Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Lidocaine/Prilocaine 5 % cutaneous patch

(lidocaine, prilocaine)

PRODUCT LICENCE NUMBER; PL 20117/0291

Morningside Healthcare Limited.

LAY SUMMARY

Lidocaine/Prilocaine 5 % cutaneous patch

(lidocaine, prilocaine)

This is a summary of the Public Assessment Report (PAR) for Lidocaine/Prilocaine 5% cutaneous patch. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Lidocaine/Prilocaine 5% cutaneous patch, patients should read the package leaflet or contact their doctor or pharmacist.

What is Lidocaine/Prilocaine 5% cutaneous patch and what is it used for?
This application is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised in the European Union (EU) called EMLA 5% patch.

This medicine is used to create local anaesthesia in intact skin, for example:
• prior to vein puncture or subcutaneous injection,
• prior to superficial, instrumental or laser skin surgery.

How does Lidocaine/Prilocaine 5% cutaneous patch work?
Lidocaine/Prilocaine 5% cutaneous patch contains two active ingredients lidocaine and prilocaine. These active ingredients belong to a group of medicines called local anaesthetics. This medicine is applied to the skin, numbing a small area before certain procedures are performed.

How is Lidocaine/Prilocaine 5% cutaneous patch used?
The pharmaceutical form of this medicine is a cutaneous patch and is for cutaneous use only.

Dosage:
The number of cutaneous patches to be applied depends on the area to be treated:
1 g (1 medicated patch) for a 10 cm^2 area to create local anaesthesia (temporary loss of feeling). The number of prescribed skin medicated patches are applied to the area to be anaesthetised, during the recommended time. In infants 0 to 3 months of age, more than 1 patch at a time should not be applied, during a maximum of 1 hour, over a maximum area of 10 cm2.

The size of the patch cannot be adapted to application on some parts of the body in neonates or infants.

For further information on how Lidocaine/Prilocaine 5% cutaneous patch is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of Lidocaine/Prilocaine 5% cutaneous patch have been shown in studies?
Because Lidocaine/Prilocaine 5% cutaneous patch is a hybrid medicine, studies in healthy volunteers consist of tests to determine that it is therapeutically equivalent to the reference medicine.

What are the possible side effects of Lidocaine/Prilocaine 5% cutaneous patch?
Because Lidocaine/Prilocaine 5% cutaneous patch is a hybrid medicine and is therapeutically equivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

Why was Lidocaine/Prilocaine 5% cutaneous patch approved?
It was concluded that, in accordance with EU requirements, Lidocaine/Prilocaine 5% cutaneous patch has been shown to be therapeutically equivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Lidocaine/Prilocaine 5% cutaneous patch?
A Risk Management Plan (RMP) has been developed to ensure that Lidocaine/Prilocaine 5% cutaneous patch is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Lidocaine/Prilocaine 5% cutaneous patch
A Marketing Authorisation for Lidocaine/Prilocaine 5% cutaneous patch was granted in the UK on 04 July 2019.

The full PAR for Lidocaine/Prilocaine 5% cutaneous patch follows this summary.

This summary was last updated in August 2019

TABLE OF CONTENTS

Contents

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Lidocaine/Prilocaine 5 % cutaneous patch (PL 20117/0291) could be approved.

The product is a topical anaesthesia of the skin prior to:

- Needle insertion (sub-cutaneous or iv)
- Superficial, instrumental and laser bean surgical intervention

Lidocaine/Prilocaine 5 % cutaneous patch contains 2 amide-type local anaesthetics ; lidocaine and prilocaine.

Lidocaine/prilocaine is an oil-in-water emulsion, in which the oil phase consists of a eutectic mixture of lidocaine and prilocaine in the ratio 1:1. The emulsion of this oil in the water allows crossing the cutaneous barrier to get an efficient analgesia of the skin. Local anaesthetics acts directly on the nerves by blocking in a reversible, total and specific manner the nerve conduction. Lidocaine and prilocaine are amide-type local anaesthetics. Both substances stabilise the membrane of the nerve cells by inhibiting the flow of ions necessary for impulse conduction, and thereby induce local analgesia. The quality of analgesia is dependent on application time and dose. The time needed to achieve reliable anaesthesia of intact skin is at least 1 hour.

The depth of cutaneous anaesthesia increases with application time. In 90% of patients the anaesthesia is sufficient for the insertion of a biopsy punch (4 mm diameter) to a depth of 2 mm after 60 minutes and 3 mm after 120 minutes lidocaine/prilocaine treatment.
Lidocaine/prilocaine is equally effective and has the same anaesthetic onset time across the range of light to dark pigmented skin (skin types I to VI).
Lidocaine/prilocaine produces a biphasic vascular response involving initial vasoconstriction followed by vasodilatation at the application site (see section 4.8 of the SmPC).

This application was submitted under Article 10(3) of Directive 2001/83/EC, as amended as bioequivalence cannot be demonstrated through bioavailability studies, claiming to be a hybrid medicinal product of the reference medicinal product EMLA 5% patch (340 007-1), which was granted a Marketing Authorisation in France on 23 January 1996. EMLA 5% patch (PL 00017/0330) was originally authorised in the UK on 26 October 1995 to the Marketing Authorisation holder Astra Pharmaceuticals Limited but the licence was cancelled in 2005, it is considered acceptable to refer to the French product; EMLA 5% patch (340 007-1). EMLA 5% patch is a line extension of the original product EMLA® cream, pertaining to the same global marketing authorisation.

No new non-clinical studies were conducted, which is acceptable given that the application is based on being a hybrid medicinal product of a reference product that has been licensed for over 10 years.

