextrins that in their view could potentially have an impact on the efficacy and the safety of the medicinal product.

2.2. Assessment of the issues raised as a potential serious risk to public health

The application was submitted as a hybrid application under Article 10(3) of Directive 2001/83/EC. Differences with respect to the reference medicinal product are possible as long as these differences do not affect the therapeutic equivalence between the reference and the test products. Relevant data are necessary to bridge the test product to the reference medicinal product.

The applicant did not conduct any clinical studies to support this application. A biowaiver is proposed based on *in-vitro* equivalence with the reference medicinal product, Strefen Direct 8,75 mg Oromucosal spray.

The issue raised by NL was that the safety and efficacy of the test product has not been sufficiently demonstrated due to the lack of appropriate demonstration of therapeutic equivalence. The waiver of clinical trials is not adequately justified, and NL considers that the quantitative and qualitative differences between the reference and test products could have an impact on the efficacy and safety profile of the test product.

The CHMP requested that the applicant justify the waiver of the pK and the clinical studies and explain why the differences in concentration, cyclodextrins and flavours are considered not to affect the local and systemic exposure of flurbiprofen.

<u>i) Waiver of pK and clinical trials</u>

According to the "Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract" (CPMP/EWP/239/95 Rev.1), if the test product is a solution at the time of administration and contains an active substance in the same concentration as the approved reference medicinal product, studies supporting equivalent efficacy and safety may be waived. However, excipient composition should be critically reviewed since excipients may affect local residence time (e.g. palatability, surface tension, viscosity, etc.), *in-vivo* solubility

(e.g. co-solvents) or *in-vivo* stability of the active substance. If there are differences in excipients, an equivalence study should be conducted, unless the differences in the qualitative and/or quantitative composition of these excipients can be adequately justified by reference to other data and taking into account Appendix II of the "Guideline on the investigation of bioequivalence" (CPMP/EWP/QWP/1401/ 98 Rev. 1/ Corr **).

NL and the other divergent MS mentioned that the guideline states that the clinical studies can be waived if the test product contains an active substance in the same concentration as the reference product. In the present application, the two products do not have the same concentration, i.e. 17.16 mg/ml for the test product and 16.20 mg/ml for the reference medicinal product.

The CHMP acknowledged that the present application diverges from the recommendations of "Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract" (CPMP/EWP/239/95 Rev.1). However, the Committee noted that the guidelines indicate certain conditions and they are a general recommendation which has to be interpreted on case by case depending on the medicinal product and its specifications. In addition the guideline allows room for differences in qualitative and/or quantitative composition of the excipients, if these differences are adequately justified.

According to the same guideline, similarity of drug release and availability at the site(s) of action are the major factors determining similar clinical responses for locally applied, locally acting medicinal products containing the same active substance.

To evaluate the similarity of drug release and availability at the site(s) of action, the applicant has tested three different batches of the reference and test products. The applicant performed *in-vitro* tests based on recommendations of the FDA "Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action" in the absence of EMA guideline for demonstrating equivalence between sprays and taking into account that the functional requirements of nasal sprays are in line with the functional requirements of oromucosal sprays. The FDA comparability requirements are similar with the requirements in the EMA "Guideline on the pharmaceutical quality of inhalation and nasal products". The bioequivalence acceptance criteria for single actuation content, droplet size distribution, drug small particles, spray pattern and priming were defined as ±15% (the products would be considered as equivalent if the 90% confidence interval for the ratio of the test and reference products was contained within the acceptance interval of 85.00-117.65%), while for plume geometry the acceptance criteria were defined at ±10% (the products would be considered as equivalent if the 90% confidence interval for the ratio of the test and reference products was contained within the acceptance interval of 90.00-110.00%).

The *in-vitro* studies showed equivalence between products in all critical quality attributes that were tested: single actuation content (amount of active substance in each dose), droplet size distribution, drug small particles, spray pattern, plum geometry and priming. These quality attributes represent the drug release and availability at the site of action and suggest that the quantitative and qualitative differences between the reference and the test medicinal products do not affect the deposition of the spray in the site of action (the buccal cavity).

