28 March 2019
EMA/304143/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 13 of Regulation (EC) No 1234/2008

Basiron AC and associated names

INN/active substance: benzoyl peroxide

Procedure number: EMEA/H/A-13/1475

Note:

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

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1. Background Information

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 names of the medicinal products and the names of the marketing authorisation holders (MAHs) currently authorised are listed in Annex I of the CHMP opinion.

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.

2. Scientific discussion

2.1. Introduction

Basiron AC and associated names contains benzoyl peroxide as active ingredient. Basiron AC and associated names is available in the strengths of 5% w/w and 10% w/w. Benzoyl peroxide is authorised as first line therapy for treatment of acne vulgaris and is available without prescription (‘over the counter’) in many member states.

Benzoyl peroxide acts as a keratolytic agent with antibacterial anti-inflammatory, exfoliant and comedolitic properties. Benzoyl peroxide destroys both surface and ductal microorganisms. Its lipophilic properties permit penetration of the pilosebaceous duct. Once applied to the skin, it is decomposed to release free oxygen radicals, which have potent bactericidal activity in the sebaceous follicles and anti-inflammatory action. Following topical application, benzoyl peroxide penetrates unchanged through the stratum corneum or into the follicles. It then diffuses into the epidermis and dermis, where it is degraded into benzoic acid.

The MAH Galderma Nordic AB submitted a type II worksharing variation for Basiron AC and associated names, 5% and 10% gel, to change the formulation of the product 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 aimed to improve the

physical stability in order to extend the shelf-life of the products in Zone IV countries (i.e. hot humid/ tropical zone) where viscosity value tends to decrease due to higher temperature. As a consequence the viscosity limits have also been amended.

The therapeutic equivalence was claimed by the MAH to be established based by two *in-vitro* studies comparing the human skin absorption and distribution of benzoyl peroxide using full thickness human skin mounted on Franz static diffusion cells over a 24-hour period. The outcomes of the *in-vitro* studies showed that there were some differences in the absorption and penetration between the old and the new formulation. No clinical data were presented for the new formulation.

In addition, to support the efficacy and safety of the new gelling agent, the MAH made reference to the dossier of Epiduo, a product containing a fixed-dose combination of adapalene 0.1% / benzoyl peroxide 2.5%, in a vehicle containing Simulgel 600 PHA. However for this product, clinical studies were performed where the mono components were included as comparator.

One of the relevant authorities of the concerned marketing authorisations in the worksharing procedure, the Netherlands, identified a potential serious risk to public health, based on the following grounds:

- The *in-vitro* models are not clinically validated for the therapeutic situation;

- The *in-vitro* absorption and penetration models do not support equivalence;

- Extrapolation of efficacy from Epiduo, another product containing Simulgel 600 PHA, is not justified.

Overall, the Netherlands considered that in the absence of new (non-)clinical data that would confirm the therapeutic equivalence between the new and the old formulation, the safety and efficacy of the product could not be determined.

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

The aim of the reformulation of the product in question was to extend the shelf-life of the 5% w/w and 10% w/w products in Zone IV countries, where viscosity value tends to decrease due to higher temperature. The targeted shelf-life was 24 months under both Zone II and Zone IV countries for the selected reformulations. The key change related to the reformulation concerns the gelling agent in order to improve physical stability.

The gelling agent currently used is degraded by benzoic acid, arising from the degradation of benzoyl peroxide. The viscosity of Basiron AC Gel under Zone IV climatic conditions is greatly impacted, due to the accelerated degradation of the benzoyl peroxide to benzoic acid under higher temperature. The release of benzoic acid leads to a decrease in pH and then to a depolymerisation of the Carbopol gelling agents, thus leading to a decrease in viscosity likely to create a phase separation.

The control of the viscosity of the product was the key parameter to improve during the reformulation process. The replacement of the previous gelling agent (Carbomer 940) by Simulgel 600 PHA (acrylamide - sodium acrylodimethyltaurate copolymer, isohexadecane, polysorbate 80, sorbitan oleate and water) was to ensure that the viscosity will remain stable during the shelf-life, even under climatic Zone IV conditions. The concentration of the acrylamide copolymer was determined for a concentration appropriate to keep viscosity specifications unchanged. The sodium hydroxide (10% solution) excipient which was essential in the current product to optimize pH has been removed. This is because acrylamide copolymer is a pH-independent excipient and it does not require a pH adjustment of the formulation. Consecutively, new limits for viscosity and pH of the medicinal product were set.