Data from one clinical study was submitted with this application. This study was to demonstrate the clinical superiority of the anaesthetic/analgesic effects of reference product and lidocaine/prilocaine 5% cutaneous patch compared to placebo and to demonstrate non-inferiority of lidocaine/prilocaine 5% cutaneous patch compared to EMLA patch (cutaneous patch). The study was conducted in line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this/these product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this/these application and are satisfactory.

A national Marketing Authorisation was granted in the UK on 04 July 2019.

II QUALITY ASPECTS

II.1 Introduction

This product is a cutaneous patch consisting of an absorbent disc of approximately 10 cm^2 impregnated with 1 gram of an emulsion containing the eutectic mixture (1:1) of the two anaesthetics lidocaine (2.5%) and prilocaine (2.5%), surrounded by an adhesive foam ring, with the entire unit adherent to a laminated backing foil acting as an occlusive dressing.

In addition to lidocaine and prilocaine, this product also contains the excipients laminated backing foil (aluminium foil with plastic film), absorbent disc (cellulose), adhesive foam tape (polyethylene coated ring with acrylate adhesive), macrogolglycerol hydroxystearate (hydrogenated castor oil), carbomers, sodium hydroxide and purified water.

Lidocaine/Prilocaine patches consists of an occlusive dressing (user part) and a protective liner (closure part). The user part is composed of an aluminium/plastic backing laminate, an absorbent cellulose disc and a foam tape ring. The tape is polyethylene foam coated with acrylate adhesive. The closure part is an aluminium/plastic laminate. A peel-off seal between the backing and closure laminates encloses the disc, which is impregnated with lidocaine/prilocaine emulsion. Pack of 1 or 20. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

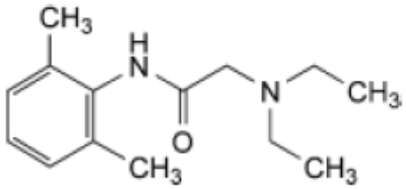
II.2 ACTIVE SUBSTANCES

rINN: Lidocaine

Chemical Name: Acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)
2-(Diethylamino)-2',6'-acetoxylide
2-Diethylamino-2',6'-dimethylacetanilide

Molecular Formula: $C_{14}H_{22}N_2O$

Chemical Structure:



Molecular Weight: 234.3

Appearance: White or almost white crystalline powder, with a characteristic odour

Solubility: In common solvents:
- Water : practically insoluble,
- Alcohol : very soluble,
- Methylene chloride : very soluble,
- Chloroform : very soluble,
- Benzene : freely soluble,
- Ether : freely soluble.

Lidocaine is the subject of a European Pharmacopoeia monograph.

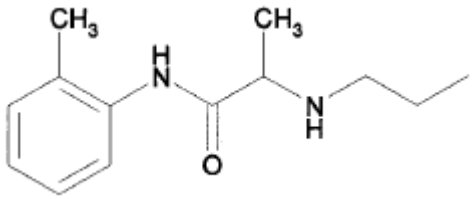
All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

rINN: Prilocaine

Chemical Name: N-(2-methylphenyl)-2-(propylamino)-propanamide
2-(propylamino)-O-propionotoluidine
N-(α-propylaminopropionyl)-o-toluidine α-propylamino-2-methylpropionanilide

Molecular Formula: $C_{13}H_{20}N_2O$

Chemical Structure:



Molecular Weight: 220.31

Appearance: White or almost white crystalline powder

Solubility: In common solvents:
- Water : slightly soluble,
- Ethanol : very soluble,
- Acetone : very soluble

Prilocaine is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* impurity profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification

The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with the storage conditions 'Do not store above 25°C, do not refrigerate. Do not freeze', is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of lidocaine and prilocaine are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for this application.

III.4 Toxicology
No new toxicology data were provided and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this is hybrid application of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
In accordance with the regulatory requirements, data from one clinical study has been submitted with this application. This study was conducted in-line with current Good Clinical Practice (GCP).

A randomised, double-blind, placebo-controlled, cross-over study to demonstrate the clinical superiority of the anaesthetic/analgesic effects of EMLA patch (cutaneous patch) and lidocaine/prilocaine (2.5%/2.5%) anaesthetic cutaneous patch compared to placebo and to demonstrate non-inferiority of lidocaine/prilocaine (2.5%/2.5%) anaesthetic cutaneous patch compared to EMLA patch (cutaneous patch).

This study consisted of two parts; Part A and Part B.

Part A (Treatment periods 1 to 4):
This part of the study was conducted as a randomised, double-blind, placebo-controlled, 4-period, cross-over study under fed conditions. In treatment periods 1 and 2 the Investigational Medicinal Product (IMP) was applied for 1 hour and in Treatment periods 3 and 4 the IMP was applied for 4 hours. The treatment periods were separated by a wash-out period of 7 to 9 calendar days between applications.

Part A: 1 cutaneous patch (25 mg lidocaine/25 mg prilocaine) per treatment period (treatment periods 1 to 4). In Part A volunteers received the test, reference and placebo products, according to the randomisation schedule, under fed conditions

Part B (Treatment periods 5 and 6)
Once Part A had been completed, Part B commenced after a wash-out period of 10 calendar days. This part of the study was conducted as a randomised, single-blind, two-period, cross-over study under fed conditions. Volunteers who completed Part A were enrolled in Part B. Periods 5 and 6 were separated by a wash-out period of 13 calendar days between applications.

Part A of the study will be discussed in section IV.4 of this report and Part B of the study will be discussed in section IV.2.

The main objectives of the study were as follows:

Primary Objectives:
- To demonstrate the clinical superiority of the anaesthetic/analgesic effects of lidocaine/prilocaine (2.5%/2.5%) anaesthetic cutaneous patch (test product) versus placebo, as well as the clinical superiority of the anaesthetic/analgesic effects of EMLA Patch (cutaneous patch) (reference product) versus placebo (2 separate analyses), by assessing pain levels. The assessments were done by means of 100 mm Visual Analogue Scale (VAS) pain scores as reported by the volunteers.
- To demonstrate non-inferiority of lidocaine/prilocaine (2.5%/2.5%) anaesthetic cutaneous patch (test product) compared to EMLA Patch (cutaneous patch) (reference product) utilising 100 mm VAS pain scores as reported by the volunteers.

