EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

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

Invented name: Lidocain/Prilocain IDETEC and associated names

INN/combination of INNs: lidocaine/prilocaine

Procedure number: EMEA/H/A-29(4)/1506

Note:

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

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1. Information on the procedure

An application was submitted by the applicant (International Drug Development) under the decentralised procedure for Lidocain/Prilocain IDETEC and associated names 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) hybrid application.
The application was submitted to the reference Member State (RMS): Denmark and the concerned Member State(s) (CMS(s)): The Netherlands.

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

The decentralised procedure (DK/H/3106/001/DC) started on 22 May 2019.

On day 210, major issues regarding therapeutic equivalence to the reference medicinal product 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 Denmark on 22 December 2020. The CMDh 60-day procedure was initiated on 04 January 2021.

Day 60 of the CMDh procedure was on 04 March 2021 and as no agreement could be reached the procedure was referred to the CHMP.

On 05 March 2021 Denmark triggered a referral under Article 29(4) of Directive 2001/83/EC, requesting the CHMP to assess the submitted data in relation with the bioequivalence to the reference medicinal products and the impact of the objections raised on this in the notification of 5 March 2021 that were considered to constitute a potential serious risk to public health[1].

2. Scientific discussion

2.1. Introduction

Lidocain/Prilocain cream IDETEC and associated names is a cream containing lidocaine and prilocaine in the strength 25 mg/g and 25 mg/g.

Lidocain/Prilocain cream IDETEC and associated names provides dermal anaesthesia through the release of lidocaine and prilocaine from the cream into the epidermal and dermal layers of the skin and the vicinity of dermal pain receptors and nerve endings.

Lidocaine and prilocaine are amide-type local anaesthetics. They both stabilise neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby producing local anaesthesia. The quality of anaesthesia depends upon the application time and the dose.

Lidocain/Prilocain cream IDETEC and associated names is indicated for:

- Topical anaesthesia of the skin in connection with:
  needle insertion, e.g., intravenous catheters or blood sampling;
  superficial surgical procedures;

[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 adults and in the paediatric population:

- Topical anaesthesia of the genital mucosa, e.g., prior to superficial surgical procedures or infiltration anaesthesia; in adults and adolescents ≥12 years;
- Topical anaesthesia of leg ulcers to facilitate mechanical cleansing/debridement in adults only.

The indications are in accordance with the reference product EMLA cream.

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

Legal scope

This procedure concerns an application submitted according to Article 10(3) of Directive 2001/83 (hybrid application) referring to the reference medicinal product EMLA cream.

In Notice to applicant section 5.3.2.2 (concerning hybrid applications), the dossier requirements for an Article 10(3) application are clarified as follows:

> *Article 10(3) of Directive 2001/83/EC requires that, in certain circumstances in the framework of an application under Article 10, the results of the appropriate pre-clinical tests or clinical trials shall be provided. These applications will thus rely in part on the results of pre-clinical tests and clinical trials for a reference product and in part on new data.*

This means that data of the reference medicinal product selected in the application form should be the basis for the non-clinical and the clinical part of the dossier and that establishing a bridge to the reference medicinal product is a prerequisite to meet the requirements for such legal basis and to cover the complete SmPC, except for the aspects that differ from the reference product.

The Notice to applicant also describes the circumstances where for an application according to Article 10(3) additional data are required to justify the difference between test product and reference product:

> *Article 10(3) considers three circumstances where such additional data (Note: meaning 'the results of the appropriate pre-clinical tests or clinical trials' see above) will be necessary:*
>
> • *where the strict definition of a 'generic medicinal product' is not met;*
>
> • *where bioavailability studies cannot be used to demonstrate bioequivalence (for example where the new product is supra-bioavailable);*
>
> • *where there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference product.*

The second situation is applicable to the current application, meaning that it is necessary to show that the product to be approved (either a generic or reformulated product) is therapeutically equivalent to the product already approved (based on a full dossier). This is further clarified in the *'Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents'*[2]. According to this Note for Guidance (NfG) clinical trials are in principle necessary in order to demonstrate therapeutic equivalence with a reference medicinal product. The NfG states that other models may be developed and used, yet these must be validated for the therapeutic situation.

