EU Risk Management Plan for Nulbia cream (2.5+2.5) % w/w (Lidocaine+Prilocaine)

RMP version to be assessed as part of this application:

RMP Version number: 4.0

Data lock point for this RMP: 01/03/2019

Date of final sign off: 14/06/2019

Rationale for submitting an updated RMP: Update RMP to RMP revision 2 format (mandatory for submissions after 30 March 2018).

Summary of significant changes in this RMP: No changes in content of RMP. Only changes in RMP format.

Details of the currently approved RMP:

Version number: 3.2

Approved with procedure: DK/H/2484/001/IB/004

Date of approval (opinion date): 08/11/2017

QPPV name: Georgios Motsios

QPPV signature:

Table of content

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Lidocaine/ Prilocaine
Pharmacotherapeutic group(s) (ATC Code)	N01BB20
Marketing Authorisation Holder	Terix Labs Ltd
Medicinal products to which this RMP refers	Nulbia
Invented name(s) in the European Economic Area (EEA)	Nulbia
Marketing authorisation procedure	Decentralised (DK/H/2484/001/DC)
Brief description of the product	Amino amide-type local anesthetics.
	Topical anaesthesia of the skin by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby producing local anaesthesia.
Hyperlink to the Product Information	PI is found in the relevant part of the technical dossier (eCTD).
Indication(s) in the EEA	Current (if applicable): Topical anaesthesia of the skin.
	Proposed (if applicable): NA
Dosage in the EEA	Current (if applicable): See SmPC section 4.2 for detailed table.
	Proposed (if applicable): NA
Pharmaceutical form(s) and strengths	Current (if applicable): Cream, (2.5+2.5)% w/w
	Proposed (if applicable): NA
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Topical anaesthesia of the skin

The product is not used for treatment of a disease. It is indicated for anaesthesia of the skin surface in cases of needle insertion or dermatological procedures such as skin grafting etc.

Incidence: NA

Prevalence: NA

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease: NA

The main existing treatment options: NA

Natural history of the indicated condition in the population, including mortality and morbidity: NA

Important co-morbidities: NA

Part II: Module SII - Non-clinical part of the safety specification

For new applications under DIR Art 10(3), the RMP elements are the same as for a generic product, according to GVP Module V (Risk Management System) Rev 2 guideline (page 32). No changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration in relation to originator product, thus not applicable for this part of the RMP.

Part II: Module SIII - Clinical trial exposure

The sponsor of the study is Verisfield (UK) Ltd. Access is given to the findings of this study to Terix Labs Ltd in order to support the Marketing Authorisation application of Lidocaine/Prilocaine Terix cream and claim essential similarity to the product EMLA® cream, which is marketed by AstraZeneca.

According to current regulation, in order to support the clinical efficacy of an essentially similar product, a therapeutic equivalence study must be conducted, comparing the new formulation to the reference product. In summary, the test product Lidocaine-Prilocaine/Verisfield (2.5+2.5)% cream was tested for therapeutic equivalence to EMLA/AstraZeneca (2.5+2.5)% cream.

The assessment of therapeutic equivalence of the two products has been performed by comparing the mean VAS score (mm) (pain level on Visual Analogue Scale). These scores have been compared between the test and the reference product and checked whether they were statistically significantly equivalent in the two products.

The main efficacy parameter was the determination of the difference in the mean VAS scores (mm) between the local treatment with Lidocaine + Prilocaine/Verisfield (2.5+2.5)% w/w cream and the reference treatment EMLA/AstraZeneca cream, as recorded by the eligible study population undergoing chronic haemodialysis immediately following the insertion of the cannula in the arteriovenous fistula.

For this study a crossover design was chosen due to the subjective nature of pain experience. Thus, having each participant acting as the control of his/her pain assessment was expected to increase the precision of the outcome.

Overall, the present study was a therapeutic equivalence study, and therefore its main objective was to show that the test treatment Lidocaine-Prilocaine/Verisfield (2.5+2.5)% w/w cream is as effective as the reference treatment EMLA/AstraZeneca (2.5+2.5)% w/w cream.