The therapeutic equivalence was claimed by the MAH based on two *in-vitro* studies. No clinical data were presented in support of the new formulation.

With regards to the absence of clinical data to support the new formulation, the MAH argued that the new formulation presents very minor differences compared to the previous one, as only the gelling agent was replaced and the deletion of sodium hydroxide (10% solution) was just a consequence since Simulgel is pH-independent excipient. Moreover, the MAH alleged that the new gelling agent, Simulgel 600 PHA has been evaluated as new excipient in the marketing authorization application for Epiduo (benzoyl peroxide and adapalene, indicated for treatment of acne vulgaris). Due to this similarity, only small, if any, differences in safety and efficacy profiles were to be expected and the possibility of detecting these in a clinical study was considered very small if not highly unlikely by the MAH. Such clinical study would require indeed a large sample size in order to detect or exclude any differences. Therefore, the MAH considered that to perform clinical studies to demonstrate non-inferiority for the reformulated versus the marketed formulation was not deemed feasible and no clinical data have been submitted in support of this application.

According to the Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents (EMA CPMP/EWP/239/95), clinical studies are essential to establish therapeutic equivalence between different formulations. In the absence of clinical data, relevant and validated *in-vitro* models may be used. Therefore, in order to assess whether clinical data can be substituted by *in-vitro* studies, the adequacy and the robustness of the models need to be established for the therapeutic situation. Argument of the feasibility of clinical studies cannot waive the need of relevant and validated *in-vitro* models in replacement of clinical data.

In-vitro studies

The two submitted *in-vitro* studies included a comparative *in-vitro* release test and a comparative skin absorption and a distribution study, comparing the human skin absorption and distribution of benzoyl peroxide using full thickness human skin mounted on Franz static diffusion cells over a 24-hour period.

The *in-vitro* release testing on current and reformulated product batches was performed to verify that the two formulations are equivalent in terms of release rate. The 90% confidence interval obtained was within 75% (0.75) and 133.33% (1.33) acceptance criteria for the 5% and 10% gel.

The *in-vitro* skin absorption and distribution method comparing the marketed and new formulation for each strength (5% and 10%) showed differences in absorption and penetration (Table 1, Table 2).

Table 1

Skin absorption and distribution of benzoyl peroxide through excised human skin for Benzoyl peroxide 5% AC Gel marketed formulation and Benzoyl peroxide 5% AC Gel new formulation [Study RDS.03.SRE.110694]

Benzoyl peroxide equivalent		Benzoyl peroxide AC Gel 5% marketed formulation	Benzoyl peroxide AC Gel 5% new formulation
		N=24	N=24
Total Skin	µg/cm²	2.25 ± 0.22	2.24 ± 0.24
	% of applied dose	0.88 ± 0.09	0.88 ± 0.10
Absorbed dose (receptor fluid + rinsing of receptor compartment)	µg/cm²	2.37 ± 0.16	1.76 ± 0.11
	% of applied dose	0.93 ± 0.06	0.69 ± 0.04
Penetrated dose (absorbed dose + total skin)	µg/cm²	4.62 ± 0.30	4.00 ± 0.25
	% of applied dose	1.81 ± 0.12	1.57 ± 0.10
Mass balance	% of applied dose	95.34 ± 0.67	96.29 ± 0.37

Table 2

Skin absorption and distribution of benzoyl peroxide through excised human skin for Benzoyl peroxide AC Gel 10% marketed formulation and Benzoyl peroxide AC Gel 10% new formulation [Study RDS.03.SRE.114080]