One *in-vitro* test (drug in small particles), showed that the test medicinal product contains slightly lower percentage of particles of less than 10 μm, than those observed in the reference medicinal product (ratio 83.70%; 90% CI 75.21-93.15%). This parameter represents the amount of the inhalable particles that reach the lung; those particles with an aerodynamic diameter of less than 10 μm are considered to be reaching the deeper lungs (Heyder et al., 1986). The CHMP considered this acceptable.

The CHMP agreed that the *in-vitro* studies showed that the test product is deposited in the site of action in the same way as the reference medicinal product. Taking into consideration that the differences in cyclodextrins and the flavours will not affect the absorption (this point will be discussed in details in following paragraphs), the systemic absorption from the mouth and the dose that will be swallowed and absorbed by the small intenstine can be assumed equivalent. Therefore, it is considered that pharmacokinetic studies to assess indirectly the absorption from the site action (i.e. with active charcoal blockade) and the systemic exposure for safety (i.e. without active charcoal) are not necessary. The delivered dose, as it has been demonstrated to be comparable between products, appears to be the relevant factor defining pharmacokinetic availability of flurbiprofen.

With regards to the waiver of clinical studies, the CHMP agreed that it was duly justified based on the similarity of the critical quality attributes as shown in the *in-vitro* tests. As it will be further explained below, the differences in cyclodextrins and flavours are considered minor. Therefore, it is anticipated that clinical endpoints will not be able to detect these minor differences and that such minor differences would not have clinical impact. It was also noted that "Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract" (CPMP/EWP/239/95 Rev.1) mentioning that "It has been shown that alternative models (including *in vitro* and *in vivo* methods) may have a higher sensitivity than traditional clinical and pharmacodynamics endpoints to detect possible differences between medicinal products containing the same active substances."

In addition, published evidence underlines that completely different formulations of flurbiprofen (e.g. lozenges, granules and spray) applied to the oral cavity have been proven to be bioequivalent. The *in-vivo* comparison between different dosage forms (e.g. lozenges, granules and spray) containing the same active substance, is deemed not to be a sensitive study to identify formulation differences. A study by Limb et al. (2009) showed that a lozenge and a spray displayed comparable efficacy and safety profiles despite the lozenge has a much greater longevity of delivery than the spray. A lozenge stays in the mouth for around 12 minutes, thus steadily delivering activity to the throat, whereas the spray triggers the gag reflex causing a high proportion of the delivered dose to be swallowed soon after deposition (and therefore unavailable to the throat for a prolonged period). If a given clinical evaluation cannot detect differences between dosages for local action, it can be assumed that this will happen even less in case of very similar oromucosal sprays. Furthermore, since the originator demonstrated bioequivalence between the oromucosal spray and lozenges, for which larger formulation differences are expected, this is not considered to be an issue in this case.

ii) Active substance concentration

The CHMP noted that despite the concentration is slightly different (17.16 mg/ml in the test medicinal product versus 16.20 mg/ml in the reference product), the dose delivered is the same (8,75 mg) because of differences of the sprayed volume. Indeed, the sprayed volume is 0.17 mL in the test and 0.18 mL in the reference product in each of the three puffs comprising one dose. The difference in concentration is translated in a difference of content of drug substance of 0.096% in weight/volume of the medicinal product. This minor difference in concentration (5.93%) is expected to be reduced even more by the volume of saliva available in the mouth, which is on average 0.77 mL (Dawes, 2004; DiSabato-Mordarski and Kleinberg, 1996).

Enhancement of local absorption resulting from increased concentration gradient driving the passive diffusion mechanism is highly unlikely in the case of oral sprays given their short residence time in the mouth and throat. The risk can be excluded in this case given the very small difference in concentration between solutions (5.93%), which will be further reduced upon dilution of the sprayed solution in the fluid available on the surface of the throat mucosa.

This is also further explained looking at the mathematic model that expresses the absorption rate; dQ/dt = A/V*Peff*C, where A is the absorption area, V is volume, Peff is the effective permeability and C is concentration. As the volume and the concentration change proportionally to keep the same administered dose (A), the absorption rate is not modified.

Therefore, this minor difference in concentration (5.93%) is considered clinically irrelevant for the efficacy, taking into consideration that eventually the same dose is administered locally. Moreover, the *in vitro* tests that describe the behaviour of the spray did not detect any relevant difference on the quality attributes investigated.

iii) Cyclodextrins

The test product contains 2 cyclodextrins: betadex *confidential information deleted* and hydroxypropylbetadex *confidential information deleted*. It is noted that the cyclodextrine content of the test product is lower than in the reference medicinal product.