These objectives also aimed to indicate that the proposed study design was adequate to assess the non-inferiority between the 2 active treatments.

Secondary Objectives:
- To assess local tolerability of the lidocaine/prilocaine (2.5%/2.5%) anaesthetic cutaneous patch.
- To investigate whether the plasma levels of lidocaine and prilocaine from the two formulations have not reached toxic levels when compared to levels reported in the literature.
- To compare Cmax and AUC(0-t) between the Test and Reference products for exploratory purposes.

IV. 2 Pharmacokinetics
In support of this application the Applicant submitted Part B of the study:

This part of the study was conducted as a randomised, single-blind, two-period, cross-over study under fed conditions. Volunteers who completed Part A were enrolled in Part B. Periods 5 and 6 were separated by a wash-out period of 13 calendar days between applications.

Part B (Treatment periods 5 and 6):
Once Part A had been completed, Part B commenced after a wash-out period of 10 calendar days. In Part B volunteers received either the test or reference product in each treatment period, according to the randomisation schedule.

Part B: a single application of 2 cutaneous patches per treatment period (Treatment periods 5 and 6). In Part B of the study, volunteers received a single application of 2 cutaneous patches of 1 ml for 10cm^2 (50 mg lidocaine/50 mg prilocaine) of each of the two formulations (test or reference) under fed conditions. according to the randomisation schedule.

Blood samples were taken pre-dose and up to 24 hours post dose, with a washout period of 13 days between applications in Part B.

A summary of the pharmacokinetic results for the test and reference products are presented below:

Summary of plasma lidocaine and prilocaine pharmacokinetic variables by treatment

Analyte	Treatment	Statistic	C_{max} (ng/mL)	$^*t_{max}$ (hr)	$AUC_{(0-t)}$ (ng.hr/mL)
Lidocaine	Reference	n	14	14	14
		Mean	17.879	4.793	110.095
		SD	6.792	(4.00 , 7.00)	34.317
		%CV	37.99		31.17
		Geometric mean	16.587		104.715
	Test	n	14	14	14
		Mean	21.186	4.429	129.286
		SD	8.811	(4.00 , 6.00)	38.962
		%CV	41.59		30.14
		Geometric mean	19.366		123.170
Prilocaine	Reference	n	14	14	14
		Mean	9.447	4.509	45.759
		SD	3.878	(4.00 , 5.00)	14.949
		%CV	41.05		32.67
		Geometric mean	8.653		43.411
	Test	n	14	14	14
		Mean	11.216	4.286	53.383
		SD	4.899	(3.00 , 6.00)	16.790
		%CV	43.68		31.45
		Geometric mean	10.217		50.896

n = number of observations; AUC = Area under the curve; C_{max} = Maximum concentration; t_{max} = Time of maximum concentration; $^*t_{max}$ is summarised by Median and range (minimum , maximum);

Summary of statistical analysis of plasma lidocaine and prilocaine pharmacokinetic variables

n = 14; dose: 2 x lidocaine/prilocaine (2.5%/2.5%) anaesthetic cutaneous patches				
Variable *(unit)*	LSMean		Mean Ratio (%)	90% Confidence Interval of Ratio (%)
	EMLA® patch (Reference product)	Lidocaine/Prilocaine (2.5%/2.5%) anaesthetic cutaneous patch (Test product)		
LIDOCAINE				
C_{max} (ng/mL)	16.587	19.366	116.75	109.89 ; 124.04
$AUC_{(0-t)}$ (h·ng/mL)	104.715	123.170	117.62	109.43 ; 126.43
PRILOCAINE				
C_{max} (ng/mL)	8.653	10.217	118.08	109.77 ; 127.01
$AUC_{(0-t)}$ (h·ng/mL)	43.411	50.896	117.24	109.64 ; 125.37

LSMean = Least square mean;

The geometric mean C_{max} was 19.366 ng/mL compared with 16.587 ng/mL for the test and reference products respectively. Similarly, for the $AUC_{(0-t)}$ the geometric mean values were 123.170 hr.ng/mL and 104.715 hr.ng/mL for the test and reference products respectively. The median tmax occurred earlier for the test product compared with the reference product with median values of 4.429 and 4.793 hours respectively.

The geometric mean Cmax was 10.217 ng/mL compared with 8.653 ng/mL for the test and reference products respectively. Similarly, for the AUC(0-t) the geometric mean values were 50.896 hr.ng/mL and 43.411 hr.ng/mL for the test and reference products respectively. The median t_{max} occurred earlier for the test product compared with the reference product with median values of 4.286 and 4.509 hours respectively.

The results show that the proposed product is supra-available when compared to the reference product with approximately 16-17% for lidocaine and prilocaine, with up to 27% in some patients. However, it is agreed that it is unlikely that more intense blood sampling around 4-5h would have been more adequate but it is unlikely to change significantly the evaluation of the difference between the two products.

Comparing the plasma concentration of the reference and the test products with the known systemic toxic plasma levels show that the exposures were very low. The pharmacokinetic (PK) parameters have been analysed for exploratory purposes and in particular, to explore the systemic exposures of lidocaine and prilocaine as compared to plasma toxic levels of such active ingredients. It has been claimed that:

- Plasma levels of approximately 5 µg/mL for both lidocaine and prilocaine are reported to be toxic (Physician Desk Reference 2007 and Product Monograph, AstraZeneca Canada Inc., May 2010).
- Comparing the plasma concentration of the reference and the test products with the known systemic toxic plasma levels shows that the exposures were very low.