Table 1. Subject disposition

	N	%
Subjects included in the study	**60**	**100.0**
Subjects randomized	**60**	**100.0**
Subjects by treatment application	**60**	**100.0**
Subjects who received the reference treatment group	*60*	*100.0*
Subjects who received the test treatment group	*60*	*100.0*
Subjects who received the placebo treatment group	*59(1)*	*98.3*
Subjects completing Visit 1	**60**	**100.0**
Subjects completing Visit 2	**60**	**100.0**
Subjects completing study participation (i.e. Visit 3)	**60**	**100.0**
	N	**%**
Subjects who prematurely discontinued study participation	**0**	**0.0**

Table 2. Study period

	N	Mean	SD	Median	Min	Max
Time from screening until study completion (days)[1]	**60**	**11.3**	**1.4**	**12.0**	**8.0**	**13.0**
Time from randomization until study completion (days)[2]	**60**	**5.1**	**0.3**	**5.0**	**5.0**	**6.0**

Table 3. Anthropometric characteristics at baseline

FAS		**N**	**Mean**	**SD**	**Median**	**Min**	**Max**
Age (years)		60	58.3	14.4	60.7	27.1	81.4
Height (cm)		60	167.9	9.8	169.0	145.0	190.0
Body weight (Kg)		60	78.8	16.9	79.3	45.4	124.8
BMI (kg/m^2)		60	27.9	5.3	27.0	19.6	43.2
		N (%)					
Gender	*Male*	40 (*66.7*)					
	Female	20 (*33.3*)					

Part II: Module SIV - Populations not studied in clinical trials

Not Applicable according to GVP Module V (rev 2) Guideline – Product authorised following a decentralised procedure under Article 10(3) of Directive 2001/83/EC, as amended.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Not Applicable

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Not Applicable

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not Applicable

Part II: Module SV - Post-authorisation experience

The product, although authorized, has not been marketed yet and thus, no data can be generated for that part of the RMP.

SV.1 Post-authorisation exposure

Not Applicable

SV.1.1 Method used to calculate exposure

SV.1.2 Exposure

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Due to the nature of the product, there is no potential for use as a recreational drug or as a means of facilitating assault.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Summary of safety concerns	
Important identified risks	• Methaemoglobinaemia • Allergic reactions including anaphylactic shock • Medication error • Drug interactions
Important potential risks	NA
Important missing information	• Use in preterm neonates (less than 37 weeks) • Use in pregnancy and lactation

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not Applicable

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not Applicable

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Justification for removal of safety concerns from Part II: Module SVIII

- Methaemoglobinaemia

The safety concern is sufficiently characterised and the active substances are well-known. Furthermore, there are no additional risk minimisation measures or additional pharmacovigilance activities associated with the active substances.

- Allergic reactions including anaphylactic shock

The safety concern is sufficiently characterised and the active substances are well-known. Furthermore, there are no additional risk minimisation measures or additional pharmacovigilance activities associated with the active substances.

- Medication error

The safety concern is sufficiently characterised and the active substances are well-known. Furthermore, there are no additional risk minimisation measures or additional pharmacovigilance activities associated with the active substances.

- Drug interactions

The safety concern is sufficiently characterised and the active substances are well-known. Furthermore, there are no additional risk minimisation measures or additional pharmacovigilance activities associated with the active substances.

- Use in preterm neonates (less than 37 weeks)

The safety concern is sufficiently characterised and the active substances are well-known. Furthermore, there are no additional risk minimisation measures or additional pharmacovigilance activities associated with the active substances.

- Use in pregnancy and lactation

The safety concern is sufficiently characterised and the active substances are well-known. Furthermore, there are no additional risk minimisation measures or additional pharmacovigilance activities associated with the active substances.