Flurbiprofen is moderately bound to these two cyclodextrins, therefore the active substance is released instantaneously even in small aqueous volume, since the drug is in a dynamic equilibrium between bounded and unbounded state. Due to the intermediate affinity constants of flurbiprofen with these cyclodextrins, the cyclodextrins are not retaining the drug, so the amount of cyclodextrin is not relevant. Once released, flurbiprofen will bind to membranes since it is a highly permeable drug with higher affinity for the membranes than aqueous media (Tsume, 2014).

As the finished product is a stable solution in both cases, the cyclodextrine overage of the reference medicinal product will not introduce a difference in the overall quality properties of flurbiprofen solution (e.g. pH, buffering capacity, viscosity, density, surface tension, osmolality). These differences in excipient composition are very unlikely to affect local residence time (e.g. palatability, surface tension, viscosity, etc.) nor *in-vivo* solubility or stability of the active substance because the formulation is a solution.

The CHMP also noted that in 2017, Radkova and colleagues demonstrated that flurbiprofen 8,75 mg spray displayed comparable efficacy and safety profiles to flurbiprofen 8,75 mg lozenges. The lozenges contain no cyclodextrins in the formulation. Based on this, any differences in cyclodextrin concentration between the reference and test products would be much lower than the differences observed between spray and lozenges, which have been shown to be therapeutically equivalent. Also, the time of residence in the mouth for lozenges is much longer compared to spray, and yet the bioequivalence between lozenges and spray was established. Therefore, the difference in cyclodextrin composition is considered insignificant.

This argument has also been supported by different bibliographical data which suggest that substantially different flurbiprofen-cyclodextrin complexes behave similarly from a pK perspective upon oral administration (Imai et al., 1988). Similarly, observed rapid sublingual absorption of very lipophilic drugs such as cannabidiol, tetrahydrocannabinol or 17-β-estradiol from formulations containing different cyclodextrins (β-CD or HP-β-CD) suggests that the solid drug/cyclodextrins complex rapidly dissolves in saliva and equilibrium forms between inclusion complexes, free cyclodextrin molecules and free drug molecules, which are the only that can penetrate across biological membranes (Loftsson et al., 2003; Mannila et al., 2006, 2007). Given that both the logP octanol/water and molecular weight of e.g. 17-β-estradiol are very similar to those of flurbiprofen (4.01 vs. 3.94 and 272.38 vs. 244.261 g/mol, respectively), this seems to confirm that a similarly rapid release of the drug from the cyclodextrins complex would be expected for flurbiprofen at the level of the throat mucosa as well.

The CHMP discussed a recent study by Holm and colleagues (2016) which demonstrated that surplus cyclodextrin concentrations can have a major effect on the PK profile of one compound and a minor effect on the PK profile of another, resulting that cyclodextrin can be a critical excipient for the absorption of compounds. The Committee considered that such effect does not apply for the present case. Indeed, whilst the amount of cyclodextrins is relevant for drugs with high affinity for the cyclodextrin (like Danazol), it is not relevant for medicinal products with intermediate affinity such as flurbiprofen.

From a safety point of view, the lower amount of cyclodextrins in the test product is considered favourable.

iv) Flavours

The test product has only one flavour agent (cherry flavour) while the reference medicinal product has two (cherry flavour and mint flavour).

It was supported by some MS that different flavours may trigger a different amount of saliva production resulting in a different local drug concentration and swallowing behaviour, leading to unequal contribution to the local action.

However, the CHMP considered that the applicant has adequately justified that the removal of one flavour (mint) does not have an impact on the clinical efficacy and safety profile of the product.

First, it was noted that it is doubtful whether the removal of the mint flavour would significantly modify the secretion of saliva. Even in the hypothetical scenario where the difference in flavours causes a difference in saliva secretion, the CHMP considered that it would be clinically irrelevant in this specific case since the saliva secretion does not play a relevant contribution in the *in-vivo* performance of the oromuscal spray. Most of the content of the spray is swallowed immediately as a consequence of the gag reflex caused by the impact of the spray in the throat, without any time to be affected by the secretion of saliva.