Conclusions of Part B of the study

The systemic absorption of lidocaine and prilocaine and, in particular, the PK parameters C_{max} and AUC, was assessed between Lidocaine/Prilocaine 5% cutaneous patch and the reference product for exploratory purposes.

Due to the particularity of its pharmaceutical form (locally applied, locally acting product: cutaneous patch made of 1g of emulsion impregnated on an adsorbent cellulose disc), the Applicant submitted an abridged application with appropriate combination of pharmaceutical equivalence and relevant clinical studies; as a topical product, the bioequivalence cannot be thus demonstrated.

The clinical superiority of the anaesthetic/analgesic effects of EMLA patch and Lidocaine/Prilocaine 5% cutaneous patch compared to placebo and the non-inferiority of lidocaine-prilocaine 5%, cutaneous patch compared to EMLA patch have been demonstrated.

The conditions set in the Bioequivalence Guideline with regards to the PK parameters to be investigated (C_{max} and AUC) and the acceptance limits to fulfil (80.00% to 125.00%) to show equivalence between and Reference products are regarded not applicable in this case. The results show that the proposed product, Lidocaine/Prilocaine 5% cutaneous patch is supra-available compared to the reference product, Lidocaine/Prilocaine 5% Cutaneous Patch and it is considered therapeutically equivalent to EMLA 5% patch.

IV.3 Pharmacodynamics

With the exception of the pharmacodynamic study submitted as part of the clinical efficacy data no new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy

In support of the application, the applicant submitted the following:

Part A (Treatment periods 1-4)
In Part A volunteers received the test, reference and placebo products, according to the randomisation schedule, under fed conditions.

This part of the study had a randomised, double-blind, placebo-controlled, 4-period, cross-over design. Volunteers completed all 4 treatment periods. In Treatment periods 1 and 2 the investigational medical product (IMP) (lidocaine [25 mg] / prilocaine [25 mg] cutaneous patch or placebo cutaneous patch) was applied for 1 hour and in Treatment periods 3 and 4 the IMP was applied for 4 hours. Treatment periods were separated by a wash-out period of 7 to 9 calendar days.

Methodology
Part A (Treatment periods 1 to 4):
The study was conducted in compliance with GCP requirements.

Placebo cutaneous patches were applied on the remaining arm. For Treatment periods 1 and 3, volunteers received either the reference and placebo products (on opposite arms) or the test and placebo products (on opposite arms) according to the randomisation schedule starting with the first subject at 07:30. For periods 2 and 4 volunteers crossed over to receive the alternative active product with placebo.

Statistical methodology and results
The assessment of clinical superiority was performed for 'placebo versus test' and 'placebo versus reference' with separate analysis for the 1- and 4-hour adhesion periods. For each of these 4 analyses, the complete 95% confidence interval for the difference between the treatments was above zero with a p-value <0.0001. This analysis shows clinical superiority for the two active treatments compared to placebo.

The assessment of clinical superiority was also performed to include test, reference and placebo in the same analysis for the 1- and 4-hour adhesion periods (original scale and transformed data). For each of the analyses the complete 95% confidence interval for the difference between the treatments was above zero with a p-value <0.0001. These analyses also

show clinical superiority for the two active treatments compared to placebo.

To assess the non-inferiority of the Test product compared to the reference product by means of absolute 100 mm VAS pain scores as reported by the volunteers during venipuncture an analysis of variance was utilised to calculate a 95% CI for the mean differences for Treatment periods 1 and 2 and for Treatment periods 3 and 4. The non-inferiority limit was calculated as half the estimated maximum difference, as reflected by the upper limit of the 95% CI calculated for the mean difference of the placebo vs. reference product VAS scores (analysis described above). Non-inferiority of the Test product compared to the Reference product was concluded if the upper limit of the calculated 95% CI for the mean difference was equal or less than the non-inferiority limit.

The study was mainly designed to demonstrate superiority. As the study contains a placebo arm statistical justification of the non-inferiority margin is not required.

The statistical analysis was done in three different ways:
- original when only the data for the formulations being compared are included
- a secondary analysis with original scale where all data are included for all the analyses, e.g. when comparing test and reference to placebo the data for test is still there and taken into account when calculating the variance etc.
- a secondary analysis with transformed data (square root) to take into account the possibility that the data are not normal. This is acceptable.

The statistical analysis of clinical superiority of test and reference treatments versus control are presented on the original scale for the pharmacodynamic (PD) (=therapeutic) population in the table below. A comparison of results presented in the original CSR (transformed data) vs. the new output (untransformed data) is also shown below, demonstrating comparable mean differences between test and reference treatment for the pain VAS and the same outcome in terms of statistical significance.

A summary of the pharmacodynamic results for the test and reference products are presented below:

Clinical superiority

A – Primary analysis *[Table 11-11 from the final CSR 2.0 of March 2013]*			**LS Mean**			**95% Confidence Interval**		
Adhesion Period	**Comparison**	**n**	**Placebo**	**Active**	**Mean Difference**	**Lower**	**Upper**	**P-value**
1-hour	Placebo vs. Reference	75	29.79	6.25	23.53	16.61	30.45	<0.0001
	Placebo vs. Test	75	38.71	6.47	32.24	24.70	39.78	<0.0001
4-hour	Placebo vs. Reference	74	30.96	6.15	24.81	17.39	32.23	<0.0001
	Placebo vs. Test	73	28.30	5.23	23.07	16.13	30.01	<0.0001
B –Untransformed data *[New output from an ANOVA model including treatment, period, sequence, subject within treatment as fixed effects]*			**LS Mean**			**95% Confidence Interval**		
Adhesion Period	**Comparison**	**n**	**Placebo**	**Active**	**Mean Difference**	**Lower**	**Upper**	**P-value**
1-hour	Placebo vs. Reference	75	34.25	6.19	28.06	21.76	34.35	<0.0001
	Placebo vs. Test	75	34.25	6.48	27.77	21.47	34.06	<0.0001
4-hour	Placebo vs. Reference	74	29.60	6.07	23.54	17.35	29.72	<0.0001
	Placebo vs. Test	73	29.60	5.24	24.36	18.15	30.57	<0.0001