Benzoyl peroxide equivalent		Benzoyl peroxide AC Gel 10% marketed formulation	Benzoyl peroxide AC Gel 10% new formulation
		N=24	N=24
Total Skin	µg/cm²	7.92 ± 1.50	7.61 ± 1.11
	% of applied dose	1.56 ± 0.29	1.48 ± 0.21
Absorbed dose (receptor fluid + rinsing of receptor compartment)	µg/cm²	3.62 ± 0.25	2.38 ± 0.21
	% of applied dose	0.72 ± 0.05	0.46 ± 0.04
Penetrated dose (absorbed dose + total skin)	µg/cm²	11.54 ± 1.59	9.99 ± 1.22
	% of applied dose	2.28 ± 0.31	1.94 ± 0.23
Mass balance	% of applied dose	98.30 ± 0.53	96.07 ± 0.49

For Basiron 5% w/w, the absorbed dose was 2.37 $\pm$ 0.16 µg/cm^3 for the previous formulation versus 1.76 $\pm$ 0.11 µg/cm^3 for the new formulation, while the penetrated dose (skin content and absorbed dose) was 4.62 $\pm$ 0.30 µg/cm^3 for the previous formulation versus 4.0 $\pm$ 0.025 µg/cm^3 for the new formulation.

For Basiron 10% w/w, the absorbed dose was 3.62 $\pm$ 0.25 µg/cm^3 for the previous formulation versus 2.38 $\pm$ 0.21 µg/cm^3 for the new formulation, while the penetrated dose was 11.54 $\pm$ 0.30 µg/cm^3 for the previous formulation versus 9.99 $\pm$ 1.22 µg/cm^3 for the new formulation.

The total penetrated dose of benzoyl peroxide was similar between benzoyl peroxide gel marketed formulation and new formulation in both 5% w/w and 10% w/w strengths. Contrary, there was lower absorption with the new formulation than with the marketed formulation. It is argued by the MAH that this difference should not be considered to be of importance for clinical efficacy, since benzoyl peroxide is exerting its action in the skin. In contrast to the above argument, the MAH claimed that the lower absorbed dose in Basiron gel 5% new formulation compared to the previous one indicates that a better systemic safety profile can be expected with the new formulation. The MAH claimed that based on the similarity of total penetrated dose of benzoyl peroxide, a similar efficacy and safety profile at the action site and similar systemic safety profile can be expected.

The justification provided by the MAH was not considered acceptable by the CHMP. Firstly, the MAH did not address the concern raised as part of the grounds of this referral procedure that the *in-vitro* models have not been validated. Secondly, the MAH did not provide justification why such validation would not be feasible. The CHMP is of the view that a clinical validation of the model for the authorised indication is important in order to rely on such models to establish the efficacy and safety in the treatment of acne vulgaris.

Regarding the results of the studies, the CHMP noted that the skin absorption and distribution studies showed that the new formulation resulted in a similar skin uptake but a lower absorption with the new formulation compared to the marketed one. The argument that *in-vitro* skin tests showing lower absorption through the skin are not of clinical relevance since benzoyl peroxide is exerting its action in the skin was not considered acceptable. Based on the available data, it cannot be excluded that the differences shown in the skin absorption and distribution *in-vitro* study have a clinical impact.

In addition, the CHMP noted several limitations of the submitted studies. Firstly, for showing therapeutic equivalence, pre-defined criteria should be used to determine the clinical relevance of the observed differences. The choice of the pre-defined acceptance criteria should be justified. The MAH

explained that the pre-defined acceptance criteria of 75 – 133% for the release of the active substance have been chosen in line with the FDA guideline[1].

The CHMP noted that although the pre-defined acceptance criteria of 75 – 133% for the release of the active substance are in line with the FDA guideline, this guideline is limited to development stages during scale up or post-approval changes to the manufacturing process and it is not intended for the purpose of comparing different formulations or as a standalone test in the absence of clinical data. The underlying reasons for setting the acceptance criteria as per FDA guideline can be considered as supportive only and cannot be used to justify in this case the absence of clinical data.

The data of the *in-vitro* release test suggest that while there is no statistically significant difference in *in-vitro* release between the previous and the new 5% w/w formulation, there is a non-significant trend for the 10% w/w formulation. However, the clinical relevance of the difference is unknown, since no positive control data were included in this test (no batches with a known clinically significant difference in efficacy were included, in order to assist in the interpretation of the observed differences). In any event, although there is no statistically significant difference (based on 90% confidence intervals) between the formulations after 4 hours in a cell free *in-vitro* release test, the *in vitro* release data cannot be considered informative in the absence of substantiated explanation for the pre-defined acceptance criteria.