[2] https://www.ema.europa.eu/en/documents/scientific-guideline/note-guidance-clinical-requirements-locally-applied-locally-acting-products-containing-known_en.pdf

For lidocaine/prilocaine 25 mg/g + 25 mg/g cream, a locally acting, locally applied (LALA) product, any changes in formulation, dosage form, method of administration or manufacturing process may significantly influence the efficacy and/or safety. In addition, lidocaine/prilocaine 25 mg/g + 25 mg/g cream is considered a complex pharmaceutical form, manufactured with non-standard and complex manufacturing process. Therefore, the bridge to the reference medicinal product should be established by demonstrating therapeutic equivalence.

In support of this application, the applicant submitted a) a clinical study IDD0301, b) comparative quality data, c) in-vitro studies to support the claim of therapeutic equivalence and d) published literature review.

Pharmacokinetics

The pharmacokinetics of the applied for lidocaine/prilocaine cream were depicted by the applicant making reference to published literature data on the approved EMLA cream (the chosen reference medicinal product for this hybrid application). The authorised EMLA cream, and applied for lidocaine/prilocaine 25 mg/g + 25 mg/g cream may be applied to the intact skin, wounded skin or genital mucosa. The proposed time of application is between 10 min and 1 hour depending on the application site and need for anaesthesia.

The absorption across intact skin led to concentrations which averaged 1/20 and 1/36 of the systemic toxic levels of lidocaine and prilocaine (5 µg/mL and 6 µg/mL respectively). The absorption across wounded skin was increased but remained well below toxic levels. Data for absorption across genital mucosa was subsequently provided. These data indicate that systemic absorption is more rapid compared with application to intact skin but however still well below toxic levels.

The steady-state volume of distribution is of 1.1 to 2.1 L/kg (mean: 1.5±0.3 SD) for lidocaine and of 0.7 to 4.4 L/kg (mean: 2.6±1.3 SD) for prilocaine after their intravenous administration. Due to its larger volume of distribution, prilocaine produces lower blood concentration than lidocaine when given in equal amount than lidocaine. Both lidocaine and prilocaine cross the blood brain and the placental barrier.

Lidocaine is metabolised in the liver to several metabolites including monoethylglycinexylidine (MGEX) and glycinexylidide (GX) which are less potent and produced in lower concentration than lidocaine. Prilocaine is metabolised in the liver and the kidneys by amidases to several metabolites including ortho-toluidine and N-propylamine. Ortho-toluidine oxidises haemoglobin to methaemoglobin, which may have a clinical impact (please refer to the below paragraph on pharmacodynamics).

Following their intravenous administration, the terminal elimination half-life is 65 to 150 minutes (mean 110±24 SD) and 10 to 150 minutes (mean 70±48 SD) for lidocaine and prilocaine respectively.

The plasma clearance is 10 to 20 ml/min/kg (mean 13±3 SD) and 18 to 64 ml/min/kg (mean 38±15 SD) for lidocaine and prilocaine respectively.

The half-life of lidocaine may be increased in case of cardiac or hepatic dysfunction. Renal impairment does not affect the clearance of lidocaine, but accumulation of its active metabolites can occur and may lead to toxicity. The half-life of prilocaine may be increased in hepatic or renal dysfunction (organs involved in the metabolism). But as already known, the rate of metabolism and elimination is governed by the rate of absorption thus, a decrease in clearance, such as in patients with severe impaired liver function, has limited effects on the systemic plasma concentration, and dose reductions is deemed not necessary.

Pharmacodynamics

Lidocaine and prilocaine are released from the emulsion into the epidermal and the dermal layers of the skin. Lidocaine and prilocaine inhibit ionic fluxes through neuronal membranes and inhibit conduction of impulses, thereby causing local anaesthetic action.

For satisfactory anaesthetic conditions for venipuncture, the cream should be applied between 10 minutes and a maximum of 4 hours before the procedure (EMLA cream 5%, Summary of Product Characteristics). Analgesia persists for one to two hours.

