Annex II

Scientific conclusions

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On 1 December 2017, a Quality type II variation application was submitted by Galderma Nordic AB in line with Article 10(1) of Commission Regulation (EC) No 1234/2008 under the worksharing procedure in accordance with Article 20 of Commission Regulation (EC) No 1234/2008 (SE/H/xxxx/WS/190) for the marketing authorisations for Basiron AC 5% w/w gel and 10% w/w gel to change the formulation by replacing the gelling agent excipient Carbomer 940 with Simulgel 600 PHA (acrylamide sodium acrylodimethyltaurate copolymer, isohexadecane, polysorbate 80, sorbitan oleate and water). The reformulation was focused on the gelling agent to improve physical stability in order to extend the shelf-life of the products in Zone IV countries where viscosity value tends to decrease due to higher temperature.

The reference authority for the worksharing procedure is Sweden.

The relevant authorities of the concerned marketing authorisations are: AT, BE, DE, DK, ES, FI, FR, IE, IT, LU, NL, NO, PT.

The worksharing procedure SE/H/xxxx/WS/190 started on 20 January 2018.

A potential serious risk to public health was raised by the Netherlands. The procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures Human (CMDh), under Article 13(1), paragraph 1 of Regulation EC No 1234/2008 by Sweden on 21 August 2018.

Day 60 of the CMDh procedure was on 25 October 2018 and as no agreement amongst member states could be reached, Sweden notified the European Medicines Agency on 26 October 2018 of a referral under Article 13 of Regulation EC No 1234/2008.

Overall summary of the scientific evaluation by the CHMP

This variation relates to a change of formulation for Basiron in order to replace the gelling agent Carbomer 940 with Simulgel 600 PHA (acrylamide - sodium acrylodimethyltaurate copolymer, isohexadecane, polysorbate 80, sorbitan oleate and water). The rationale for the change in the formulation was to extend the shelf-life of the products in Zone IV countries. The CHMP noted that according to the ICH Quality Guidelines, none of the Member States of the EU is considered a Zone IV region.

As per the Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents (EMA CPMP/EWP/239/95), clinical data are in principle necessary to establish therapeutic equivalence between two products. In absence of clinical data, non-clinical validated models can be accepted. However, in support of this application neither clinical data nor validated non-clinical data have been submitted.

The MAH conducted two *in-vitro* studies which showed that there were differences in the absorbed dose (35% lower absorbed dose) and less significant differences in the penetrated doses. However, since the tests have not been validated for the therapeutic situation, the clinical relevance of the test results is unclear. The clinical significance of the observed differences cannot be determined, since the criteria for the selected non-inferiority margins have not been adequately justified, and therefore these results cannot support the efficacy and safety of the new formulation. Furthermore, the CHMP considered that the submitted *in-vitro* studies had several methodological limitations including the absence of a positive control, the duration, and the high heterogeneity among the donors.

As documented in the scientific literature[1] changes in the qualitative composition of semi-solid topical formulation can have an impact on drug release and efficacy of the topical products. The change in composition due to the replacement of the gelling agent cannot be considered minor per se, and the available data from *in-vitro* tests are not considered suitable to fully elucidate the clinical impact of this reformulation.

Safety data of the new gelling agent Simulgel 600 PHA has been evaluated in 2008 for Epiduo 0.1%, which contains adapalene 0.1% and benzoyl peroxide 2.5%, in a vehicle containing Simulgel 600 PHA. In the clinical studies performed in support of the Epiduo gel, approximately 2500 subjects above 9 years of age were exposed to Simulgel 600 PHA. There may be differences in absorption and stability of the active substance between the Epiduo and the new Basiron formulation, which cannot be determined in the absence of relevant data for Basiron. Taking into consideration the qualitative and quantitative differences between Epiduo gel and the re-formulated Basiron, it cannot be concluded based on the data provided that the data from Epiduo gel can be extrapolated to the new formulation of Basiron AC

The CHMP concluded that the submitted data are not sufficient to demonstrate therapeutic equivalence of the new and the currently marketed formulation. Therefore, the safety and the efficacy of the re-formulated product cannot be considered established.

Grounds for the CHMP opinion

Whereas

- The Committee considered the referral under Article 13 of Regulation (EC) No 1234/2008;
- The Committee considered the totality of the data submitted by the MAH in support of the type II quality variation for Basiron AC gels 5% w/w and 10% w/w;
- The Committee reviewed the available data submitted in support of the new formulation of Basiron containing the new gelling agent excipient Simulgel 600 PHA;
- The Committee noted that the *in-vitro* tests indicated differences between the marketed formulation and the new proposed formulation containing the new gelling agent Simulgel 600 PHA. Moreover the Committee noted that the *in-vitro* tests used were not validated for the therapeutic situation and that they had several methodological limitations. The clinical relevance of the test results therefore could not be determined;
- The Committee noted the absence of clinical data generated with the reformulated product containing the gelling agent excipient Simulgel 600 PHA for Basiron and associated names;
- The Committee considered the supportive clinical data of another medicinal product containing benzoyl peroxide 2.5% in combination with adapalene 0.1%, in a vehicle containing Simulgel 600 PHA, and concluded that data of the reformulated Basiron AC gels 5% w/w and 10% w/w could not be extrapolated from the dossier of another product in view of qualitative and quantitative differences between Basiron AC gels 5% w/w and 10% w/w and the other medicinal product;
- Having assessed the totality of the data, the Committee was of the view that the available data were not sufficient to demonstrate therapeutic equivalence of the new and the currently marketed formulation. Therefore, the safety and the efficacy of the re-formulated product cannot be

[1] Mohamed 2004 n7 Mohamed MI. Optimisation of chlorphenesin emulgel formulation AAPS Journal 6 (2004) 3;81-87

considered established. Therefore the benefit/risk balance of the reformulated medicinal product is considered unfavourable.

The Committee, as a consequence, recommends the refusal of the variation to the terms of the marketing authorisation application for the medicinal products referred to in Annex I of the CHMP opinion.