Annex II

Scientific conclusions

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This referral Article 29(4) concerns a hybrid application for Lidocain/Prilocain IDETEC (lidocaine/prilocaine 25 mg/g + 25 mg/g) cream product and associated names applied according to Article 10(3) of Directive 2001/83/EC under the decentralised procedure. The reference product is Emla cream.

An application was submitted by International Drug Development under the decentralised procedure for Lidocain / Prilocain IDETEC and associated names (lidocaine/prilocaine 25 mg/g and 25 mg/g) cream on 19 April 2019.

The legal basis under which the application was submitted is: Article 10(3) of Directive 2001/83/EC hybrid application.

This application was submitted to the reference Member State (RMS): Denmark and the concerned Member State (CMS): the Netherlands.

The reference medicinal product is "EMLA 5 POUR CENT" cream (EMLA cream) from Aspen Pharma Trading Limited registered since 1990 in France. It has been marketed in European countries including Denmark, Norway, Sweden, Finland and France for more than 10 years. According to IMS database, approximately 1.5 million units of the product were sold in Europe in 2019.

During the initial assessment, the Netherlands raised major concerns regarding the therapeutic equivalence to the reference medicinal product, which remained unresolved during the CMDh procedure; hence the procedure was further referred to the CHMP, on 05 March 2021, under Article 29(4) of Directive 2001/83/EC by Denmark. Denmark requested the CHMP to assess the impact of the objections raised in the notification of 5 March 2021 that were considered to constitute a potential serious risk to public health[1].

Overall summary of the scientific evaluation by the CHMP

Hybrid medicinal products rely in part on the results of pre-clinical tests and clinical trials from the chosen reference medicinal product and in part on new data. In accordance with article 10(3) of Directive 2001/83/EC, one of the main requirements to rely on the data from the dossier of the reference medicinal product is to establish a bridge to the reference medicinal product.

For locally acting, locally applied (LALA) medicinal products, changes in formulation, dosage form, method of administration or manufacturing process may significantly influence the efficacy and/or safety. In addition, creams are considered a complex pharmaceutical form, consisting of two distinct phases i.e. lidocaine and prilocaine together as an internal oily mixture, water as external phase and emulsifying agents. This gives a complex structure to the cream, with bigger and smaller droplets, from which the active pharmaceutical ingredients have to be released before they can exert their intended action (local anesthesia in the present case). The cream is manufactured using a non-standard, complex manufacturing process and the conditions used during the manufacturing process can influence the quality and consistency of the cream (e.g. homogenisation settings can influence the particle size of the oily phase droplets). Notably, due to these aspects, demonstration of equivalence by comparison of the two medicinal products cannot be done with respect to quality data only.

Therefore, it is necessary to demonstrate that the medicinal product to be approved is therapeutically equivalent to the chosen reference medicinal product.

[1] The definition of the "potential serious risk to public health" can be found in the Guideline on the definition of a potential serious risk to public health

In order to support this hybrid application the applicant submitted a clinical study (study IDD0301), comparative quality data, an in vitro skin permeation study (IVPT), an in vitro release testing (IVRT) and published literature.

Clinical study IDD0301, a randomised, double-blind, controlled, single centre study to check acceptability, efficacy and safety of lidocaine/prilocaine 25 mg/g + 25 mg/g cream as compared to EMLA cream after a venepuncture in paediatric patients. The primary endpoint of the study was acceptability of the cream, which was measured by a questionnaire. The secondary endpoint was pain as evaluated by the faces pain scale revised (FPS-R). Later the study was put forward in support of non-inferiority between both products. However, this study cannot be accepted to provide data to establish equivalence between the medicinal product to be approved and the reference medicinal product, as the intention to evaluate equality, superiority or non-inferiority between the treatment products was not predefined. In this respect, a statistically non-significant result of the 'between groups test' on the secondary endpoint cannot be used to claim that the two treatments are considered equal and therapeutically equivalent. Moreover, the bioequivalence margin was not pre-defined. The CHMP noted that the post-hoc non-inferiority analysis (study IDD19033), performed over study IDD0301, did not have a predefined non-inferiority (NI) margin and it could not be used to show therapeutic equivalence.

The applicant presented quality comparative data on critical quality attributes and corresponding acceptance criteria that should be implemented to demonstrate pharmaceutical equivalence between two medicinal products. However, it was not agreed that the proposed critical quality attributes could fully characterise this complex pharmaceutical form and thus pharmaceutical equivalence is not considered established.

To support this hybrid application, the applicant also provided an in vitro release testing (IVRT). This IVRT has been developed and validated as per the EMA recommendations outlined in the draft Guideline on Quality and Equivalence of Topical Products. The test does not model in-vivo performance, but is considered a relevant test for quality control of the finished product at release and at end of shelf-life. The IVRT is also considered suitable for comparability between the medicinal product and the reference medicinal product, but cannot be used alone to demonstrate equivalence of the two medicinal products in case of a complex formulation. Since the product is a complex formulation, in addition to pharmaceutical equivalence, permeation kinetic and, if possible, pharmacodynamic equivalence tests are normally required to establish therapeutic equivalence.

In further support of the application the applicant also provided an in vitro skin permeation (IVPT) study in combination with other in vitro data (IVRT) to support the claim of therapeutic equivalence. The product was developed to be similar to the reference product regarding pH, viscosity and homogeneity of globule dispersion. The clinical validation and technical validation of the in vitro permeation model have, however, not been adequately performed and the data have not demonstrated therapeutic equivalence between the test medicinal product and the reference medicinal product.

Furthermore, the applicant provided information from literature on the efficacy of the EMLA cream on non-intact skin or genital mucosa. A comprehensive reference list was submitted to demonstrate a clinically relevant local anaesthetic effect of the fixed drug combination product of lidocaine/prilocaine 25 mg/g + 25 mg/g cream in both children and adults. However, the submitted literature cannot substantiate further therapeutic equivalence because there were no bridging data to the products described in the literature.

In conclusion, for this application under Article 10(3) of Directive 2001/83/EC, a satisfactory bridge to the reference product EMLA has not been established on the basis of the data provided by the applicant. As a result, this hybrid application cannot rely on the data contained in the dossier of the

reference medicinal product and a positive benefit/risk balance in the claimed indication cannot be considered as established.

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 data submitted and presented in an oral explanation by the applicant, in particular the results of the clinical study IDD0301 and its post-hoc analysis, the results of the in vitro percutaneous/absorption (IVPT) study, the results of the in vitro release study (IVRT) and the published literature. Based on these data, an equivalent anaesthetic effect between the medicinal product and the reference medicinal product could not be established.
- Based on the assessment of all the data provided and due to the limitations of all the studies submitted, the Committee was of the view that these were not sufficient to establish a bridge to the reference medicinal product and therefore pharmaceutical and therapeutic equivalence was not demonstrated.

The Committee, as a consequence, considers that the benefit-risk balance of Lidocain/Prilocain IDETEC and associated names is not favourable.

Therefore, the Committee recommends the refusal of the marketing authorisation of Lidocain/Prilocain IDETEC and associated names in the reference and concerned Member State(s).