Secondary pharmacology includes the formation of oxidation of haemoglobin to methaemoglobin by ortho-toluidine, one metabolite of prilocaine. No toxic levels have been observed in the proposed posology.

Comparative quality data

Lidocaine/prilocaine 25 mg/g + 25 mg/g cream is considered a complex pharmaceutical form, manufactured with a non-standard and 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).

The provided data on the extended chemical-physical characterisation of the test and reference medicinal products (by analysis of the creams for critical aspects) is considered suitable to establish the specification of the test medicinal product and justify the chosen manufacturing process. However, since the product is a complex pharmaceutical form, manufactured with a non-standard, complex manufacturing process, the CHMP did not agree with the applicant's conclusions that the proposed critical quality attributes could fully characterise this complex pharmaceutical form and thus CHMP conclude that pharmaceutical equivalence between the test and reference medicinal product cannot be considered as established, as it is also explained below.

Bioequivalence

Study IDD0301

The applicant submitted as pivotal study the results of study IDD0301, a randomised, double-blind, controlled, monocentre study to demonstrate non-inferiority of IDD lidocaine/prilocaine 25 mg/g + 25 mg/g cream as compared to EMLA cream after a venepuncture in paediatric patients. The main outcome criterion was acceptability which was measured by a questionnaire, the secondary criteria were efficacy and safety. Efficacy was assessed by the Faces pain scale – revised (FPS-R) which is a commonly used scale for the self-report of pain intensity in children and adolescents. The applicant argued that for ethical reasons related to the paediatric population, a study design including a placebo arm had been excluded. This is in principle agreed. However, the applicant could have conducted a three-arm (placebo-controlled) study in adults to overcome the ethical reasons.

Clinical study IDD0301 was not initially designed as a non-inferiority study. As a consequence, a non-significant result on the 'between groups test' cannot be used to claim that the two treatments are equivalent. In addition, the number of subjects included in such study is too small to demonstrate equivalence. A non-significant result on the 'between groups test' in the primary analysis cannot be used to claim that the two treatments are therapeutically equivalent. The study lacks assay sensitivity.

Finally, in the post-hoc non-inferiority analysis of the study IDD0301 (study IDD19033) the applicant argued that according to information available in the literature, the minimal clinically significant difference (MSCD) for pain (VAS score) ranges from 11 to 20 mm. In the case of study IDD19033, the product lidocain/prilocain 25 mg/g + 25 mg/g cream exhibits non-inferiority as compared to the

reference medicinal product EMLA cream: upper bound of 95% CI is 10.1 mm < NI margin of 14 mm. A variability in mean VAS score up to 3 mm is considered as non-significant. The CHMP noted that, in the post-hoc non-inferiority analysis, the applicant's product performs worse than EMLA cream (12 mm vs. 9 mm, respectively), which is a relative difference of 25% in pain score. Also the CHMP concluded that the post-hoc non-inferiority analysis performed over study IDD0301 can also not be used to demonstrate therapeutic equivalence between the test and reference medicinal products, since it does not have a predefined non-inferiority (NI) margin.

The applicant's approach of defining the non-inferiority margin based on literature data and extrapolating the assay sensitivity from published studies was not considered acceptable by the CHMP. In pain studies, the patient's expectation of efficacy differs when they know they will be receiving an active treatment (as in the applicant's study) or a placebo. The justification of the non-inferiority margin by means of the Kelly and colleagues (2001) article was discussed by the applicant, no new articles to support NI margin were submitted in the dossier and the CHMP concluded that is the applicant's definition of the non-inferiority margin is considered insufficiently substantiated.

In vitro studies

The test medicinal product has been developed to be equivalent to the reference medicinal product EMLA cream 5%, and the applicant claimed therapeutic equivalence based on in vitro data.