Another limitation of the *in-vitro* release study was the duration of the test which was limited to 4 hours, taking into consideration that usually *in-vitro* permeation studies using human cells show differences after 24 hours incubation. Furthermore, in the *in-vitro* absorption and distribution study, the tests were conducted on 4 replicates performed on 6 different donors, among which a high inter-donor and intra-donor heterogeneity is observed. Given the high variance between the donors, the test was not considered to be sensitive enough to discern whether differences would result in clinically relevant differences.

The CHMP noted that Basiron gel is a hydrogel consisted of a hydrophilic polymer network in water. Theoretically, in a hydrogel the active substance is transported and released from the formulation via diffusion in the water. Based on the small size of the benzoyl peroxide molecule compared to the polymer network, it is expected that the diffusion is not impaired by the polymer network, unless there are any interactions between the active substance and the polymer. It was argued by the MAH that the *in-vitro* release testing would have detected such interactions. However, as discussed above, the results from the *in-vitro* release test cannot be considered informative taking into consideration the study limitations and the absence of a robust justification regarding the predefined acceptance criteria.

Extrapolation of data from Epiduo to the new formulation of Basiron AC

To support the safety of the new gelling agent, the MAH made reference to the data of Epiduo 0.1% Gel, a product containing a fixed-dose combination of adapalene 0.1% / benzoyl peroxide 2.5%, in a vehicle containing Simulgel 600 PHA. Epiduo is indicated for the treatment of acne. The proposed new formulations of Basiron contain 3.0% (w/w) Simulgel 600 PHA compared with 4.0% (w/w) in the Epiduo monad formulation. The MAH presented the composition of the current and final formulation in comparison to the composition and the mono components of Epiduo.

[1] Guidance for Industry Nonsterile Semisolid Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) May 1997.

Safety data for Simulgel 600 PHA was evaluated during the procedure SE/H/664/01/DC in 2008 for Epiduo Gel containing 0.1% adapalene and 2.5% benzoyl peroxide. The MAH made reference to the clinical studies performed in support of the Epiduo 0.1+2.5% strength. Approximately 2,500 subjects above 9 years old were exposed to Simulgel 600 PHA. The approval for the second Epiduo formulation was based on clinical studies with approximately 500 subjects above 12 years old. The gelling agent Simulgel 600 PHA has been used in Epiduo for more than 10 years with no known safety related issues.

The MAH argued that the results of the performed clinical studies for Epiduo confirm the efficacy and the safety of the combination of Simulgel 600 PHA with benzoyl peroxide. Based on the similarity of the two products and the post-marketing experience that has been obtained from the extensive use of Epiduo, the MAH argued that these data support the efficacy and safety of the new formulation of Basiron AC Gel.

CHMP noted that the toxicity of the Simulgel 600 PHA excipients is not of concern. However, differences in absorption and stability of the active component of benzoyl peroxide between the Epiduo and the newly formulation of Basiron cannot be excluded, since there are several qualitative and quantitative differences between the two products.

Literature data demonstrate that changes in the qualitative composition of the vehicle may have an impact in safety and efficacy of the medicinal product[2], while changes in vehicle characteristics may markedly influence the cutaneous deposition, delivery, and pharmacokinetic properties of active ingredient with topical formulations[3,4]. Regarding the proposed change in the formulation, the MAH has also applied for a variation to change the limit of viscosity of the proposed medicinal product hence the physico-chemical properties seem to have changed between the two formulations. This has not been further addressed by the MAH and hence it is still unknown if the changes in physical-chemical properties affect efficacy and safety.

Therefore, based on the data provided, there is no sufficient evidence available to allow a conclusion that the data generated with Epiduo Gel can be extrapolated to support the new formulation of Basiron AC Gel.

3. Conclusions

This variation concerns 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

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

[3] Del Rosso 2008 p336 Del Rosso J.Q. Benzoyl Peroxide Cleansers for the Treatment of Acne Vulgaris: Status Report on Available Data Cutis. 2008; 82:336-342.

[4] Tanghetti 2009 p17 Tanghetti E., Karl F. Popp A. Current review of topical benzoyl peroxide: new perspectives on formulation and utilization. Dermatol Clin. 2009;27:17–24.