n = number of observations; LS Mean = Least squares

The assessment of clinical superiority was performed for 'placebo versus test' and 'placebo versus reference' with separate analysis for the 1-hour and 4-hour adhesion periods. As this study design proved suitable to demonstrate clinical superiority of the active treatments versus placebo, the study design was therefore deemed adequate to demonstrate non-inferiority of the test product versus the reference product. These analyses show clinical superiority for the two active treatments compared to placebo. Both test and reference products are superior to placebo ($p<0.0001$) and both have similar magnitude treatment effects at 1-hour and 4-hour adhesion period.

Superiority against placebo was demonstrated for both the Reference and the Test treatments. Comparison between both active treatments showed very little difference between the products with very narrow 95% CI intervals. It can be concluded that the treatments are equivalent with regards to efficacy, which is also corroborated by the secondary endpoints below.

Assessment of pain during venepuncture

Treatment	Statistic	1-hour adhesion period	4-hour adhesion period
Reference	n	75	74
	Mean	6.3	6.1
	SD	12.67	11.54
	Minimum	0	0
	Maximum	66	56
Test	n	75	73
	Mean	6.5	5.2
	SD	10.77	11.64
	Minimum	0	0
	Maximum	62	60
Placebo	n	150	147
	Mean	34.2	29.6
	SD	29.70	28.87
	Minimum	0	0
	Maximum	100	100

n = number of observations; SD = standard deviation

Data source: Section 14.2, Table 14.2.4.3

Subjective assessment of discomfort during and after patch removal

Treatment	Statistic	1 hour adhesion period		4 hour adhesion period	
		During	After	During	After
Reference	n	75	75	74	74
	Mean	6.6	1.6	4.0	1.8
	SD	12.80	3.72	8.76	3.69
	Minimum	0	0	0	0
	Maximum	61	15	59	17
Test	n	75	75	73	73
	Mean	6.8	1.7	5.8	2.6
	SD	13.46	4.06	10.27	7.25
	Minimum	0	0	0	0
	Maximum	81	26	45	41
Placebo	n	150	150	147	147
	Mean	5.4	2.1	5.7	2.5
	SD	10.93	4.94	10.47	6.09
	Minimum	0	0	0	0
	Maximum	58	33	57	39

n = number of observations; SD = standard deviation

Data source: Section 14.2, Table 14.2.4.6

Change from baseline in heart rate during venepuncture

Treatment	Statistic	1 hour adhesion period (bpm)	4 hour adhesion period (bpm)
Reference	n	75	74
	Mean	-1.4	-0.1
	SD	6.25	4.85
	Minimum	-22	-14
	Maximum	16	15
Test	n	75	73
	Mean	-1.4	0.4
	SD	6.56	5.01
	Minimum	-15	-13
	Maximum	35	16
Placebo	n	150	147
	Mean	-0.8	1.0
	SD	4.56	5.16
	Minimum	-17	-17
	Maximum	11	14

bpm = beats per minute; n = number of observations; SD = standard deviation

Data source: Section 14.2, Table 14.2.4.2

Subjective assessment of local skin sensation

Treatment	Statistic	1 hour adhesion period			4 hour adhesion period		
		Itching	Burning	Tingling	Itching	Burning	Tingling
Reference	n	75	75	75	74	74	74
	Mean	1.7	1.3	2.5	1.3	0.9	0.6
	SD	5.21	2.98	6.59	3.44	4.18	1.59
	Minimum	0	0	0	0	0	0
	Maximum	31	18	35	23	35	9
Test	n	75	75	75	73	73	73
	Mean	1.1	1.6	2.1	1.6	0.8	0.9
	SD	3.13	5.42	6.78	4.05	3.07	2.87
	Minimum	0	0	0	0	0	0
	Maximum	22	43	55	22	22	22
Placebo	n	150	150	150	147	147	147
	Mean	2.3	1.6	2.6	1.5	1.2	1.1
	SD	6.10	5.06	8.01	3.43	4.93	3.22
	Minimum	0	0	0	0	0	0
	Maximum	44	40	78	17	43	30

n = number of observations; SD = standard deviation

Data source: Section 14.2, Table 14.2.4.7

Objective assessment of degree of adhesion of cutaneous patches

Treatment	Statistic	1 hour adhesion period	4 hour adhesion period
Reference	n	75	74
	Mean	97.5	99.6
	SD	6.70	1.97
	Minimum	52	84
	Maximum	100	100
Test	n	75	73
	Mean	94.8	99.0
	SD	13.20	3.50
	Minimum	0	79
	Maximum	100	100
Placebo	n	150	147
	Mean	96.4	99.3
	SD	7.63	1.94
	Minimum	55	85
	Maximum	100	100

n = number of observations; SD = standard deviation

Data source: Section 14.2, Table 14.2.4.8

Objective assessment of local skin reaction

Treatment	Statistic	1-hour adhesion period			4-hour adhesion period		
		Pallor	Redness	Piloerection	Pallor	Redness	Piloerection
Reference	n	75	75	75	74	74	74
	Mean	7.6	4.8	1.4	1.1	27.1	1.4
	SD	11.63	11.68	3.71	4.00	23.19	4.77
	Minimum	0	0	0	0	0	0
	Maximum	54	67	23	20	88	30
Test	n	75	75	75	73	73	73
	Mean	6.9	4.8	1.5	1.1	25.7	0.9
	SD	9.75	8.58	3.91	3.48	23.52	3.66
	Minimum	0	0	0	0	0	0
	Maximum	32	39	20	17	75	27
Placebo	n	150	150	150	147	147	147
	Mean	1.9	5.4	0.8	2.2	3.3	0.4
	SD	3.98	7.72	1.71	5.40	6.31	1.37
	Minimum	0	0	0	0	0	0
	Maximum	25	44	9	24	49	8

n = number of observations; SD = standard deviation
Data source: Section 14.2, Table 14.2.4.9