To demonstrate therapeutic equivalence between the test medicinal product and the reference medicinal product the applicant submitted the following test combination:

a. A permeation kinetic equivalence study, if diffusion through the skin is relevant to efficacy[2]. In the case of lidocaine/prilocaine 25mg/g + 25mg/g, cream, the medicinal product provides dermal analgesia by the release of lidocaine and prilocaine from the cream into the epidermal and dermal layers of the skin and by the accumulation of lidocaine and prilocaine in the vicinity of dermal pain receptors and nerve endings.

b. In vitro release assay (synthetic membrane) [2] required to support pharmaceutical equivalence. In the case of lidocaine/prilocaine 25mg/g + 25mg/g, it has been demonstrated that the 90% confidence interval for the ratio of means of the test and reference medicinal products for the parameters Release Rate (R) is contained within the acceptance interval.

a. In vitro percutaneous absorption (IVPT)

The study was submitted to the ANSM as part of the hybrid application for lidocaine/prilocaine 2.5%/2.5% cream based on the same dossier as submitted for the current application (a MA was granted in France in 2005). In this application the method and the results are briefly detailed, information on skin source, receptor fluid (phosphate buffer pH 7.4 saline solution with 1% sodium azide), temperature receptor compartment (37°C), epidermal surface temperature (32°C), agitation of receptor fluid, administration amount (200 mg cream containing 5 mg lidocaine and 5 mg prilocaine, corresponding to 2.5 mg/cm^2), occlusion by paraffin film as per SmPC, contact time periods (30 min, 1 hrs, 3 hrs and 6 hrs), washing of surface after contact time (washing liquid), tissue analysis (horny layer, epidermis and dermis) for mass balance. Forty diffusion cells were mounted i.e., five diffusion cells per formulation for each contact time period. The integrity of the skin barrier and the water tightness of the experimental model were verified for each diffusion cell before application of the studied products, by measurement of the trans epidermal water loss.

The statistical comparison between the two formulations at each contact time period was done in the study report by a Student's "t" test, the level of significance was taken at p ~ 0.05. The results were

then considered as per the EMA draft Guideline on quality and equivalence of topical products[3] reflecting the current requirement to convert the raw data into total cumulated dose (A_{total}) and maximum rate of absorption (J_{max}). The 90% confidence interval for the ratio of means of the test and comparator was then calculated.

The applicant acknowledged that a negative control such as a formulation with 50% of the proposed product strength is missing in the study as it was not recommended as a quality control at the time of the design of the study. Nevertheless, this lack of information is likely to be leveraged by the extensive experience of PMIC at the time of the conduct of the study and the particular study design where each measure at each timepoint was independent from one another. Moreover, according to the applicant, the mass balance and consistent results at different times for each analyte were used as quality control.

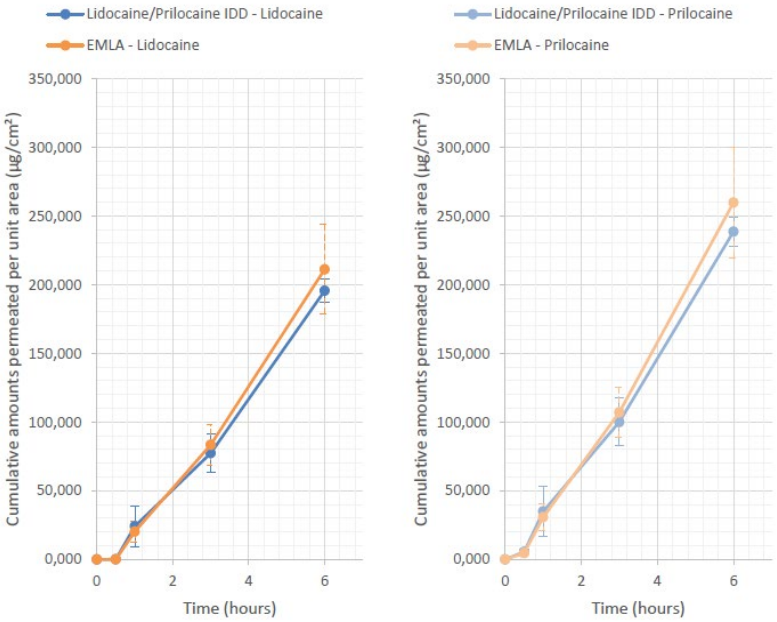

Figure 1 – Plots of the cumulative amounts permeated per unit area (mass unit/cm^2) as function of time for Lidocaine (left) or prilocaine (right)

