EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 September 2014
EMA/707790/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pursuant to Article 30 of Directive 2001/83/EC

EMLA cream and associated names

INN of the active substance(s): lidocaine/prilocaine

Marketing authorisation holder: AstraZeneca group of companies and associated companies

Procedure no: EMEA/H/A-30/1388

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 the procedure

1.1. Background information on the basis of the grounds for referral

On 11 October 2013 Germany (BfArM) presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC in order to harmonise the national summary of product characteristics, labelling and package leaflet of the medicinal products:

EMLA cream and associated names (see Annex I of CHMP opinion).

Further to the CHMP's consideration of the matter, the referral procedure was initiated at the October 2013 meeting. The marketing authorisation holder was informed of the start of the procedure.

The CHMP appointed Martina Weise (Germany) as rapporteur and Greg Markey (United Kingdom) as co-rapporteur.

EMLA cream medicinal products are authorised in the following EU Members States: 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.

2. Scientific discussion during the referral procedure

2.1. Introduction

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).

As a result of the paediatric work sharing procedure SE/W/008/pdWS/001 (Article 45 of Regulation (EC) No1901/2006) the MAH was requested to update sections 4.1 and 4.2 of the summary of product characteristics (SmPC) and respective sections of the package leaflet (PL), of each member state where the product is authorised.

However, this has not resulted in a harmonised outcome and several divergences between the SmPCs of this product have been identified. An analysis has shown that the main divergences are found in section 4.1 (Therapeutic indications) and consequently also in section 4.2 (Posology and method of administration). It was assumed that further divergences exist with respect to e.g. section 4.3 (Contraindications) and section 4.4 (Special warnings and precautions for use).

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 Product Information (PIs) and thus to harmonise its divergent PIs across the EU.

2.2. Critical Evaluation

In general, the MAH proposed a harmonised text aligned with the product information (PI) approved in the Member States and taking into account the latest information from:

- AstraZeneca's Core Data Sheet (CDS) latest revision dated 18 May 2009,
- the Core Safety Profile (CSP) agreed wording from the last PSUR work sharing procedure (IE/H/PSUR/0019/002) dated 24 September 2012,
- the paediatric work sharing procedure (SE/W/008/pdWS/001) published on 31 July 2013.

The PI was presented using the latest version of the QRD template, version 3, published on 11 April 2013 and was adapted in accordance with the excipients guideline (EC Guideline CPMP/463/00).

It is hereafter summarised the main points discussed for the harmonisation of the different sections of the Summary of Product Characteristics (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 wording is consistent with the wording in the majority of countries and this indication is previously approved and well-established. 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.

In some national texts, examples of superficial surgical procedures are listed in section 4.1, such as use in association with *"split skin grafting*" mentioned in the UK SmPC. The MAH proposed to display examples for superficial surgical procedures only in the posology table in section 4.2 which was endorsed by the CHMP.

- *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 17 countries and only five countries are still missing the paediatric indication text in section 4.1. In these countries, the variations have been submitted and are now put on hold given the initiation of this referral procedure.

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. The wording is consistent with the wording in the majority of countries. The indication has been previously approved and supported by the recommendations of the paediatric work sharing SE/W/008/pdWS/001. Efficacy and safety in intact skin indications such as venipuncture and vaccination has been demonstrated in a number of clinical studies in children and is 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. In two countries the product is not approved in neonates (0 to 2 months) and in one country the product is approved for use from 1 month of age. The MAH proposed to harmonise the age groups as per the SmPCs of the majority of the EU countries.

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. Therefore, the MAH proposed the following harmonised wording for the paediatric population:

"*EMLA is indicated in the following age groups: neonates 0-2 months, infants 3-11 months, children 1-11 years and adolescents ≥12 years, as follows: Topical anaesthesia of the skin in connection with needle insertion e.g. intravenous catheters or blood sampling and in superficial surgical procedures.*"

The CHMP commented that the clarification for the adolescents is endorsed but stated that for the definition of ages the Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population - CPMP/ICH/2711/99 should be followed. Nevertheless, since all age groups are covered a more simplified wording was recommended, e.g. "indicated in all paediatric population".

