Annex II

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation

Scientific conclusions

Overall summary of the scientific evaluation of EMLA cream and associated names (see Annex I)

EMLA is a fixed combination product consisting of an oil/water emulsion and eutectic mixture of lidocaine and prilocaine in equal quantities (by weight) with 2.5% of each active substance included. The active substances are both local anaesthetics of the amide type with long-standing clinical experience. EMLA 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 stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby producing local anaesthesia.

EMLA was first approved in Sweden in 1984 and is currently nationally approved in 22 countries of the European Economic Area (EEA): Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Latvia, Luxembourg, Malta, the Netherlands, Poland, Portugal, Spain, Sweden and United Kingdom and also in Iceland and Norway.

As a result of the implementation of the outcome of the paediatric work sharing procedure SE/W/008/pdWS/001 (Article 45 of Regulation (EC) No1901/2006) several divergences between the summaries of product characteristics (SmPCs) of this product, namely in sections 4.1 and 4.2 and respective sections of the package leaflet (PL) have been identified. In view of this, Germany (BfArM) notified the CHMP/EMA Secretariat of an official referral under Article 30 of Directive 2001/83/EC in order to resolve divergences amongst the nationally authorised Products Information (PIs) and thus to harmonise its divergent PIs across the EU.

The CHMP addressed a list of questions to the MAH, pointing out the sections of the products SmPC where divergences existed. The SmPC harmonisation considered all relevant therapeutic and regulatory guidelines in the EU. The proposal presented by the MAH reflected the latest scientific information using as basis the MAH's Core Data Sheet (CDS), the Core Safety Profile (CSP) agreed wording from the last PSUR work sharing procedure (IE/H/PSUR/0019/002) and the result of the paediatric work sharing procedure (SE/W/008/pdWS/001).

It is hereafter summarised the main points discussed for the harmonisation of the different sections of the SmPC.

Section 4.1 – Therapeutic indications

Topical anaesthesia of the skin

- *Adults*

The indication "t*opical anaesthesia of the skin*" is approved in all countries where EMLA has a marketing authorisation. There are some linguistic differences between the countries, such as "*local anaesthesia*", "*topical analgesia*" and "*topical anaesthesia*". Most countries include the examples "*needle insertion, e.g. intravenous catheters or blood sampling*" and "*superficial surgical procedures*".

The CHMP considered "*topical anaesthesia*" to be the optimal description. The efficacy in intact skin indications such as "*needle insertion*" and "*superficial surgical procedures*" has been demonstrated in a number of clinical studies and is considered acceptable.

- *Paediatric population*

Following the paediatric work sharing procedure SE/W/008/pdWS/001, the use of EMLA in "*topical anaesthesia of the skin*" in paediatric patients has been implemented nationally in the vast majority of the member states.

The CHMP noted that there are several clinical data supporting the inclusion of "*topical anaesthesia of the skin in connection with needle insertion e.g. intravenous catheters or blood sampling and in superficial surgical procedures*" in paediatric population. Efficacy and safety in intact skin indications such as venipuncture and vaccination has been demonstrated in a number of clinical studies in children and was considered acceptable.

In the majority of the countries the following age ranges are approved: neonates 0-2 months, infants 3-11 months and children 1-11 years. Regarding adolescents ≥12 years, no wording has been previously implemented in the SmPCs with the exception of two countries. The CHMP agreed that the use in adolescents is specifically supported by clinical studies which provide evidence for the similarity of the thickness of the stratum corneum (the rate-limiting barrier for percutaneous absorption) in adults and adolescents.

The final agreed wording for the indication "t*opical anaesthesia of the skin*" was:

"*Topical anaesthesia of the skin in connection with*
- needle insertion, e.g. intravenous catheters or blood sampling
- superficial surgical procedures
in adults and in the paediatric population."

Topical anaesthesia of the genital mucosa

There are some linguistic differences on the national texts but the CHMP considered "*topical anaesthesia of the genital mucosa*" to be the optimal description.

The CHMP was of the view that efficacy in genital mucosa indications such as application prior to superficial surgical procedures or infiltration anaesthesia when used in adults has been demonstrated in a number of clinical studies.

The specified use on genital mucosa in adolescents is included in the SmPC of two countries. There is a clinical need for the use of EMLA as a topical anaesthetic of the genital mucosa in this population.

