COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Lidbree 42 mg/mL intrauterine gel

(lidocaine)

NL/H/4625/001/DC

Date: 13 April 2021

This module reflects the scientific discussion for the approval of Lidbree 42 mg/mL intrauterine gel. The procedure was finalised on 17 June 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CNS	Central Nervous System
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
IMP	Investigational Medicinal Product
IUD	Intrauterine Device
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
VAS	Visual Analogue Scale

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Lidbree 42 mg/mL intrauterine gel from Gedeon Richter Plc.

The product is indicated for topical anaesthesia for moderate acute pain during cervical and intrauterine procedures, in adults and adolescents from 15 years of age.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application. The reference product is Xylocaine 20 mg/mL solution for injection (MAH: AstraZeneca/Aspen), originally approved in Sweden on 7 July 1949, based on a full application. Xylocaine is indicated for local and regional anaesthesia (infiltration anaesthesia, epidural anaesthesia and sympathetic nerve blocker) in adults and children from 12 years of age.

Lidocaine is the most commonly used local anaesthetic owing to its rapid onset, moderate duration of action and topical anaesthetic activity, and has due to these properties been selected as the local anaesthetic of choice for the new intrauterine gel. Lidbree is a novel, sterile, thermogelling and preservative-free topical formulation of the well-documented local anaesthetic lidocaine: Lidbree 4% intrauterine gel. The formulation was developed as a topical anaesthetic for painful therapeutic or diagnostic procedures in gynaecology.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

The clinical development program was designed to document local tolerability, systemic safety, and efficacy of the new intrauterine gel when used in connection with painful cervical and intrauterine gynaecological procedures. The regulatory strategy was discussed in scientific advice meetings in a number of member states.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the UK.

II. QUALITY ASPECTS

II.1 Introduction

Lidbree 42 mg/mL is a sterile, clear to almost clear, slightly brown-yellow viscous liquid that is a gel at body temperature. Each mL of gel contains 42 mg/mL of lidocaine.

The gel is packed in a sterile 10 mL prefilled syringe (cyclic olefin copolymer) with bromobutyl rubber tip-cap and stopper, packed in the same blister with the plunger rod.

The excipients are: macrogolglycerol ricinoleate (castor oil polyoxyl), poloxamer (containing butylated hydroxytoluene (E 321)), sodium ascorbate (E 301), hydrochloric acid for pH adjustment, sodium hydroxide for pH adjustment, water for injection.

II.2 Drug Substance

The active substance is lidocaine, an established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance is a white crystalline powder which is very soluble in water and freely soluble in alcohol and methylene chloride. No polymorphism has been reported for lidocaine in the literature and no chiral centres are present.

For both active substance manufacturers the CEP procedure is used. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is in line with the Ph. Eur. monograph for lidocaine. The specification is considered acceptable.
Batch analysis results have been provided for several production scaled batches of lidocaine, which show compliance to the specification.

Stability of drug substance
A retest period of 5 years has been granted for the active substance and is in line with the information provided on the CEPs.

II.3 Medicinal Product

Pharmaceutical development

The development of the test product has been described, the choice of excipients is justified and their functions explained. The application is made as hybrid application and reference has been made to Xylocaine 2% solution for injection. No pharmaceutical equivalence study has been performed with test and reference product, which is acceptable as non-clinical and clinical studies have been performed. Rheological properties of the drug product have been determined. Results of batches used in these studies have been provided and differences between these batches and commercial batches/manufacturing process has been explained. The differences are acceptable.

As the drug product is also indicated in the paediatric population (15 years of age and older), the MAH discussed the suitability of the dosage form, graduation scale/dosing instructions, applicator dimensions and composition in line with requirements of Note for Guidance on Pharmaceutical development of medicines for paediatric use.

Sodium ascorbate is added as antioxidant to protect lidocaine from oxidation during manufacturing. The MAH has established that the chosen concentration is suitable. As the antioxidant is used up during manufacturing (including holding time of bulk and sterilisation process) no test for content of the antioxidant is necessary in the specification of the drug product.

A flexible composition for the individual poloxamers (188 and 407) is proposed with a fixed quantity of the total of poloxamers. The ratio between the two poloxamers used for a commercial batch will depend on an evaluation of the specific poloxamer batches to ensure acceptable gel transition temperature (critical quality attribute) of the drug product. The use of this flexible composition is acceptable, based on the provided results and as gel transition temperature will be routinely tested for the drug product at release. The details of the flexible formulation are explicitly stated in the batch formula of commercial batches.