Finally, three countries stated in their national texts of the PI that efficacy is not demonstrated in "*heel lancing*" in newborn infants, whereas, one member state has the corresponding information in section 4.2. 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 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."

<u>Topical anaesthesia of the genital mucosa</u>

This indication is approved in all but one country where EMLA has a marketing authorisation. 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 wording is consistent with the one in the majority of countries and this indication is previously approved and well-established.

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. Application prior to laser treatment of condylomata on genital mucosa of vulva, thermocauterization of genital warts on mucous mebranes, cervical curettage, portio biopsy,

biopsy on genital mucosa, local anesthetic injection, intrauterine device (IUD) insertion, vacuum abortion has been investigated.

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. For instance the removal of genital warts (condylomata acuminata, caused by human papillomavirus (HPV)), may be required, especially in the sexually active age range 15-17 years, in order to reduce the risk of viral transmissions. Some HPV subtypes have been linked to the development of genital cancer.

The CHMP agreed to harmonise the indication in the genital mucosa to include the use in adolescents. The CHMP noted that data on efficacy in adults in this indication can be extrapolated to adolescents. In fact, the relevant studies included mainly young adults (median age 25) as well as a limited number of patients aged at minimum 16 years. 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 MAH proposed the wording "*topical anaesthesia of leg ulcers to facilitate mechanical cleansing/debridement*". The CHMP commented that this wording is consistent with the one in the majority of countries and that this indication is previously approved and well-established.

The efficacy of EMLA for mechanical (sharp) debridement of leg ulcers has been demonstrated in a number of clinical studies. Altogether 13 clinical trials in a total of 651 patients, of who 431 received EMLA Cream 5%, were performed in adult patients with leg ulcers, the great majority of them geriatric patients (aged 65 or older). A meta-analysis was performed including six randomised, controlled, parallel-group trials including a total of 407 patients of whom 206 were treated with EMLA which showed significant reduction of visual analog scale (VAS) scores in the EMLA treated group.

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.*"

Topical anaesthesia of genital skin in adolescents

Regarding the "*topical anaesthesia of the genital skin*" in adolescents that is mentioned in the SmPCs of five countries, the CHMP agreed that this is part of the general skin indication and should not be mentioned separately in section 4.1. The proposal of the MAH to include specific dose recommendations for the use on genital skin in section 4.2 was endorsed.

Topical anaesthesia of genital skin in children younger than 12 years

The CHMP noted that efficacy and safety of EMLA in the paediatric population has not indisputably been demonstrated and was of the view that information regarding the non-recommendation for the use of EMLA on genital skin for children is missing and should also be introduced in section 4.2, 4.4 and 5.1.

The paediatric work sharing SE/W/008/pdWS/001 Assessment Report also states that the available data on the use of EMLA for circumcision demonstrate insufficient analgesic efficacy for this indication,

thus deletion of a respective wording in section 4.4 as proposed by the MAH was supported. The non-recommendation for circumcision was introduced in sections 4.2, 4.4 and 5.1.

Topical anaesthesia in paediatric patients with atopic dermatitis prior to curettage of mollusca

The MAH proposed the harmonised wording for the indication for topical anaesthesia in paediatric patients with atopic dermatitis prior to curettage of mollusca, however this was not supported by the CHMP as it was agreed that this indication is already covered by the general skin indication.

In addition, the CHMP commented that according to the SmPC Guideline 2009 dosage adjustments or other posology related information in specific patient groups (e.g. patients with concomitant disease) should be stated separately in section 4.2 since the skin of patients with atopic dermatitis shows an impaired stratum corneum barrier function and a more rapid percutaneous absorption of EMLA.