[3] Draft guideline on quality and equivalence of topical products (europa.eu)

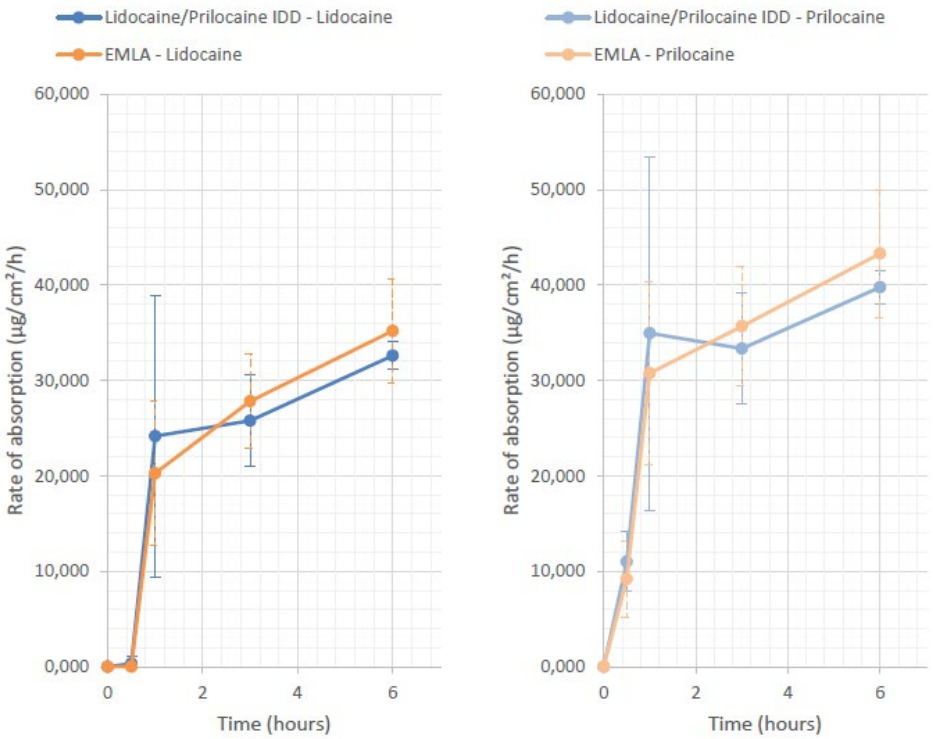

Figure 2 – Plots of the rate of absorption (mass unit/cm2/h) as a function of time for Lidocaine (left) and prilocaine (right)

A slight but similar lag-time was observed for lidocaine, for which permeation increased significantly after 0.5 h and no lag-time was observed in the permeation of prilocaine. Moreover, despite higher variability in the measures at the 1-hour timepoint, a significant difference in the mean rate of absorption is also observed between the test and reference medicinal products, whatever the analyte considered. Indeed, amounts of lidocaine and prilocaine assessed in the receptor fluid are higher for the test medicinal product than for the reference medicinal product. Nevertheless, the diffusion of both analytes continues at the 3-hour and the 6-hour timepoint and the rates of absorption of both analytes are then found similar between the test and reference medicinal products.

It is also worth noting that the duration of the experiment based on the recommendation from the summary of the product characteristics (up to five hours) did not allow to determine a maximum rate of absorption. The statistical analyses were then performed at the last timepoint of the experiment (6 hour-timepoint).