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 literature[5] 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 2,500 subjects above 9 years old 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.

4. Grounds for 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;

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

- 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 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.

Appendix 1

Divergent positions

Article 13 of Regulation (EC) No 1234/2008

Procedure No: EMEA/H/A-13/1475

Basiron AC (INN: benzoyl peroxide)

Divergent statement

The following CHMP Members consider that the variation application for Basiron AC gels 5% and 10%, to change the formulation by replacing the gelling agent excipient Carbomer 940 with Simulgel 600 PHA is considered approvable based on the following grounds:

- Simulgel 600 PHA is considered well known since it is an approved excipient in Epiduo®, marketed since 10 years ago.
- From a quality perspective, the change in pharmaceutical composition is considered minor which has been adequately documented by the MAH. Basiron gel is a hydrogel built up by a hydrophilic polymer network in water, in which the gelling agent/polymer has been switched from carbomer to Simulgel 600 PHA. In a hydrogel the active substance will be transported and released from the formulation via diffusion in the water. When the molecule is small compared to the polymer network, which is the case for benzoyl peroxide, the diffusion will not be hindered by the polymer network, i.e. the diffusion will be as fast as in the pure solvent, unless there are any interactions between the active substance and the polymer network. Such an interaction would be seen when measuring the in vitro release rate as a change in slope when plotting amount released vs square root of time. The submitted IVRT report shows that the release rate of benzoyl peroxide from the current and reformulated product are equivalent, for both strengths of the gel (5% and 10%), indicating that there are no interactions between the active substance and the gelling agent. Thus, the performance of the formulations is the same and penetration into the skin will be the rate controlling step.
- To perform clinical studies was considered unnecessary for a minor change in the pharmaceutical composition, based on knowledge of the gelling agent Simulgel 600 PHA, and similarity between the proposed formulations and the Epiduo® vehicle.

The benefit-risk of the proposed reformulation of Basiron AC gels 5% and 10% is considered positive since the change in formulation is considered minor, and the proposed new gelling agent Simulgel 600 PHA is well known in marketed acne vulgaris products since 10 years ago.

CHMP Members expressing a divergent opinion:

- Simona Badoi
- Ewa Balkowiec Iskra
- John Joseph Borg
- Frantisek Drafi
- Kristina Dunder
- Agnes Gyurasics
- Blanka Hirschlerova

- Natalja Karpova
- Romaldas Mačiulaitis
- Outi Mäki-Ikola
- Koenraad Norga
- Sinan B. Sarac
- Bruno Sepodes
- Ondřej Slanař
- Bart Van der Schueren
- Katarina Vučić

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- From a quality perspective, the change in pharmaceutical composition is considered minor which has been adequately documented by the MAH. Basiron gel is a hydrogel built up by a hydrophilic polymer network in water, in which the gelling agent/polymer has been switched from carbomer to Simulgel 600 PHA. In a hydrogel the active substance will be transported and released from the formulation via diffusion in the water. When the molecule is small compared to the polymer network, which is the case for benzoyl peroxide, the diffusion will not be hindered by the polymer network, i.e. the diffusion will be as fast as in the pure solvent, unless there are any interactions between the active substance and the polymer network. Such an interaction would be seen when measuring the in vitro release rate as a change in slope when plotting amount released vs square root of time. The submitted IVRT report shows that the release rate of benzoyl peroxide from the current and reformulated product are equivalent, for both strengths of the gel (5% and 10%), indicating that there are no interactions between the active substance and the gelling agent. Thus, the performance of the formulations is the same and penetration into the skin will be the rate controlling step.
- To perform clinical studies was considered unnecessary for a minor change in the pharmaceutical composition, based on knowledge of the gelling agent Simulgel 600 PHA, and similarity between the proposed formulations and the Epiduo® vehicle.

The benefit-risk of the proposed reformulation of Basiron AC gels 5% and 10% is considered positive since the change in formulation is considered minor, and the proposed new gelling agent Simulgel 600 PHA is well known in marketed acne vulgaris products since 10 years ago.

CHMP Members expressing a divergent opinion:

- Bjørg Bolstad
- Hrefna Guðmundsdóttir