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 as follows:

Indication/Procedure	Dosage and Application Time
Skin	
Minor procedures, e.g. needle insertion and surgical treatment of localised lesions.	2 g (approx. half a 5 g tube) or approx. 1.5g/10 cm^2 for 1 to 5 hours.
Dermal procedures on newly shaven skin of large body areas, e.g. laser hair removal (self-application by patient)	Maximum recommended dose: 60 g. Maximum recommended treated area; 600 cm^2 for a minimum of 1 hour, maximum 5 hours.
Dermal surgical procedures on larger areas in a hospital setting, e.g. split-skin grafting.	Approx. 1.5-2 g/10 cm^2 for 2 to 5 hours.
Skin of male genital organs Prior to injection of local anaesthetics Skin of female genital organs Prior to injection of local anaesthetics	 1 g/10 cm^2 for 15 minutes 1-2 g/10 cm^2 for 60 minutes
Genital mucosa	
Surgical treatment of localised lesions, e.g. removal of genital warts (condylomata acuminata) and prior to injection of local anaesthetics	Approx. 5-10 g of cream for 5-10 minutes.
Prior to cervical curettage	10 g of cream should be administered in the lateral vaginal fornices for 10 minutes.
Leg ulcer(s)	
Adults only Mechanical cleansing/debridement	Approx. 1-2 g/10 cm^2 up to a total of 10 g to the leg ulcer(s). Application time: 30-60 minutes.

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, i.e. "*Maximum recommended dose: 60 g. Maximum recommended treated area; 600 cm^2 for a minimum of 1 hour, maximum 5 hours*" are previously approved and are in line with the CSP agreed in 2012. The wording that is proposed (i.e. self-application by patient) was a decision made for clarity during the PSUR work sharing procedure as being more easily understood than "out-patient setting". The text was endorsed by the CHMP.

- *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. However, the CHMP noted that no maximum dose or maximum area to be treated was specified in the harmonised proposed text. The MAH stated that the clinical development program in 405 patients involving exposure of skin areas up to 1,500 cm^2 together with supportive data from a human volunteer study with exposure to 400 cm^2 did not identify a maximum skin area where there was a risk for systemic toxicity. There were no indications of higher systemic plasma levels of lidocaine and prilocaine in geriatric patients than in non-geriatric patients.

The CHMP agreed with the non-inclusion of the maximum dose or maximum area to be treated in section 4.2 but was of the view that although from the data available no maximum area to be treated may be derived, it seems reasonable to briefly introduce the available information in section 5.2 as this may be helpful for the prescriber. The MAH made a relevant proposal for section 5.2 which was endorsed by the CHMP (see assessment of section 5.2 below).

- *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 (male: "*1g/10 cm^2 for 15 minutes*", female "*1-2g/10 cm^2 for 60 minutes*") 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. In addition, the mean bioavailability of lidocaine after a 15 min application of EMLA under plastic film occlusion was 13.8% in a randomized, open label comparative, parallel group study which evaluated the efficacy and safety of EMLA cream and 1% Xylocaine infiltration in males for relief of pain associated with the removal of genital warts by cryotherapy. 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.

<u>Genital mucosa</u>

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, i.e. "approx. 5-10 g of cream for 5-10 minutes" and "10 g of cream should be administered in the lateral vaginal fornices for 10 minutes" 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 "*Approx. 1-2 g/10 cm^2 up to a total of 10 g to the leg ulcer(s), Application time: 30-60 minutes*" were previously approved and well-established. Of note, study D0695C00001 (an open, non-comparative multicentre study) evaluated pharmacokinetics, safety and efficacy in 10 day repeated application of 10 g EMLA to leg ulcers performed in 2006. The outcome was that daily application of EMLA for 60 min for 10 days results in plasma concentrations of the active substances well below critical values with no apparent accumulation over 10 days.