A sterilisation process which uses moist heat is applied. The rationale for the choice for this process has been adequately explained. The process has been shown to give an acceptable Sterility Assurance Level. Phase separation possibility has been investigated and a test has been included in the drug product specification which will address phase separation if it occurs after sterilisation.

Lidocaine 42 mg/mL intrauterine gel is presented in a prefilled syringe; SCHOTT TopPac® Sterile 10 ml, integrated luer lock with Tip Cap and plunger stopper. The prefilled syringe is labelled with a label with a printed volume scale, 0-8.5 ml, with graduation lines every 0.5 ml. The prefilled syringe is terminally sterilised by an autoclave procedure and packed together with the piston in a blister tray with paper foil. The tertiary container is a carton. A sterile polypropylene applicator is provided with the drug product for which a CE certificate has been provided. The label with graduation marks which is glued to the syringe is controlled for dimensions. The ease of interpretation and readability of the graduation has been discussed. The uniformity of mass of minimum and maximum doses as well as accuracy

of the doses in case of worst case label position, have been established, according to Ph.Eur. requirements.

Manufacturing process

The production process consists of the following steps: dissolution of the poloxamers, dissolution of the drug substance, addition of antioxidant to the poloxamers, addition of the lidocaine/macrogolglycerol ricinoleate to the poloxamer/antioxidant solution, homogenization, pH adjustment homogenisation, adjustment to final weight, homogenization, filtration of the bulk, intermediate storage, filling in syringes, labelling of syringes, sterilization, secondary packaging. The manufacturing process is considered a non-standard process. The manufacturing process is considered acceptable as it is under sufficient control. Sufficient details regarding the critical process parameters are laid down for commercial batches. An in-process control (IPC) for the correct application of the glued label on the syringes has been included. This IPC is considered suitable with regard to accuracy of delivered mass. A second IPC on label adhesion and quality of artwork and print after sterilisation has also been included, thereby giving sufficient control of the position of the label. It is acceptable to glue the label to the syringe. The manufacturing process has been validated on three commercial-scale batches.

Control of excipients

All excipients comply with their current Ph. Eur. monographs. Antioxidants may be present in the poloxamers, which has been stated in relevant sections of the dossier. The specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance (including option to detect phase separation), pH, identification of lidocaine, assay of lidocaine, related substances, gel transition temperature, extractable volume, sterility, container closure integrity test, tip cap removal force and extrusion force with applicator. The specification is acceptable. The analytical procedures have been adequately described and validated.
Batch analysis data are presented for five production-scale batches, demonstrating compliance with the release specification. The risk regarding presence of nitrosamines has been discussed and no risk was identified.

Stability of drug product

Stability data has been provided for four industrial-scale batches packaged in the container closure system proposed for marketing and stored at 25°C ± 2°C/60% ± 5% RH (one batch 24 months, three batches 18 months), 30°C/65% RH (one batch 24 months and three batches 18 months) and 40°C ± 2°C/75% ± 5% RH (four batches 6 months). In addition, results of a batch of drug product manufactured with the second active substance supplier up to 3 months accelerated and intermediate conditions have been provided. The proposed shelf life of 24 months is acceptable. The product is not sensitive to light or storage at 5°C (up to 3 months).

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Lidbree 42 mg/mL intrauterine gel has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

With regard to safety pharmacology, it is known that high systemic exposure to lidocaine causes adverse reactions on the CNS, respiratory and cardiovascular systems, with CNS effects being the lowest threshold effects. In the toxicology studies with Lidbree, effects on CNS, respiratory and cardiovascular system (ECGs) are monitored. In addition, an acute neurotoxicity study has been performed. No treatment-related effects on respiratory function, heart rate, RR interval, P-R interval, QRS, QT interval or QT interval were observed.
It is noted that in the non-clinical overview, it is indicated in the section on safety pharmacology that the no observable effect level (NOEL) for CNS effects of Lidbree containing 50 mg/mL of lidocaine was 1 ml/kg and that the absence of CNS adverse reactions was also confirmed in the 28-day toxicity study with Lidbree. However, in the 28-day toxicity study, sciatic nerve lesions were observed at all dose levels, although minor and with no clear dose relationship. This is possibly related to the presence of macrogolglycerol ricinoleate (KoEL) in the formulation and the repeated administration of Lidbree in this study. KoEL is known to induce neurotoxicity after repeated administration, especially in combination with ethanol, but not following a single dose. It can be concluded that Lidbree mediated CNS effects occur at doses at least 10 fold above the therapeutic dose level in women.