Objective assessment of overall efficacy

Treatment	Statistic	1-hour adhesion period	4-hour adhesion period
Reference	n	75	74
	Mean	64.1	61.0
	SD	34.34	32.90
	Minimum	0	0
	Maximum	100	100
Test	n	75	73
	Mean	63.4	57.8
	SD	33.72	33.09
	Minimum	0	0
	Maximum	100	100
Placebo	n	150	147
	Mean	46.3	27.2
	SD	34.32	32.61
	Minimum	0	0
	Maximum	100	100

n = number of observations; SD = standard deviation
Data source: Section 14.2, Table 14.2.4.10

Conclusions of Part A of the study

The objective assessment of overall efficacy showed that the test patch performed as well as the reference patch, and that both patches performed similarly over the 1- and 4-hour adhesion periods.

For the reference patch the mean VAS scores were 64.1 and 61.0 after the 1- and 4-hour adhesion periods, respectively. The mean VAS scores for the test patch were similar at 63.4 and 57.8 for the 1- and 4-hour adhesion periods, respectively. Both the reference and the test patch had a greater degree of efficacy then the placebo patch.

The mean placebo VAS scores for the 1- and 4-hour adhesion periods were 46.3 and 27.2, respectively.

In conclusion, the test product behaved in a very similar manner to the reference product across all the assessments in this study, and the test product has been demonstrated to be non-inferior to the reference product.

Superiority against placebo was demonstrated for both the Reference and the Test treatments. Comparison between both active treatments showed very little difference between the products

with very narrow 95% CI intervals. It can be concluded that the treatments are equivalent with regards to efficacy.

IV.5 Clinical safety

With the exception of the safety data from the clinical study submitted with this application, no new safety data were submitted. The safety data submitted showed that the product was well-tolerated. No new or unexpected safety issues were raised from these data.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION

The Patient Information Leaflet (PIL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified.

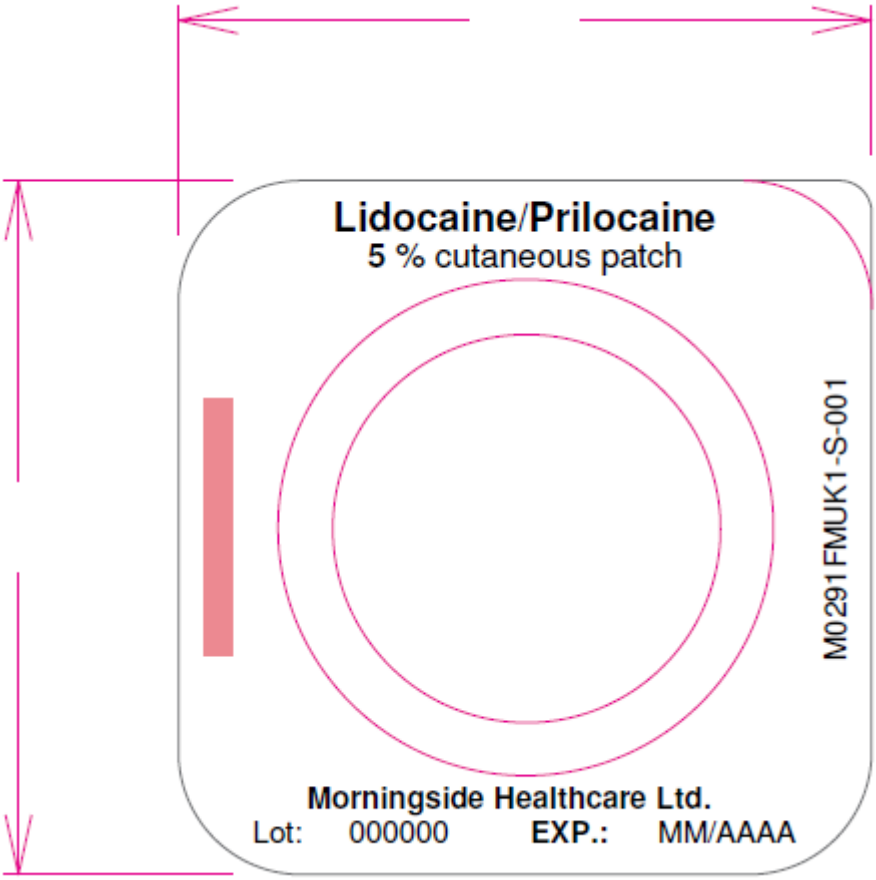
Extensive clinical experience with lidocaine and prilocaine has considered to have demonstrated the therapeutic value of the product. The results from the clinical study demonstrate that lidocaine/prilocaine (2.5%/2.5%) anaesthetic patch is therapeutically equivalent to the reference product EMLA patch.