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, as follows:

Age group	Procedure	Dosage and Application time
	Minor procedures, e.g. needle insertion and surgical treatment of localised lesions.	Approx. 1g/10 cm^2 for one hour (see details below)
Neonates 0-2 months		Up to 1 g and 10 cm^2 for one hour
Infants 3-11 months		Up to 2 g and 20 cm^2 for one hour
Children 1-5 years		Up to 10 g and 100 cm^2 for 1-5 hours
Children 6-11 years		Up to 20 g and 200 cm^2 for 1-5 hours
Paediatric patients with atopic dermatitis	Prior to removal of mollusca	Application time: 30 minutes

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. The MAH highlighted that the youngest age group the neonates below 3 months of age has evidence for efficacy, local tolerability and systemic safety of EMLA cream from the age of 0 days (term neonates) and that appropriate posology is available. As regards the dose interval the following wording was proposed "*in neonates and infants below 3 months, the maximum recommended dose should not be given more than two times, separated by at least 12 hours, within any 24-hour period*". Some of the considerations that were used as basis for these proposals are presented below.

- The methaemoglobin (metHb) reducing capacity of NADH-reductase is not fully developed in neonates but reach adult capacity at the age of 3 months. This was the basis for the stepwise increase in maximum recommended dose and application time, from the age of 3 months. A systematic review of 12 studies by *Taddio et al 1998* concluded that single doses of EMLA ranging from 0.5 to 2.0 g do not cause methaemoglobinaemia in neonates.
- In the clinical studies, metHb concentrations (normal range 1-2%) after EMLA treatment in neonates and infants rarely exceeded 3%. A 3-month-old infant given the currently recommended maximum single dose, 2 g, for a period 4 times longer than currently recommended, 4 hours, had a post-treatment maximum metHb concentration of 3.7% (in infants concentrations below 5-6% are considered clinically insignificant). The same clinical trials show that metHb concentrations after EMLA treatment in neonates and infants are somewhat elevated and returns to baseline values after 13 h.
- In the latest 5-year PSUR period involving an estimate of 94 million patients exposed to EMLA, there were 10 reports causally related to overdose, 4 in adults and 6 in paediatric patients (1 per 9 million exposed patients). In all cases the overdose was given as a single-dose.

Repeated use of EMLA in paediatric patients is primarily practised in-hospital, particularly in departments of neonatology and oncology, where the prevention of procedure-related pain is essential. The MAH commented that altogether, clinical studies and post-marketing surveillance demonstrate that health professionals are able to use EMLA appropriately for the relief of procedure-related pain in paediatric patients without the restrictions imposed by a dose-interval. Nevertheless, the MAH was of the view that considering the existence of either a total daily dose or a minimum dose-interval in the SmPCs of four countries, the inclusion of a maximum number of doses within a 24 h period for the age group where the maturity of NADH-reductase is not fully developed (i.e. neonates and infants below 3 months of age) is better expressed as follows "*in neonates and infants below 3 months, the maximum recommended dose should not be given more than two times, separated by at least 12 hours, within any 24-hour period*".

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 following wording to be included as a footnote to the posology table was agreed: "*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.*"

Regarding the application time prior to removal of mollusca the CHMP noted that the analgesic efficacy of EMLA for the curettage of molluscum contagiosum was evaluated in 3 clinical studies in children with and without a history of atopic dermatitis. Of a total of 168 patients, 64 (38.1%) had a history of atopic dermatitis. Two further studies investigating systemic safety and local tolerability of a 2 h dermal EMLA application also included children with a history of atopic dermatitis and found plasma concentrations of the local anaesthetics well below the critical level in this patient subgroup. The results of the studies suggest that a 30 min application of EMLA under occlusive dressing prior to curettage of mollusca provides effective local analgesia for this intervention in children with atopic dermatitis.

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 wording proposed by the MAH was: "*Available paediatric data do not demonstrate adequate efficacy for circumcision*". The CHMP did not agreed with the proposed wording and was of the opinion that according to the SmPC guideline the following additional sentence should be introduced: "*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 CMHP commented that the definition of ages should be in line with the Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population - CPMP/ICH/2711/99 and thus should be revised as follows:

- preterm newborn infants: ≤36 weeks of gestation (Guideline on the Investigation of Medicinal Products in the Term and Preterm Neonate)

- newborn infants: aged 0-27 days

- infants and toddlers: aged 28 days to 23 month

- children: aged 2 years to 11 years

- adolescents: aged 12 years to 17 years

The MAH adapted the nomenclature of the age groups and further suggested the age ranges to reflect the degree of maturity of NADH reductase and the paediatric patients included in clinical studies (e.g. "newborn infants and infants 0 to 2 months"). This proposal was endorsed by the CHMP.