III.2 Pharmacokinetics

The submitted summary of the pharmacokinetics of lidocaine is considered sufficient, since the different administration route is not considered to influence plasma binding, organ distribution, metabolism or excretion of lidocaine, except for a higher local exposure. Since in the toxicology studies it has been shown that there are no local adverse effects of Lidbree, this is considered acceptable.

Exposure of Lidbree (C_{max} and AUC) was studied following single or repeated administration. It was shown that C_{max} and the AUC increased less than expected assuming dose proportionality and that there was no accumulation after administration every 4 days. In addition, it was shown that single dogs in oestrus showed slightly higher C_{max} and AUC values compared with dogs in anoestrus, however, since the differences were < factor2, this is not considered to be clinically relevant.

III.3 Toxicology

The MAH briefly summarised the toxicology of lidocaine. In addition, an acute neurotoxicity, 7 days repeated dose and 28 days repeated dose toxicity study with the new formulation Lidbree, and using the new administration route (intra-uterine) showed no clinical signs indicating systemic toxicity, and no observations indicating local irritation were observed, except for minor sciatic nerve lesions in the 28 day repeated dose toxicity study. These lesions were likely due to the excipient macrogolglycerol ricinoleate in the formulation and is not considered relevant for humans, since no such effect was seen in the single dose neurotoxicity study.

According to the MAH, lidocaine does not induce reprotoxic effects in animals. It is noted that, according to the information included in the harmonised SmPC text of other lidocaine products, embryotoxic or fetotoxic effects of lidocaine were detected at doses of 25 mg/kg s.c. in the rabbit.

III.4 Ecotoxicity/environmental risk assessment (ERA)

It is agreed that, according to the low logKow of lidocaine, further screening for persistence, bioaccumulation and toxicity is not required.
The MAH has, for the calculation of the $PEC_{surfacewater}$, not used the default parameter for the Fpen (default value of 0.01), but used a refinement based on prevalence and of treatment.
This refinement approach is in line with the 'Refinement based on treatment regime' as stated in Q4 (and 'End note 1') of the Q&A document on the Guideline on the environmental risk assessment of medicinal products for human use (adopted by the CHMP on 26 May 2016), if it is based on the SmPC. As this posology is clearly reflected in the SmPC, this approach is agreed.
Since the combined calculated $PEC_{surfacewater}$ is below the action limit, a further environmental risk assessment is not deemed necessary.

III.5 Discussion on the non-clinical aspects

The non-clinical overview briefly comments on the pharmacodynamics, pharmacokinetics and toxicology of lidocaine. In addition, an acute neurotoxicity, 7 days repeated dose and 28 days repeated dose toxicity study with the new formulation Lidbree were conducted. This is considered sufficient. This product is a hybrid formulation of Xylocaine 20 mg/mL solution for injection, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. The non-clinical overview justifies why there is no

need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical development program was designed to document local tolerability, systemic safety, and efficacy of the new intrauterine gel when used in connection with painful cervical and intrauterine gynaecological procedures. The clinical program consisted of one exploratory and one multi-centre therapeutic confirmatory study evaluating Lidbree as a topical anaesthetic in a pain model for gynaecological interventions, placement of an intrauterine device (IUD). A second therapeutic exploratory study evaluated the feasibility, safety and local tolerability for use in hysteroscopy. The feasibility included the visibility for performing the hysteroscopy. In total, 244 women with the targeted indication were included in the clinical development program.