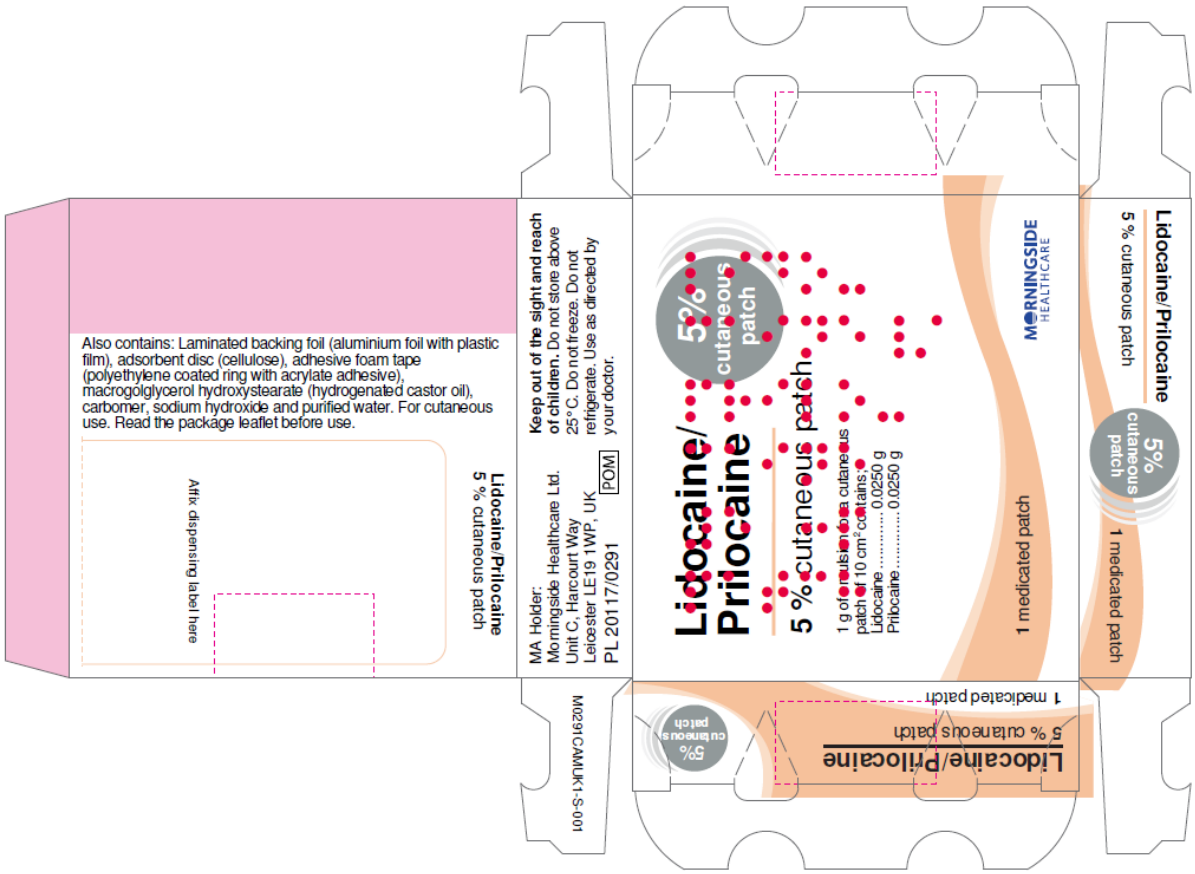
The benefit/risk is, therefore, considered to be positive.

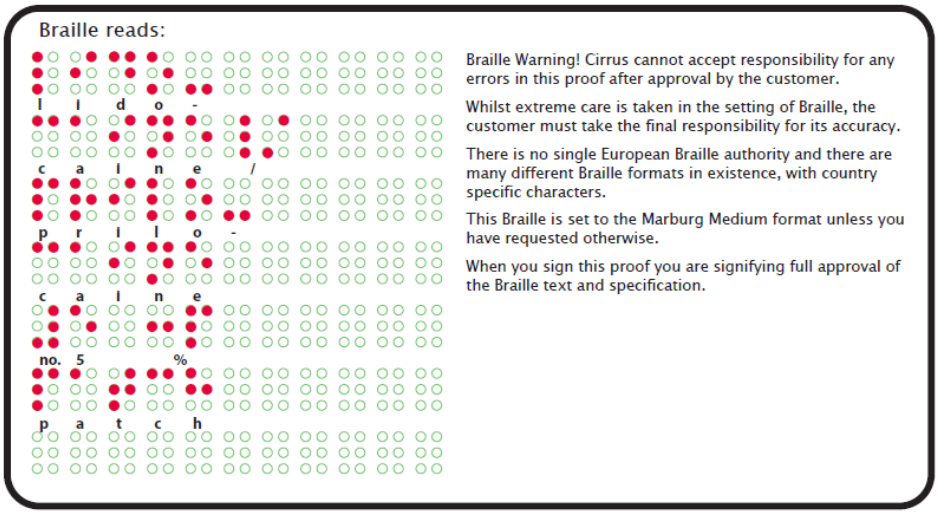
The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory and in line with current guidelines.