In support of the above argument, the applicant has also discussed the publication of Rasmussen (2018) which showed that mint flavoured nicotine lozenges are bioequivalent to cherry flavoured lozenges. The lozenges do not produce a gag reflux and they need to dissolve in saliva to release the drug. This downplays the significance of the saliva production for the buccal absorption. The CHMP noted that the nicotine is systematically acting, and that direct comparison with flurbiprofen cannot be made. However the nicotine data can be seen as supportive of the hypothesis that saliva concentration does not affect buccal absorption, especially taking into account that nicotine is an extremely highly permeable drug and differences in the *in-vivo* dissolution rate would be easily detected.

3. Benefit-risk balance

Flurbiprofen Geiser 8,75 mg oromucosal spray, is a non-steroidal anti-inflammatory (NSAID) with analgesic, antipyretic, and anti-inflammatory properties. The drug inhibits the synthesis of prostaglandins by mixed inhibition of the enzymes COX-1/COX-2 with some selectivity towards COX-1. The proposed indication is short-term symptomatic relief of sore throat.

The therapeutic equivalence has been claimed to be demonstrated based on *in-vitro* data only. The applicant has requested a waiver of the need to conduct clinical studies.

The test product has some quantitative and qualitative differences with the reference product, namely;

i) different concentration: 17.16 mg/ml in the test product vs 16.20 mg/ml in the reference product (0.096% difference of content of drug substance in weight/volume)

ii) lower amount of cyclodextrins

iii) one flavour less: in the test product one flavour is employed (cherry) instead of two flavours employed in the reference product (cherry and mint)

The present referral was triggered on the grounds that the waiver for clinical studies is not in line with the "Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract" (CPMP/EWP/239/95 Rev.1) and that the differences may impact on the clinical performance of the test product.

Results from the *in-vitro* tests performed by the applicant have shown equivalence in the critical quality attributes that were tested (single actuation content, droplet size distribution, drug small particles, spray pattern, plum geometry and priming), suggesting that the quantitative and qualitative differences between the reference and the test medicinal products do not affect the deposition of the spray in the site of action (the buccal cavity).

Moreover, it was emphasised that the originator has demonstrated bioequivalence between the oromucosal spray (Strefen Direct 8,75 mg Oromucosal spray) and lozenges (Strepflam 8,75 mg Lozenges), for which more significant formulation differences exist. In addition, published evidence underline that completely different formulations of flurbiprofen (e.g. lozenge, granules and spray) applied to the oral cavity has demonstrated bioequivalence. If bioequivalence has been established among such different formulations, the minor differences in the present case will not affect the pharmacokinetic and clinical profile of the test product. This justification was accepted by the CHMP.

With regards to the different concentration (17.16 mg/ml vs. 16.20 mg/ml), it was noted that that due to the different sprayed volumes (0.17 mL vs. 0.18 mL), the delivered dose is eventually the same. This minor difference in concentration (5.93%) is expected to be reduced even more by the available saliva in the mouth. On the top of that, flurbiprofen is a highly permeable and passively absorbed drug of which the permeability is not altered by a difference in concentration. Therefore, this difference in concentration is considered insignificant and clinically irrelevant, taking into consideration that eventually the same dose is administered locally.

The CHMP also considered that the different amount of cyclodextrins is not of concern. First, the lower amount of cyclodextrins is preferable from a safety point of view. Second, flurbiprofen is moderately bound to the cyclodextrins and the release of the active substance is immediate when it comes in contact with the buccal membrane. Literature data (Radkova et al., 2017, Imai et al., 1988) demonstrate that different formulations of flurbiprofen (spray and lozenges) displayed comparable efficacy and safety profiles, despite the lack of cycloextrins from lozenges, and were also taken into consideration.

The removal of one of the flavours from the formulation had been discussed as a factor that could potentially affect the saliva secretion resulting in an unequal contribution to the local action. The CHMP considered that the removal of the mint flavour is considered clinically irrelevant in this specific case. The saliva secretion does not play a relevant contribution in the *in-vivo* performance of the buccal spray since most of the content of the spray is swallowed as a consequence of gag the reflex caused by the impact of the spray in the throat, without any time to be affected by the secretion of saliva. So in the hypothetical scenario of a difference in the amount of produced saliva this would not impact on the absorbed amount of the active substance.