The below wording was agreed:

Age group	*Procedure*	*Dosage and Application time*
	Minor procedures, e.g. needle insertion and surgical treatment of localised lesions.	*Approx. 1g/10 cm^2 for one hour (see details below)*
Newborn infants and infants 0-2 months[1) 2) 3)]		*Up to 1 g and 10 cm^2 for one hour[4)]*
Infants 3-11 months[2)]		*Up to 2 g and 20 cm^2 for one hour[5)]*
Toddlers and children 1-5 years		*Up to 10 g and 100 cm^2 for 1-5 hours[6)]*
Children 6-11 years		*Up to 20 g and 200 cm^2 for 1-5 hours[6)]*
Paediatric patients with atopic dermatitis	*Prior to removal of mollusca*	*Application time: 30 minutes*

[1)] 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.
[2)] EMLA should not be used in infants up to 12 months of age receiving treatment with methaemoglobin-inducing agents, because of safety concerns, see sections 4.4 and 4.8.
[3)] EMLA should not be used at less than 37 weeks gestational age because of safety concerns, see section 4.4.
[4)] Application for > 1hour has not been documented.
[5)] No clinically significant increase in methaemoglobin levels has been observed after an application time of up to 4 hours on 16 cm^2.

[6)] *After longer application time anaesthesia decreases.*

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.

Elderly, hepatic impairment, renal impairment

There were no significant divergences regarding the wording in these special populations; no dose reduction is considered necessary. Generally the rate of elimination of amide local anaesthetics is rapid. In patients with liver disease the metabolism and clearance of amide local anaesthetics may be altered depending on the degree of liver impairment. However, due to the slow absorption process from topical application, and the resulting absorption-dependent rate of elimination, maximum plasma concentrations are not expected to be influenced to a significant degree by severe hepatic dysfunction. Reduction of the currently recommended dose of EMLA in severe hepatic insufficiency is not considered necessary.

The MAH proposed to include in section 5.2 a description of the absorption-dependent rate of elimination for clarity and increased comprehension of the pharmacokinetic implications of topical absorption. This was supported by the CHMP.

Method of administration

The proposed harmonised wording by the MAH regarding the general instructions on application was consistent with the wording in the majority of the countries. It was specified that a thick layer of EMLA should be applied to the skin, including genital skin under an occlusive dressing and that in the presence of atopic dermatitis the application time should be reduced. It was also specified that for procedures related to genital mucosa, no occlusive dressing is required and that for procedures related to leg ulcers cleansing should start without delay after removal of the cream. The text was endorsed by the CHMP.

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.

There were other contraindications found in the SmPCs of different countries for which the CHMP was of the view that they do not fulfil the criteria of strict contraindications but rather constitute warnings and precautions and should be only reflected in section 4.4 (e.g. hereditary or idiopathic methaemoglobinaemia, glucose-6-phosphate dehydrogenase deficiency, application on open wounds except for leg ulcers, application among children aged between 0 and 12 months who are being treated with methaemoglobin-inducing agents, applications during which EMLA can get into the middle ear, atopic dermatitis).

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 proposed.

For patients with defective glucose-6-phosphate dehydrogenase hereditary or idiopathic methaemoglobinaemia the following text was initially proposed:

"*Patients with defective glucose-6-phosphate dehydrogenase hereditary or idiopathic methaemoglobinaemia are more susceptible to drug-induced signs of methaemoglobinaemia. In glucose-6-phosphate dehydrogenase deficient patients the antidote methylene blue is ineffective at methaemoglobin reduction, and is capable of oxidising haemoglobin itself, and therefore methylene blue therapy cannot be given. 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*".