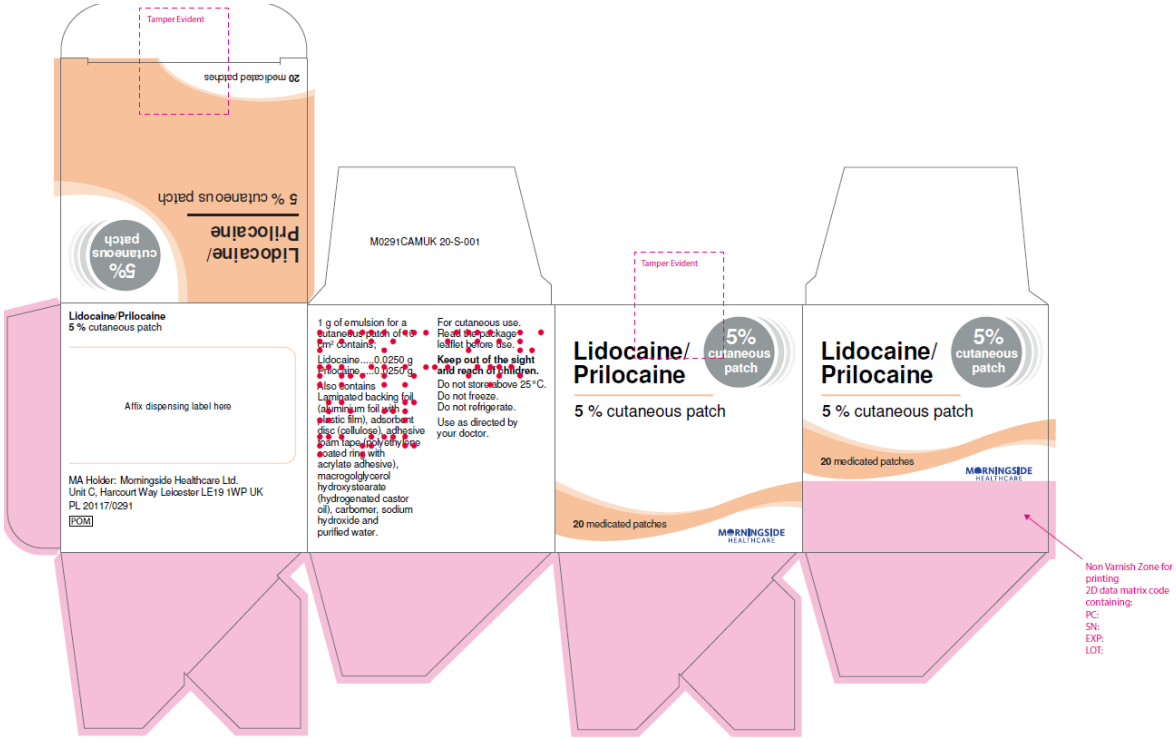
In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.


Lidocaine/Prilocaine
5 % cutaneous patch
M0291FMUK1-S-001
Morningside Healthcare Ltd.
Lot: 000000 EXP.: MM/AAAA


Also contains: Laminated backing foil (aluminium foil with plastic film), adsorbent disc (cellulose), adhesive foam tape (polyethylene coated ring with acrylate adhesive), macrogolglycerol hydroxystearate (hydrogenated castor oil), carbomer, sodium hydroxide and purified water. For cutaneous use. Read the package leaflet before use.
Affix dispensing label here
Lidocaine/Prilocaine
5 % cutaneous patch
Keep out of the sight and reach of children. Do not store above 25°C. Do not freeze. Do not refrigerate. Use as directed by your doctor.
MA Holder:
Morningside Healthcare Ltd.
Unit C, Harcourt Way
Leicester LE19 1WP, UK
POM
PL 20117/0291
M029(CAMLK1-S-001
5% cutaneous patch
Lidocaine/ Prilocaine
5 % cutaneous patch
1 g of emulsion in a cutaneous patch of 10 cm² contains:
Lidocaine ..... 0.0250 g
Prilocaine ..... 0.0250 g
1 medicated patch
MORNINGSIDE HEALTHCARE
Lidocaine/Prilocaine
5 % cutaneous patch
5% cutaneous patch
1 medicated patch
1 medicated patch
Lidocaine/Prilocaine
5 % cutaneous patch
5% cutaneous patch


Braille reads:
l i d o -
c a i n e /
p r i l o -
c a i n e
no. 5 %
p a t c h
Braille Warning! Cirrus cannot accept responsibility for any errors in this proof after approval by the customer.
Whilst extreme care is taken in the setting of Braille, the customer must take the final responsibility for its accuracy.
There is no single European Braille authority and there are many different Braille formats in existence, with country specific characters.
This Braille is set to the Marburg Medium format unless you have requested otherwise.
When you sign this proof you are signifying full approval of the Braille text and specification.


Tamper Evident
20 medicated patches
5 % cutaneous patch
Lidocaine/
Prilocaine
5% cutaneous patch
M0291CAMUK 20-S-001
Tamper Evident
Lidocaine/
Prilocaine
5% cutaneous patch
5 % cutaneous patch
20 medicated patches
MORNINGSIDE HEALTHCARE
Lidocaine/Prilocaine
5 % cutaneous patch
Affix dispensing label here
MA Holder: Morningside Healthcare Ltd.
Unit C, Harcourt Way Leicester LE19 1WP UK
PL 20117/0291
POM
1 g of emulsion for a cutaneous patch of 10 cm² contains:
Lidocaine..... 0.0250 g
Prilocaine..... 0.0250 g
Also contains:
Laminated backing foil (aluminium foil with plastic film), adsorbent disc (cellulose), adhesive foam tape (polyethylene coated ring with acrylate adhesive), macrogolglycerol hydroxystearate (hydrogenated castor oil), carbomer, sodium hydroxide and purified water.
For cutaneous use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 25°C.
Do not freeze.
Do not refrigerate.
Use as directed by your doctor.
Non Varnish Zone for printing
2D data matrix code containing:
PC:
SN:
EXP:
LOT:

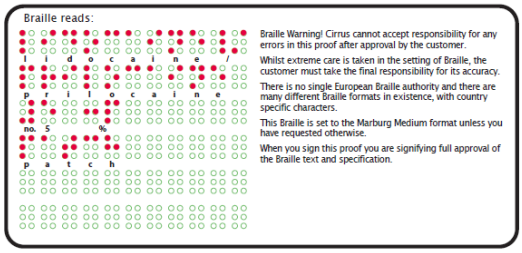

Braille reads:
lidocaine/
prilocaine
no. 5
%
patch
Braille Warning! Cirrus cannot accept responsibility for any errors in this proof after approval by the customer.
Whilst extreme care is taken in the setting of Braille, the customer must take the final responsibility for its accuracy.
There is no single European Braille authority and there are many different Braille formats in existence, with country specific characters.
This Braille is set to the Marburg Medium format unless you have requested otherwise.
When you sign this proof you are signifying full approval of the Braille text and specification.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**