The assessment was performed having in mind that this was this is a hybrid application under Article 10(3) of Directive 2001/83/EC. Differences with respect to the reference medicinal product are

possible, as long as it is demonstrated that these differences do not affect the therapeutic equivalence between the reference and the test product. The CHMP considered that the noted differences between the reference and test product are minor and the applicant has sufficiently demonstrated why these differences do not affect the local efficacy, safety or the systemic absorption of the product.

Acknowledging that deviations from the guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract (CPMP/EWP/239/95 Rev.1) could be accepted if they are justified appropriately and having reviewed all the data submitted and the responses submitted by the applicant, the CHMP considered that the waiver of the clinical trials to demonstrate therapeutic equivalence has been adequately substantiated.

The benefit-risk balance of the applied medicinal product is considered positive.

4. Grounds for Opinion

Whereas

- The Committee considered the referral under Article 29(4) of Directive 2001/83/EC;
- The Committee considered the totality of the data submitted by the applicant in relation to the objections raised as potential serious risk to public health and the questions asked by the CHMP;
- The Committee considered (Co-)Rapporteur's assessment report;
- The Committee was of the view that the submitted *in-vitro* studies and bibliographical data demonstrate sufficiently the safety and efficacy of the medicinal product.

The Committee, as a consequence, considers that the benefit-risk balance of Flurbiprofen Geiser 8,75 mg oromucosal spray, solution and associated names is favourable and therefore recommends the granting of the marketing authorisation(s) for the medicinal products referred to in Annex I of the CHMP opinion. The product information remains *as per* the final version achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion.

References

Guideline on the equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract (CPMP/EWP/239/95 Rev.1) https://www.ema.europa.eu/en/equivalence-studies-demonstration-therapeutic-equivalence-locally-applied-locally-acting-products

Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf

Guideline on the pharmaceutical quality of inhalation and nasal products https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-quality-inhalation-nasal-products_en.pdf

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Appendix 1

Divergent positions

Article 29(4) of Directive 2001/83/EC

Procedure No: EMEA/H/A-29(4)/1487

Flurbiprofen Geiser 8,75 mg oromucosal spray, solution and associated names (INN: flurbiprofen)

Divergent statement

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Flurbiprofen Geiser 8.75 mg oromucosal spray. Flurbiprofen Geiser 8.75 mg oromucosal spray was submitted under the decentralised procedure. This decentralised application concerns a hybrid version of flurbiprofen. The originator product for the exclusivity period is Strepflam® 8.75 Lozenges by Crookes Healthcare/Reckitt Benckiser Healthcare, registered since June 06th, 2001.

The reasons for divergent opinion are the following:

Flurbiprofen oromucosal spray cannot be considered therapeutically equivalent to Strefen Direct oromucosal spray because the following major issues on bioequivalence remain unresolved:

- The criteria on same concentration between Test and Reference spray to waive studies is not fulfilled and this hampers the waiver for efficacy and safety {Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract (CPMP/EWP/239/95 Rev. 1, Corr.1*) and Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)}. The justification that the same dose is administered (due to administration of a different volume) is not accepted particularly in light of the other outstanding concerns;

- The differences in cyclodextrines could impact local availability and absorption. Therefore, it cannot be excluded that the differences in composition between test and reference formulation have an effect on local exposure and this precludes a conclusion of a similar 'rate and extent of absorption' or similar 'therapeutic efficacy' which is necessary in line with the Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract (CPMP/EWP/239/95 Rev. 1, Corr.1*);

- Finally, the test formulation contains different flavors and also the total amount is different. It is well known that different flavors may trigger saliva production differently. A different saliva production may result in a different local drug concentration and swallowing behavior, which can result in an unequal contribution to the local action.

For the aforementioned reasons the marketing authorisation application is considered to be not approvable.

CHMP Member expressing a divergent opinion:

- Johann Lodewijk Hillege (NL)
- Nithyanandan Nagercoil (UK)
- Martina Weise (DE)

- Alexandre Moreau (FR)
- Jayne Crowe (IE)
- Konstantinos Markopoulos (EL)
- Jan Mueller-Berghaus (co-opted member)