The CHMP agreed to harmonise the indication in the genital mucosa to include the use in adolescents. The Committee also noted that data on efficacy in adults in this indication can be extrapolated to adolescents. In addition, no safety concerns could be identified in the population younger than 12 years using EMLA on genital mucosa provided appropriate dosage was applied. The final agreed wording was:

"*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

The efficacy of EMLA for mechanical (sharp) debridement of leg ulcers has been demonstrated in a number of clinical studies. As a result the CHMP endorsed the MAH's proposal for this indication with the addition of the related population (i.e. adults only). Thus, the agreed wording was "*topical anaesthesia of leg ulcers to facilitate mechanical cleansing/debridement in adults only.*"

Section 4.2 – Posology and method of administration

Adults and adolescents

The harmonised information on posology and on application time was presented by the MAH per indication (i.e. skin, genital mucosa, leg ulcers) and per related procedure in a tabular format.

Skin

- *Minor procedures, e.g. needle insertion and surgical treatment of localised lesions*

There were some divergences in the wording used in some countries (e.g. injuries or lesions and superficial surgical procedures, minor abnormalities) but the CHMP agreed on the above wording as it was consistent with the one approved in the majority of the countries. The agreed dosage and application time was "*2g (approx. half a 5g tube) or approx. 1.5g/10 cm^2 for 1 to 5 hours*". This dosage was previously approved and supported by the clinical study program. The clinical justification for the dosage in adolescents referring to the similarity of the thickness of the stratum corneum (the rate-limiting barrier for percutaneous absorption) in adults and adolescents was considered acceptable by the CHMP.

- *Dermal procedures on newly shaven skin of large body areas, e.g. laser hair removal (self-application by patient)*

The proposed wording for use on newly shaven skin on large body areas as well as the proposed dosage are previously approved and are in line with the CSP agreed in 2012. The wording was improved for clarity to include "self-application by patient".

- *Dermal procedures on larger areas in a hospital setting, e.g. split-skin grafting*

The MAH's proposal was supported by the CHMP as it was consistent with the wording in the majority of the countries. The dosage "*Approx. 1.5-2 g/10 cm^2 for 2-5 hours*" was previously approved and is in line with the CSP agreed in 2012. No maximum dose or maximum area to be treated was specified in the harmonised proposed text. The CHMP noted that from the data available no maximum area to be treated may be derived but agreed to briefly introduce the available information in section 5.2 as this may be helpful for the prescriber.

- *Skin of male & female genital organs - prior to injection of local anaesthetics*

The MAH's proposal was supported by the CHMP as it was consistent with the wording in the majority of the countries. The dosage was previously approved and is in line with the CSP agreed in 2012. The CMHP agreed with the 15 minute application time for male genital organs as the thin male genital skin enables faster absorption than other skin. For female genital skin a footnote was added stating that EMLA alone applied for 60 or 90 min does not provide sufficient anaesthesia for thermocautery or diathermy of genital warts.

Genital mucosa

The proposed harmonised wording from the MAH for both procedures, i.e. "surgical treatment of localised lesions, e.g. removal of genital warts (condylomata acuminata) and prior to injection of local anaesthetics" and "prior to cervical curettage" was considered acceptable by the CHMP as it was consistent with the one in the majority of the countries. In addition, efficacy in genital mucosa indications such as application prior to superficial surgical procedures or infiltration anaesthesia has been demonstrated in a number of clinical studies. The proposed dosage and application time for each of the above procedures was also endorsed and was in line with the approved wording in most of the countries.

Leg ulcers

- Mechanical cleansing/debridement

The wording "*mechanical cleansing/debridement*" is consistent with one approved in the majority of the countries. The proposed dose and application time were previously approved and well-established.

Paediatric population

Regarding the posology and the application time for paediatric patients the information was presented by the MAH per age group and per related procedure in a tabular format.

The posology used for minor procedures like needle insertion and surgical treatment of localised lesions in the paediatric population has previously been harmonised in most countries. However, there were some divergences in the national SmPCs with regard to the youngest age group, and the presence of a minimum recommended dose-interval.

In general the proposed paediatric posology was considered acceptable by the CHMP except for the frequency of dosing in the population between 0-3 months. It is the view of the CHMP that this age group should only be dosed once in 24 hours and as a result the CHMP was of the view that a restriction in this regard should be introduced in this SmPC section. A similar restriction (with caveats) for children 3 months and above was also considered necessary. As a result, the final agreed wording was: "*In term newborn infants and infants below 3 months, only one single dose should be applied in any 24 hour period. For children aged 3 months and above, a maximum of 2 doses, separated by at least 12 hours can be given within any 24 hour period, see sections 4.4 and 4.8.*"

The CHMP was also of the view that similar to the dose recommendations that are given for adults and adolescents for the use on genital skin, information regarding the non-recommendation of EMLA on genital skin for children should be introduced in this section. The agreed wording was: "*Safety and efficacy for the use of EMLA on genital skin and genital mucosa have not been established in children younger than 12 years. Available paediatric data do not demonstrate adequate efficacy for circumcision.*"

Finally, the age ranges were amended in line with the Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population - CPMP/ICH/2711/99 and also to reflect the degree of maturity of NADH reductase in paediatric patients.