The CHMP mentioned that only the first sentence should be included in this section and the rest of the paragraph should be moved to section 4.9 as it includes information on how to deal with overdose. It was also suggested to replace "*drug-induced*" by "*active substance-induced*". The MAH agreed to move the last sentence referring to the considerations in section 4.9 and further proposed to keep this information in this section as it warns the prescriber that a group of patients (G6PDD) cannot be treated with normal antidotes for overdose. It was agreed to add a reference for section 4.4 in section 4.9. This proposal was endorsed by the CHMP.

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 MAH proposed the following text: "*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. In term newborns and infants <3 months, only one single dose should be applied in any 24 hour period. If, based on clinical need, a decision is nevertheless taken to use two applications in children under the age of 3 months, the child should be clinically monitored for systemic adverse reactions (see section 4.2, 4.8 and 4.9)*". The Committee considered that this wording weakens the recommendation for using EMLA only once in 24 hours in infants <3 months and agreed the wording to be changed as follows:

"*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).*"

As stated earlier in this assessment report, 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, i.e. "*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".

Of note, some warnings and precautions found in some national SmPCs (e.g. hepatic insufficiency, acute injuries in herpes zoster, positive result of doping test) have not been included in the proposed harmonised wording. This is because they are either obsolete or have been included in other sections of the SmPC or because the CHMP considered that they do not fulfil the criteria for inclusion as warnings or precautions.

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 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 was:

"*Prilocaine in high doses may cause an increase in methaemoglobin levels particularly in conjunction with methaemoglobin-inducing medicinal products (e.g. sulphonamides, nitrofuradantin, phenytoin, phenobarbital). This list is not exhaustive.*

With large doses of EMLA, consideration should be given to the risk of additional systemic toxicity in patients receiving other local anaesthetics or medicinal products structurally related to local anaesthetics, since the toxic effects are additive.

Specific interaction studies with lidocaine/prilocaine and anti-arrhythmics class III (e.g. amiodarone) have not been performed, but caution is advised (see also section 4.4).

Medicinal products that reduce the clearance of lidocaine (e.g. cimetidine or betablockers) may cause potentially toxic plasma concentrations when lidocaine is given in repeated high doses over a long time period.

Paediatric population

Specific interaction studies in children have not been performed. Interactions are likely to be similar to the adult population".

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 text reads:

"*Although topical application is associated with only a low level of systemic absorption, the use of EMLA in pregnant women should be undertaken with care because insufficient data are available concerning the use of EMLA in pregnant women. However, animal studies do not indicate any direct or indirect negative effects on pregnancy, embryo-foetal development, parturition or postnatal development. Reproduction toxicity has been shown with subcutaneous/intramuscular administration of high doses of lidocaine or prilocaine much exceeding the exposure from topical application (see section 5.3).*

Lidocaine and prilocaine cross the placental barrier and may be absorbed by the foetal tissues. It is reasonable to assume that lidocaine and prilocaine have been used in a large number of pregnant women and women of childbearing age. No specific disturbances to the reproductive process have so far been reported, e.g. an increased incidence of malformations or other directly or indirectly harmful effects on the foetus".

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.

In addition, in the paragraph for the paediatric population a table was proposed by the MAH containing the number of paediatric patients, up to 12 months old, included in clinical studies with EMLA, by age group. The CHMP did not consider this table useful for the prescribers as it would give the impression that all information in the SmPC is based on this limited number of subjects, whereas the SmPC is also updated based on post-marketing experience. The CHMP proposed deletion of this table and of the corresponding introductory paragraph which was agreed with the MAH.

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 as explained in section 4.4 of this assessment report.

"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".

As already stated in section 4.4 a reference for section 4.4 was 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 MAH proposed as ATC code N01BB20. There was some discussion if a more specific code such as N01BB52 (lidocaine, combinations) or N01BB54 (prilocaine, combinations) would apply. The ATC-classification of combination products states that the 5th level codes 20 or 30 should be used when containing two or more active ingredients belonging to the same 4th level (in this case the 4th level for both lidocaine and prilocaine is N01BB). As a result, the ATC code N01BB20 was agreed.