Permeation parameters		Lidocaine/Prilocaine cream	EMLA® cream	Ratio of means of test *versus* reference			
		Test product	*Reference product - France*	Mean	Lower limit of $CI_{90\%}$	Upper limit of $CI_{90\%}$	Significant difference
Lidocaine	A_{total} - 6h (µg)	395.06 ±17.52 $CI_{90\%}$ = [382.21;407.91]	426.52 ± 65.47 $CI_{90\%}$ = [378.50;474.54]	0.94 ± 0.13	0.85	1.04	NO
	J_{max} - 6h (µg/cm²/h)	32.60 ± 1.45 $CI_{90\%}$ = [31.54;33.66]	35.19 ± 5.40 $CI_{90\%}$ = [31.23;39.15]	0.94 ± 0.13	0.85	1.04	NO
Prilocaine	A_{total} - 6h (µg)	481.99 ± 21.23 $CI_{90\%}$ = [466.42;497.56]	524.73 ± 81.15 $CI_{90\%}$ = [465.22;584.25]	0.94 ± 0.13	0.84	1.03	NO
	J_{max} - 6h (µg/cm²/h)	39.77 ± 1.75 $CI_{90\%}$ = [38.48;41.05]	43.29 ± 6.70 $CI_{90\%}$ = [38.38;48.21]	0.94 ± 0.13	0.84	1.03	NO

Table 1. - Statistical analyses of IVPT results

The 90% confidence intervals (CI) for the ratio of means of the test and comparator products are contained within the acceptance interval of 80.00-125.00%, whatever the analyte considered (lidocaine or prilocaine). No significant difference is observed between the test and the reference medicinal products.

The applicant argued that when lidocaine and prilocaine diffusions were compared for each tested product, a significant difference is observed demonstrating the discriminative power of the method. Each analyte may thus be considered as an internal control for one another in each measurement.

The applicant acknowledged that the IVPT study conducted in 2003 may have gaps compared to the current requirements as depicted in the EMA draft Guideline on quality and equivalence of topical products. Nevertheless, the methodology, the study design and the results are consistent and considered reliable enough to allow the comparison between the test medicinal product Lidocaine/Prilocaine IDETEC cream and the reference medicinal product EMLA cream.

The CHMP noted that the results of the in vitro percutaneous absorption study indicate similar absorption through the skin layers. The IVPT model presented remained not clinically validated, as amongst others the timepoints included in the study do not correlate with the effect required in patients (e.g., 30 min first sampling point in in vitro permeation versus 5 min effect required as per the SmPC). A significant difference in the mean rate of absorption is observed between test and reference medicinal products at the 1-hour timepoint, whatever the analyte considered, and the amounts of lidocaine and prilocaine assessed in the receptor fluid are higher for the test product than for the reference product. Also, the test duration was not considered adequate (maximum rate of absorption was not reached) and no negative control was included. Hence, the clinical and technical validation (i.e. use of adequate controls) of the in vitro permeation model have not been adequately performed. In addition, the results do not support the demonstration of therapeutic equivalence between the test and the reference medicinal product.

b. In vitro release testing (IVRT)

Different acceptor media and synthetic membranes have been investigated in order to adapt the method and allow sufficient discriminatory power.

After development of the method, EtOH/10 % PBS pH 7.4 (25:75 v/v) and Millipore GNWP membrane have been selected as acceptor medium and membrane, respectively. The method has been validated using different batches.

The IVRT results for failed batches and batches with different drug substances contents (linearity) are provided (see figures below).

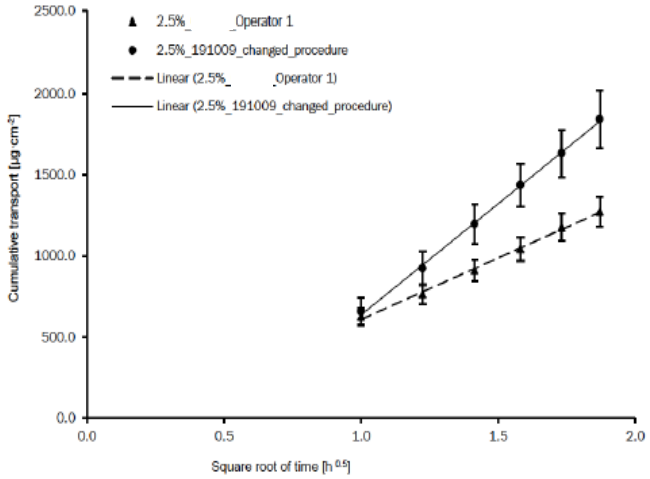

Figure 3 – Release of Lidocaine from lidocaine/prilocaine 25 mg/g + 25 mg/g cream and lidocaine/prilocaine 25 mg/g + 25 mg/g cream (failed batch) over 3.5 hours (linear range Higuchi plot). The values shown are the mean values from the experiment performed with twelve replicates. The cumulative transport into the acceptor compartment is expressed in microgram pe cm^2 of membrane area against the square root of time.