SVII.3 Details of important identified risks, important potential risks, and missing information

Not Applicable

SVII.3.1. Presentation of important identified risks and important potential risks

SVII.3.2. Presentation of the missing information

Part II: Module SVIII - Summary of the safety concerns

Not Applicable

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

The Applicant has a structured plan for the identification of new safety concerns, further characterization of known safety concerns and for investigation whether a potential safety concern is real or not.

As far as the product is concerned, the existing safety concerns that are described in the SmPC of the product (in the respective paragraphs – 4.3 to 4.9) are covered by routine pharmacovigilance activities, as described in the Pharmacovigilance System Master File (PSMF), and (briefly) include PSUR and ICSR submission, EudraVigilance integration and weekly literature review for APIs.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities have been performed or planned for the product. Safety of the product is well established with more than 20 years of use in the market and no new signals have risen to support further PV activities besides routine PV activities.

III.3 Summary Table of additional Pharmacovigilance activities

No planned additional pharmacovigilance activities to date.

Part IV: Plans for post-authorisation efficacy studies

Since product is circulated in the market since 1996 (EMLA, Astra Zeneca), there are no post-authorisation efficacy studies planned for this product.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Not Applicable

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Not Applicable

Part VI: Summary of the risk management plan

Summary of risk management plan for Nulbia cream (2.5+2.5)% w/w (Lidocaine+Prilocaine)

This is a summary of the risk management plan (RMP) for Nulbia cream (2.5+2.5)% w/w. The RMP details important risks of Nulbia cream (2.5+2.5)% w/w, how these risks can be minimised, and how more information will be obtained about Nulbia 's risks and uncertainties (missing information).

Nulbia's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Nulbia cream (2.5+2.5)% w/w should be used.

I. The medicine and what it is used for

Nulbia cream (2.5+2.5)% w/w is authorised for topical anaesthesia of the skin (see SmPC for the full indication). It contains Lidocaine and Prilocaine as the active substances and it is given by cutaneous administration.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Nulbia cream (2.5+2.5)% w/w, together with measures to minimise such risks and the proposed studies for learning more about Nulbia's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Nulbia cream (2.5+2.5)% w/w is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Nulbia cream (2.5+2.5)% w/w are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there

is sufficient proof of a link with the use of Nulbia cream (2.5+2.5)% w/w. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

Not Applicable

II.C.2 Other studies in post-authorisation development plan

Not Applicable

Part VII: Annexes

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Annex 1 – EudraVigilance Interface

Annex 1 of the RMP is not required to be submitted in eCTD; the electronic file should be submitted in accordance to GVP Module V section V.C.2 and the guidance on the website[i].

Leave Annex 1 empty.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table 2 Annex II: Completed studies

Study	Description	Countries	Study Design	Number of patients	Duration of follow up	Completion Date
Lidocaine/ Prilocaine study	Multicenter, randomized, double blind (patients and investigators), placebo-controlled, crossover study of Lidocaine + Prilocaine/Verisfield (2.5+2.5)% w/w cream and EMLA/AstraZeneca cream, in patients undergoing haemodialysis.	Greece	Multicenter, randomized, double blind, placebo-controlled, crossover study	60 (Full analysis set), 60(Per protocol set), 59 (Per protocol set, outliers excluded)	11.3±1.4 days	04 July 2013

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Study report is found in the relevant part of the technical dossier (eCTD).

Annex 4 - Specific adverse drug reaction follow-up forms

Not Applicable

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not Applicable

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not Applicable

Annex 7 - Other supporting data (including referenced material)

1. EMLA cream 5% - Summary of Product Characteristics [Internet]. Available from: http://www.medicines.org.uk/emc/medicine/171/SPC/EMLA+Cream+5/

2. AstraZeneca Canada Inc. EMLA Product Monograph [Internet]. Available from: http://www.scribd.com/doc/36105174/EMLA-Product-Monograph

Annex 8 – Summary of changes to the risk management plan over time

Version	**Approval date** **Procedure**	**Change**
4.0	DK/H/2484/001/IB/004	Switch to new RMP format (revision 2 – mandatory for submissions after 30 March 2018).