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 inclusion of data on safety studies with respect to the formation of methaemoglobin and on the potential effect on the immunogenicity of vaccines in the paediatric population was agreed. Also, the description of a controlled study evaluating separately the pain of injection of the vaccine, as compared to the pain of inserting the needle, and one placebo-controlled efficacy study on the paediatric indication in superficial surgical procedures, were included.

The CHMP agreed to the inclusion of a paragraph describing the interaction of EMLA with vaccines.

The CHMP 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.

Finally, the CHMP agreed that the inclusion of additional efficacy data in this section is not required as the efficacy profile of the product is now well known.

The MAH proposed a new comprehensive overview including the statement on circumcision procedures which was endorsed by the CHMP with some amendments (i.e. deletion of a general paragraph on methaemoglobin levels as it does not refer directly to the products and minor amendments for clarity of the time interval). The final agreed wording for the paediatric population is as follows:

"*Clinical studies involved more than 2,300 paediatric patients of all age groups and demonstrated efficacy for needle pain (venipuncture, cannulation, sc and im vaccinations, lumbar puncture), laser treatment of vascular lesions, and curettage of molluscum contagiousum. EMLA diminished the pain of both needle insertion and injection of vaccines. Analgesic efficacy increased from 15 to 90 minutes application on normal skin but on vascular lesions 90 minutes provided no benefit over 60 min. There was no benefit of EMLA versus placebo for liquid nitrogen cryotherapy of common warts and no adequate efficacy for circumcision could be demonstrated.*

Eleven clinical studies in newborn infants and infants showed that peak methaemoglobin concentrations occur about 8 hours after epicutaneous EMLA administration, are clinically insignificant with recommended dosage, and return to normal values after about 12-13 hours. Methaemoglobin formation is related to the cumulative amount of prilocaine percutaneously absorbed, and may therefore increase with prolonged application times of EMLA.

The use of EMLA prior to measles-mumps-rubella or intramuscular diphtheria-pertussis-tetanus-inactivated poliovirus-Haemophilus influenzae b or Hepatitis B vaccines did not affect mean antibody titres, rate of seroconversion, or the proportion of patients achieving protective or positive antibody titres post immunization, as compared to placebo treated patients."

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.

As stated earlier in this assessment report, 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 the exception of the following text "*No drug-related adverse effects were seen in the reproduction toxicity studies, using either compound separately or together. An impairment of the fertility of male or female rats by lidocaine or prilocaine was not observed.*" which was replaced by "*In studies on reproduction toxicity, embryotoxic or fetotoxic effects of lidocaine were detected at doses of 25 mg/kg s.c. in the rabbit and for prilocaine starting at doses of 100 mg/kg i.m. in the rat. At doses below the maternal toxic range in the rat, lidocaine has no effect on the postnatal development of the offspring. An impairment of the fertility of male or female rats by lidocaine or prilocaine was not observed. Lidocaine crosses the placental barrier by means of simple diffusion. The ratio of the embryofetal dose to the maternal serum concentration is 0.4 to 1.3.*".

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.

2.3. Risk Management Plan

The CHMP did not require the MAH to submit a risk management plan.

2.4. Recommendation

Based on the assessment of the proposals submitted by the MAH, the responses to the LoQ, responses to the LoOIs and following the discussions of the committee, the CHMP recommended the revision and harmonisation of the Product Information for EMLA cream and associated names and adopted the following harmonised indications:

EMLA Cream is indicated for:

- *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, 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*

2.5. Conclusions

The basis for this referral procedure was a harmonisation of the SmPC, labelling and package leaflet.

The CHMP having considered:

- the rapporteur and co-rapporteur assessment reports,
- scientific discussion within the Committee,
- comments and commitments from the marketing authorisation holder,

The CHMP was of the opinion that the benefit/risk ratio of EMLA cream and associated names is considered to be favourable. The CHMP adopted a positive opinion recommending the harmonisation of the SmPC, labelling and package leaflet as set out in Annex III of the CHMP opinion for EMLA cream and associated names.