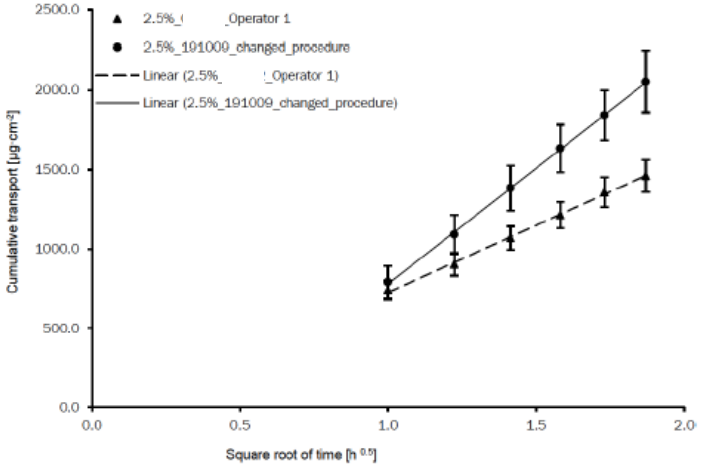

Figure 4 – Release of prilocaine from lidocaine/prilocaine 25 mg/g + 25 mg/g cream and lidocaine/prilocaine 25 mg/g + 25 mg/g (failed batch) over 3.5 hours (linear range Higuchi plot). The values shown are the mean values from the experiment performed with twelve replicates. The cumulative transport into the acceptor compartment is expressed in microgram pe cm^2 of membrane area against the square root of time.

The IVRT was then conducted with three batches of the test medicinal product lidocaine/prilocaine 25 mg/g + 25 mg/g cream versus one batch of the reference medicinal product EMLA cream 5%.

Statistical comparison between the test and reference medicinal products is provided for the slope and the cumulative transport of lidocaine and prilocaine separately.

There was no statistical difference between either the slopes or the cumulative transport assessed from all the test formulations (lidocaine/prilocaine 25 mg/g + 25 mg/g cream) and the reference formulation (EMLA cream 5%).

Overall, the CHMP noted that the in vitro release test (which uses a Franz Cell system with synthetic membrane) is considered suitable for characterisation of the test medicinal product; it could be used for comparison of two different medicinal products, but only as supportive evidence and hence the model cannot replace the need for appropriate clinical trials or other models to demonstrate therapeutic equivalence. testing.

Published literature

The applicant provided information from the literature on the efficacy of the EMLA cream on non-intact skin or genital mucosa. A comprehensive list of 74 references was submitted to support the demonstration 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.

The applicant's approach of defining the non-inferiority margin based on literature data and extrapolating the assay sensitivity from published studies, is not considered acceptable. In pain studies, the patient's expectation of efficacy differs when they know they will be receiving an active treatment (as in the applicant's study) or a placebo. The justification of the non-inferiority margin by means of the Kelly and colleagues (2001) article was discussed by the applicant, and the new articles to support NI margin were not submitted in the dossier and the CHMP concluded that is the applicant's definition of the non-inferiority margin is considered is thus still insufficiently substantiated.

The fact that no therapeutic equivalence has been demonstrated with the submitted studies cannot be substantiated by the submitted literature.

In conclusion, the CHMP is of the view that a satisfactory bridge to the reference medicinal product EMLA cream has not been established on the basis of the data provided by the Applicant with this hybrid application. A therapeutic equivalence to the reference medicinal product is not considered demonstrated on the basis of the provided clinical study or the in-vitro studies. In addition no bridging data has been submitted between the test medicinal product and the other medicinal products described (which are different from the chosen reference medicinal product) in the submitted literature.