Table 1: Overview of clinical development program of LIDBREE

Study ID	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Primary Endpoint
PH-UID-01	Open, uncontrolled single centre	8.5 ml of 4% gel applied cervical/ intrauterine 5 minutes prior to insertion	PK, Safety. Local tolerability, efficacy	17/16	Single dose	Parous (n=4) and nulliparous (n=11) women requesting placement of intrauterine contraception 26 (20-36)	PK
PH-HYS-01	Open, uncontrolled single centre	8.5 ml of 4% gel applied cervical/ intrauterine 5 minutes prior to insertion	Feasibility, safety, local tolerability	10	Single dose	Women scheduled for hysteroscopy mean 38,6 (31-46)	Feasibility for hysteroscopy (Visibility)
PH-IUD-02	Double-blind placebo-controlled multicentre	8.5 ml of 4% Lidbree gel or 8.5 ml placebo gel applied cervical/ intrauterine 5 minutes prior to	Efficacy, safety, local tolerability	110 AT 108 PB	Single dose	Nulliparous women requesting placement of intrauterine contraception	Maximum Pain intensity during and within 10 minutes

	insertion	(18-45)	after start of IUD placement assessed on 100 mm VAS

Abbreviations: AT= active treatment, PB= placebo, PK= pharmacokinetics, VAS= visual analogue scale

The MAH declared that all studies were performed according to current requirements of Good Clinical Practice (GCP) as defined by the International Conference on Harmonisation (ICH E6, 1997), and all studies were conducted in accordance with the ethical principles set forth by the Declaration of Helsinki 2008.

IV.2 Pharmacokinetics

The MAH submitted a pharmacokinetic study, PH-IUD-01, and a clinical overview in which the pharmacokinetics of lidocaine after intrauterine administration of Lidbree, a 4% (w/w) lidocaine gel, has been described and compared to dermal IV and after parenteral administration. Based on pharmacokinetic study PH-IUD-01 it can be concluded that the rate of absorption after intrauterine administration is slower than after injection and more variable between subjects. The C_{max} and total exposure is within the safe range. The study is considered sufficient to allow bridging between the safety data in literature and Lidbree 4% lidocaine.

The MAH only investigated the pharmacokinetics after administration of 8.5 ml Lidbree 4% lidocaine intrauterine gel; other concentrations and other amounts of gel have not been studied.

Potential covariates that may attribute to the variability have not been evaluated. Further no information has been provided on the pharmacokinetics in post-menopausal women although absorption characteristics may be different in these subjects due to hormonal changes and vaginal atrophy.

The proposed maximum amount of gel (10 ml of Lidbree 4%) is larger than tested (maximum) amount (8.5 ml of Lidbree 4%) in studies PH-IUD-0, PH-HYS-01, and PH-IUD-02. As the total amount absorbed will be related to the total dose administered, the MAH has justified that the maximum amount administered is larger than tested in the clinical studies.

The MAH provided the following justification for the safe use of a single 10 mL dose:

- The maximum recommended single dose of 10 mL is based on the clinical need in some individuals with large uteri, such as some parous women. The volume of the endometrial cavity of the uterus varies in different individuals between approximately 1.2 and 10 mL with a mean of approximately 5 mL.
- The pharmacokinetic study PH-IUD-01 demonstrated that plasma concentrations of lidocaine after the 8.5 mL dose are well below those associated with initial signs of toxicity, with a 6 to 7 fold safety margin.

- Additionally, non-clinical data from intrauterine administration of the Lidbree formulation in beagle dogs provide evidence that the increase in peak plasma concentration with increasing mg/kg doses of lidocaine, is less than dose-proportional. In a repeat dose study intrauterine doses of 20 mg/kg or 50 mg/kg of lidocaine were given every second day for a total of three doses. There were no clinical signs indicating systemic lidocaine toxicity. The mean peak plasma concentration of lidocaine was 2870 and 3280 ng/ml on Day 1 at 20 mg/kg and 50 mg/kg, respectively. The mg per kg dose-increase of 2.5 times therefore resulted in an increase in peak concentration of a factor 1.14.
- The maximum recommended dose of 10 mL is well justified and raises no safety concern given the long clinical experience of lidocaine and its well-studied relation between plasma concentrations and the occurrence of CNS and cardiovascular toxicity.

The MAH provided the following literature information to support the safe and effective use in postmenopausal women:

- The effect of decreased levels of oestrogen after menopause, i.e. thinner genital epithelium and reduced number of blood vessels and reduced blood flow will theoretically unlikely result in a higher exposure.
- women in their menstrual phase have open mucosal blood vessels and less functional mucosal barrier. Although only 4 women were included in their menstrual cycle days 1-6, the PK variables were evaluated in a population with a high rate of trans mucosal absorption, high local blood flow, and a high degree of systemic exposure to the local anaesthetic.
- Studies in dogs indicate that postmenopausal women may show reduced plasma levels of lidocaine compared with fertile women.
- The urinary tract structures also contain oestrogen receptors that are affected by decreased oestrogen levels. The urinary epithelium becomes thinner. However, no dose adjustment is required for menopausal women for urinary catheterization or cystoscopy for registered lidocaine products. This indicates that the efficacy and safety is unchanged in postmenopausal women.
- Tabulated overview of studies in pre and postmenopausal women showing comparable efficacy.