The final agreed wording for this section of the SmPC can be found in Annex III.

Section 4.3 – Contraindications

The contraindication proposed by the MAH and endorsed by the CHMP was "*Hypersensitivity to lidocaine and/or prilocaine or local anaesthetics of the amide type or to any of the excipients listed in section 6.1.*". This wording was in line with the wording of the latest work sharing CSP.

Section 4.4 – Special warnings and precautions for use

The MAH made a proposal in line with the wording of the latest work sharing CSP. Additionally, information on pulse oximetry and antidotes in glucose-6-phosphate dehydrogenase deficiency has been agreed.

The wording proposed for other warnings and precautions (e.g. application on open wounds, atopic dermatitis, application in the vicinity of the eyes or to an impaired tympanic membrane) was considered acceptable by the CHMP.

The CHMP requested the inclusion of a warning for the paediatric population as regards the maximum number of doses in 24 hours. The following wording was agreed: "*In newborn infants/infants younger than 3 months a transient, clinically insignificant increase in methaemoglobin levels is commonly observed up to 12 hours after an application of EMLA within the recommended dosing. If the*

recommended dose is exceeded the patient should be monitored for system adverse reactions secondary to methaemoglobinaemia (see sections 4.2, 4.8 and 4.9)."

The CHMP agreed to display the note on "heel lancing" in section 4.4 according to the agreed CSP from 24 September 2012. The final wording is "*Studies have been unable to demonstrate the efficacy of EMLA for heel lancing in newborn infants*".

Finally, the CHMP was of the view that the non-recommendation for the use of EMLA on genital skin for children should be introduced in section 4.4 as well in accordance with the wording in 4.2.

The final agreed wording for this section of the SmPC can be found in Annex III.

Section 4.5 - Interaction with other medicinal products and other forms of interaction

The MAH made a proposal in line with the agreed CSP wording (IE/H/PSUR/0019/002) which in general was considered acceptable by the CHMP. However, the Committee flagged that as per the SmPC Guideline, this section should be presented in the simplest possible way to highlight the interactions resulting in a practical recommendation regarding the use of the medicinal product.

The MAH's proposal included results of a single study for the paediatric population but the CHMP stated that the information for the paediatric population should not consist of a single study data. A statement like "*Specific interaction studies in children have not been performed. Interactions are likely to be similar to the adult population*" is preferred.

In addition it was recommended that this section should include a list of the most commonly concomitantly used medicines relevant to the population in which they are prescribed making also clear that this list is not exhaustive. The MAH proposed to include the medicinal products more commonly used in paediatric practice (e.g. sulphonamides, nitrofuradantin, phenytoin, phenobarbital) which was endorsed by the CHMP.

The final agreed wording for this section of the SmPC can be found in Annex III.

Section 4.6 – Fertility, pregnancy and lactation

The wording proposed by the MAH was the CSP agreed wording from the last PSUR work sharing procedure (IE/H/PSUR/0019/002) with additions to be in accordance with the latest QRD template and to provide a recommendation for pregnant and breast feeding women.

The proposed text for fertility and breast-feeding was endorsed by the CHMP.

The CHMP did not fully support the proposal for the paragraph on pregnancy as it was not aligned with the wording given in the SmPC guideline. In addition, since no adequate data are available on the use of EMLA in pregnant women, a more careful wording is suggested and animal data - although not relating to dermal application- should nevertheless be cited.

The MAH provided an updated text for pregnancy taking into consideration the comments of CHMP and the new wording was endorsed by the Committee.

The final agreed wording for this section of the SmPC can be found in Annex III.

Section 4.7 – Effects on ability to drive and use machines

The MAH proposed the following harmonised SmPC text in line with the agreed CSP. The CHMP agreed with the wording proposed by the MAH, as follows:

"EMLA has no or negligible influence on the ability to drive and use machines when used at the recommended doses".

Section 4.8 – Undesirable effects

The wording of the CSP from the last work-sharing procedure as well as the recent PSURs served as basis for the harmonised text proposed by the MAH. The harmonised paediatric wording has been taken from the UK SmPC.

The CHMP did generally agree with the text proposed by the MAH. However, there was a discrepancy in the table of adverse reactions, in the section "*immune system disorders*". The MAH listed as rare undesirable effect "*anaphylactic reaction (in the most severe cases anaphylactic shock)*". The CHMP commented that in the CSP and in the German SmPC "*allergic reactions* (*in the most severe cases anaphylactic shock*)" is listed instead. The MAH agreed that "*anaphylactic reaction*" should not be used for allergic reactions; however as there is no Preferred Term (PT) for "*allergic reactions*" in the current MedDRA coding (version 17) the PT term "*hypersensitivity*" will be used instead. This was endorsed by the CHMP.

