Annex II

Scientific conclusions

Scientific conclusions

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 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.

Overall summary of the scientific evaluation by the CHMP

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 versus 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.

Grounds for the CHMP 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.