IV.3 Pharmacodynamics

The rationale for the proposed dose is based on release of lidocaine from the formulation, rapid absorption and lack of systemic toxicity. The MAH refers to a 5% lidocaine-prilocaine mixture (EMLA cream 5%, NL licence RVG 11015) for the development of the product, e.g. formulation design and *in vitro* testing of the product.

The selected dose should be well below toxic levels and a rapid relief should be achieved, to ensure the least amount of hinder/ interference with the common practice of the different gynaecological procedures. A clear rational for the 4% formulation was lacking, therefore the MAH was requested to discuss this in the light of the efficacy of the available formulation

and the data from the clinical study. The MAH argued that the 4% formulation (42 mg/ml) had only minor potential differences from the Emla 5% (50 mg/ml) formulation. Higher % of lidocaine may not necessarily result in a greater reduction of pain, as the benefit of the 5% was more effective than the 10% spray in reduction of tenaculum pain. In addition, the differences observed between the placebo and 5% gel was on the 100mmVAS, which is clinically meaningful.

IV.4 Clinical efficacy

Main study
A randomized, double-blind, placebo controlled, parallel group study was performed to investigate the analgesic effect and safety and tolerability of the intrauterine gel during and after placement of an IUD.

Methods
Study Participants
This placebo-controlled study only recruited nulliparous women. Both hormone containing Intrauterine Systems and non-hormone containing devices could be used in this study, according to the wish of the patient.

Treatments
The investigational medicinal products (IMP, active or placebo) were administered in a dose of up to 8.5 mL using step-wise procedure as follows: 2 mL viscous liquid applied on the surface of portio, followed by a 2-minute wait for anaesthetic onset. Thereafter 3 mL introduced into the cervical canal, followed by a 2-minute wait for anaesthetic onset, and the rest of the viscous liquid (up to 3.5 ml) was slowly introduced into the uterine cavity. A total of at least 7 mL IMP had to be given to all patients.

Objectives
The primary objective was to evaluate the maximum pain intensity experienced by the patient during and within 10 minutes after the start of IUD placement when treated with active treatment (4% lidocaine base formulation) in comparison to placebo gel.

Outcomes/endpoints
The primary endpoint was the maximum pain intensity experienced during IUD placement when treated with active treatment vs placebo, using a 100 mm VAS.
Secondary objectives included evaluation of the time course of pain intensity, the need of additional oral analgesics, the discomfort experienced during the intracervical and intrauterine administration, and the safety and tolerability based on eliciting of adverse events.

Discomfort from administration of investigational medicinal product (active treatment or placebo) was assessed immediately after the administration IMP and before IUD placement. Discomfort was rated on a five-grade ordinal scale as: no, a little, some, large, very large.

IUD placement began 5 minutes after end of administration of IMP. After pain evaluation and some rest for the patient, ultrasound was used to visualise the position of the IUD within the uterine cavity, 10 to 60 min after the placement.

Assessments involved:

- Maximal pain intensity during the first 10 minutes
- Pain recorded also after 30 minutes and 1 and 2 hours
- Pain recorded on days 2, 3 and 4
- Reported use of rescue medication (analgesic)
- Questions on discomfort
- Recording of adverse events, elicited and non-elicited
- A follow-up phone call was made after 5-10 days

Blinding

The study was carried out as a double-blind study. The investigational drug and the placebo are similar with regard to viscosity and color to both the patient and the study staff.

Randomization

The patients were assigned to the next unused randomization number based on the randomization list prepared by the study statistician (Appendix 16.1.7.2). The randomization list was used by Recipharm for labeling the vials before sending them to the hospital pharmacies. The list was kept without access for any of the study related personnel until clean file was declared and the treatment code was broken. A detailed instruction was written for the midwives to assign the patients their participation number.
Originally, the OpenClinica™ system presented the next number for the midwife when a new patient was eligible for participation. However, this system resulted in a consumption of numbers, which were not used. After a decision between the data manager, sponsor and project manager a new “Instruction for entering data in OpenClinica™ (here translated from Swedish by the author) was provided on Nov 11, 2012. Thereafter the midwives entered the numbers manually and this was identical to the label on the next vial.