The final agreed wording for this section of the SmPC can be found in Annex III.

Section 4.9 – Overdose

The wording proposed by the MAH was the CSP agreed wording from the last PSUR work sharing procedure. This text was endorsed by the CHMP with the addition of the below paragraph.

"Consideration should be given to the fact that pulse oximeter values may overestimate the actual oxygen saturation in case of increased methaemoglobin fraction; therefore, in cases of suspected methaemoglobinaemia, it may be more helpful to monitor oxygen saturation by co-oximetry".

A reference for section 4.4 was also added in section 4.9 as follows: "*Clinically significant methaemoglobinaemia should be treated with a slow intravenous injection of methylene blue (see also section 4.4)*".

The final agreed wording for this section of the SmPC can be found in Annex III.

Section 5.1 – Pharmacodynamic properties

The wording in section 5.1 is based on the MAH's Core Data Sheet (CDS) with some minor rearrangements to present the text per respective indication (i.e. skin, genital mucosa, leg ulcers).

Data on vascular response and ease of venepuncture including skin thickness was included in this section mainly to address frequent questions on the effect of EMLA on the technical performance of vascular punctures. This information explains the time-course of the dynamic effects and how health care professionals can adapt to facilitate the procedures.

For the paediatric population the CHMP agreed to the inclusion of the paragraph describing the interaction of EMLA with vaccines. The CHMP also recommended shortening the detailed study descriptions for the paediatric population to provide a more comprehensive overview about the

relevant paediatric study program and the relevant paediatric features. Also, due to the off label use of EMLA in paediatric circumcision procedures it was agreed to introduce the statement of SE/W/008/pdWS/001 that the available paediatric data do not demonstrate adequate efficacy during circumcision procedures.

Overall, the MAH proposed a new comprehensive overview including the statement on circumcision procedures which was endorsed by the CHMP with some minor amendments.

The final agreed wording for this section of the SmPC can be found in Annex III.

Section 5.2 – Pharmacokinetic properties

The wording in section 5.2 is based on the MAH's CDS with some amendments. An additional subheading section on repeated application to leg ulcers was proposed compared to the CDS; this was discussed during the PSUR work sharing procedure and agreed to be included in this section. An introductory paragraph describing the differences in distribution and subsequent plasma concentrations between lidocaine and prilocaine, and a description of the effect of absorption-dependent rate of metabolism and elimination have also been added. An additional sentence describing the ceiling plasma concentration for symptoms of local anaesthetic toxicity was present in several national SmPCs, and was also proposed to be included to put the ranges of concentrations reported in context. All these amendments were considered relevant by the CHMP and were endorsed.

The CHMP agreed with the non-inclusion of the maximum dose or maximum area to be treated in section 4.2 but proposed to briefly introduce the available information in section 5.2 as this may be helpful for the prescriber. The following text was agreed: "*In studies of split-skin grafting in adults application for up to 7 hours 40 minutes to the thigh or upper arm to an area of up to 1,500 cm^2 resulted in maximum plasma concentrations not exceeding 1.1 µg/mL lidocaine and 0.2 µg/mL prilocaine.*"

For the paediatric population, the MAH proposed a text stating the plasma concentrations of lidocaine and prilocaine per age group including the applied amount of cream and the application time of the cream on the skin. The CHMP agreed to introduce this information in tabular format as this would be more clearly represented and easier to read.

The final agreed wording for this section of the SmPC can be found in Annex III.

Section 5.3 – Preclinical safety data

The wording in section 5.3 is based on the MAH's CDS expect for a change from "mutagenic" to "genotoxic" and the addition of fertility data. In general, the CHMP was in agreement with the proposed wording with some minor amendments.

The final agreed wording for this section of the SmPC can be found in Annex III.

Labelling and Package Leaflet

The labelling and the package leaflet were revised and brought in line with the adopted harmonised SmPC as discussed above and reflected in Annex III.

Grounds for the variation to the terms of the marketing authorisation(s)

Whereas

- The committee considered the referral under Article 30 of Directive 2001/83/EC
- The committee considered the identified divergences for EMLA and associated names regarding the therapeutic indications, posology and method of administration, as well as in the remaining sections of the SmPCs
- The committee reviewed the data submitted by the MAH on clinical studies, post-marketing data and published literature justifying the proposed harmonisation of the product information
- The committee agreed the harmonisation of the summary of product characteristic, labelling and package leaflet proposed by the marketing authorisation holder

the CHMP has recommended the variation to the terms of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet are set out in Annex III for EMLA and associated names (see Annex I).