3. Benefit-risk balance

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.

Lidocaine/prilocaine 25 mg/g + 25 mg/g cream has been approved based on the same dossier submitted with the current hybrid application by France in 2005 and by Denmark in 2007. Since then, it has been marketed in European countries including Denmark, Norway, Sweden, Finland and France for more than10 years. According to the IMS database, approximately 1.5 million units of the product were sold in Europe in 2019.

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 therapeutic 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.

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 applicant claimed that such study supported a claim of non-inferiority between both the test and reference medicinal 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 predefined. 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 demonstrate 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, the CHMP did not consider that the proposed critical quality attributes could fully characterise such complex pharmaceutical form and thus a pharmaceutical equivalence is currently 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 test medicinal product and the reference medicinal product but cannot be used alone to demonstrate therapeutic equivalence of the two medicinal products in case of a complex formulations. 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.

To further support this 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 test

product was developed to be similar to the reference product regarding a number of critical quality attributes. The clinical and technical validation (i.e. use of adequate controls) of the in vitro permeation model have, however, not been adequately performed. The results therefore cannot support the demonstration of a therapeutic equivalence between the test 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.

In conclusion, for this application under Article 10(3) of Directive 2001/83/EC, a satisfactory bridge to the reference product EMLA cream 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).

Appendix

Divergent positions

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

Procedure No: EMEA/H/A-29(4)/1506

Lidocain/ Prilocain IDETEC (INN: lidocaine, prilocaine)

Divergent statement

The following CHMP Members consider that the benefit risk ratio of Lidocain/Prilocain IDETEC 25 mg/g + 25 mg/g cream is positive given the totality of both pharmaceutical and clinical data.

The applied product and the reference product are relatively simple emulsions including the two active ingredients forming the lipophilic phase, an emulsifying agent, viscosity increasing agent, pH adjustment and water.

The product was developed to be similar to the reference product regarding a number of critical quality attributes.

The in vitro release testing (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 end-of shelf-life. Even though permeation through a synthetic membrane might not simulate in vivo conditions, the method can be seen at a suitable tool for comparing products and the comparative results of the IVRT can serve as support of a claim of therapeutic equivalence.

The results of the in vitro percutaneous absorption (IVPT) study indicate similar absorption through the skin layers. Even though the study was not performed in accordance with current draft guidance on Quality and Equivalence of Topical Products (CHMP/QWP/708282/2018) the data is supportive.

The mechanism of action for lidocaine/prilocaine is well known. After application, lidocaine/prilocaine is absorbed through the epidermal and dermal layers, reaching the nociceptors (nerve endings). By inhibiting the ionic fluxes at the nerve endings, the neuronal membranes are stabilized and thereby, the conduction of the impulses of pain are inhibited (local anaesthetic effect).

The clinical study Trial IDD0301 was not designed to confirm therapeutic equivalence, but it is considered, that the study results sufficiently indicate that there is no clinically meaningful difference in either efficacy or safety.

Lidocaine/prilocaine 25mg/25mg cream approved with the same dossier has been widely used since it was marketed in France in 2005, in Denmark in 2007, as well as in other member states. Approximately 1.5 million units of the product were sold in Europe in 2019. In Denmark, only 1 adverse event (a patient with 'Asthenia', 'Dizziness' and 'Pallor') has been reported and there have been no reports of lack of efficacy.

In conclusion, the in vitro studies comparing the lidocaine and prilocaine permeation through skin layers (IVPT) indicate similarity, as well as the studies made with synthetic membrane (IVRT) support the claim of therapeutic equivalence. Even though the IVPT study was not performed in accordance with the draft guidance on Quality and Equivalence of Topical Products, the overall claim of similarity is considered supported, based on the totality of both pharmaceutical and clinical data.

CHMP Members expressing a divergent opinion:

- Jan Mueller-Berghaus
- Martina Weise
- Sinan B. Sarac
- Sol Ruiz
- Maria Concepcion Prieto Yerro
- Hrefna Gudmundsdottir
- Ingrid Wang