Sample size

The study involved three different clinics in Sweden with 15 participating investigators (midwives) and recruited in total 218 patients. This placebo-controlled study only recruited nulliparous women. Both hormone containing Intrauterine Systems and non-hormone containing devices could be used in this study, according to the wish of the patient.

Statistical methods

The primary efficacy analysis was a comparison of LIDBREE with placebo based on the primary outcome variable VAS, i.e. the maximum pain intensity experienced during and within 10 minutes after the IUD placement. The comparison was performed using an ANOVA model with VAS as the dependent variable and treatment and clinic as fixed factors in the model. This means that the overall mean difference between treatment groups is to be calculated as the weighted mean difference from the three sites with the number of patients

per site as weights. The associated 95 % confidence interval is calculated using point estimate and standard error from this model.

Results

Summary of main efficacy results

The following table summarises the efficacy results from the main study.

Table 2. Summary of efficacy for trial PH-UID-02

Title: PH-IUD-02			
Study identifier	PH-UID-02		
Design	Double-blind randomized placebo-controlled study evaluating the pain relief of a single administration of Lidbree administered before insertion of an IUD in women of 18 years, or more of age. Patients were given 24 paracetamol tablets of 500mg, which could be used to alleviate pain in the days post treatment		
	Duration of main phase: Duration of Run-in phase: Duration of Follow-Up:		One visit Not applicable 5 – 10 days after IUD insertion
Hypothesis	Superiority of of a topical formulation of lidocaine administered over placebo for pain relieve caused by insertion of an Intra Uterine Device		
Treatments groups	Lidbree (topical formulation of lidocaine)		Single administration of up to 8.5ml 4% lidocaine gel.
	Placebo		Single administration of up to 8.5ml placebo gel.
Endpoints and definitions	Primary endpoint	Maximum VAS pain intesnity	during and within 10 minutes after start of IUD insertion
	Secondary endpoint	VAS scale	Intensity of pain after 30 minutes, 1hour, 2hours and 1-3 days after IUD insertion
	Secondary endpoint	Safety & Tolerability	
	Secondary endpoint	Rescue medication	A maximum of 24 x500mg paracetamol tablets could be used during the 3 next consecutive days post treatment.
	Secondary endpoint	Application discomfort	degree of discomfort experienced by the patient
Database lock	<date>		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	218 patients were included in 3 clinics across Sweden.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Lidbree
	Number of subject	110	108
	Mean maximum VAS pain intensity	44.2	28.3
	SD	26.0	24.6
	Rescue at Clinic	30.5% (33)	15.4% (17)
	Rescue during follow-up (4 days)	76.2%	72.0%
Effect estimate per comparison	Primary endpoint	Comparison groups	Lidbree vs Placebo
		Mean difference *	15.9
		CI (95%)	9.1;22.8
		P-value	P<0.0001
	Secondary endpoint VAS 30min	Comparison groups	Lidbree vs Placebo
		VAS (SD)	24.7 (21.9) vs 35.8 (24.1)
		P-value	P=0.0017
	Secondary endpoint VAS 60min	Comparison groups	Lidbree vs Placebo
		VAS (SD)	21.7 (21.2) vs 23.0 (19.2)
		P-value	Not significant
Notes	Both hormone and non-hormone IUDs could be used in this study, according to the wish of the patient. *mean difference is estimated from the ANOVA model Abbreviations: CI= Confidence Interval, IUD = Intra Uterine Device, Lidbree= a topical formulation of 4% lidocaine, VAS= Visual Analogue Scale		

Outcomes and estimation

The analysis of the primary efficacy variable gave a compelling statistical significance in favour of the active group (p<0.0001) with an estimated effect size of 15.9 mm (mean difference) corresponding to a 36% lower mean VAS pain score in the active group compared to placebo.

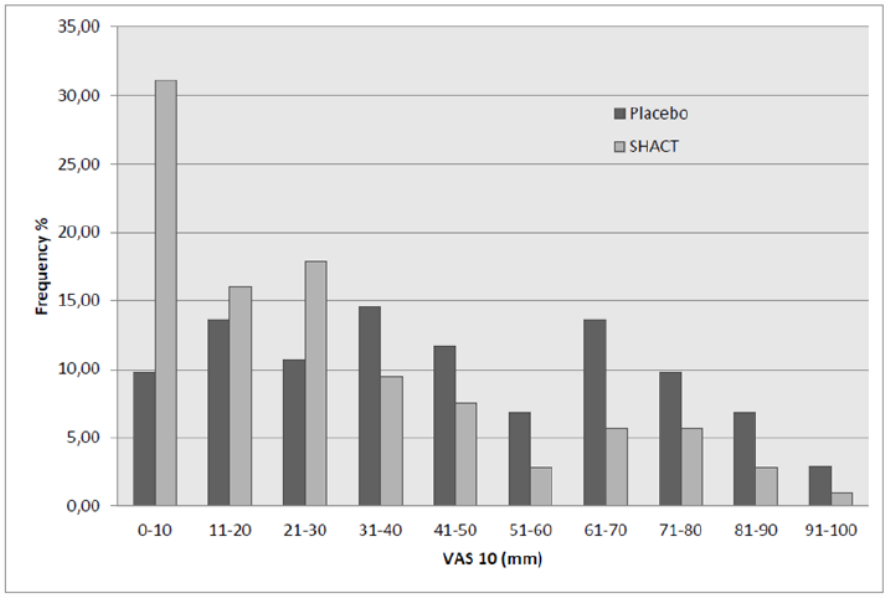
Table 3. Primary efficacy analysis study and descriptive statistics. Maximum VAS pain intensity by centre and total

	Treatment group								
	Placebo			SHACT					
Clinic	n	Mean	SD	n	Mean	SD	Mean difference	CI (95%)	p-value
Karolinska	82	42.5	25.1	81	28.6	25.7	14.3	6.5; 22.2	
Linköping	8	33.6	30.8	10	25.1	13.8	8.5	-14.5; 31.5	
Norrköping	13	61.4	23.6	15	31.4	25.2	30.0	10.9; 49.0	
Total	103	44.2	26.0	106	28.3	24.6	15.9 *)	9.1; 22.8	P < 0.0001

Maximum pain experienced by the subject during and within 10 minutes after the start of IUD placement. *) The mean difference is estimated from the ANOVA model. Source: Table 11.6 in CSR PH-IUD-002.

The distribution of pain scores by 10 mm VAS intervals is illustrated in Figure 1. The proportion of patients with virtually pain free values (0-10 mm) is three times as high in the active treatment group compared to the placebo group (31.1 % vs.9.7 %). The proportion of patients with high scores indicating moderate or severe pain (51-100) was 18% and 40% in the active and placebo group, respectively.

Figure 1. Distribution of maximum VAS pain scores from IUD placement procedure, by 10 mm VAS intervals, by treatment group (study PH-IUD-02)



*Maximum pain experienced by the subject during and within 10 minutes after the start of IUD placement. VAS: Visual Analogue Scale
Source: Figure 11.1. in CSR PH-IUD-02

Duration of effect
The difference between the groups in mean pain intensity after 30 minutes was still statistically significant but with a numerically smaller difference. After 60 minutes, the difference had disappeared indicating a duration of effect lasting 30-60 minutes.

Discomfort from administration of gel
Regarding the assessment of discomfort from IMP administration, there is a difference in favour of Lidbree in the accumulated proportion up to the level of 'a little' discomfort. A difference favouring active treatment is retained as the degree of discomfort increases up to and including the level 'large'. The difference in the distribution of discomfort levels between treatment groups is statistically significant with p = 0.023 using the Wilcoxon rank-sum test for ordinal data stratified for clinic (Table 4).

Lidbree and placebo gave almost identical adverse events with symptoms normally seen in connection with IUD placement. Most of these were related to the gastrointestinal tract such as nausea and general disorders. Neither penetration of the IUD through the uterine wall nor any other serious adverse events were reported.

Table 4: Number of patients (% and accumulated %) reporting different degrees of discomfort from administration of gel in placebo and active treatment groups (Study PH-IUD-02)

Category	Placebo			SHACT		
	n	%	Acc. %	n	%	Acc. %
No	34	31.5	31.5	38	34.5	34.5
A little	17	15.7	47.2	32	29.1	63.6
Some	21	19.4	66.7	15	13.6	77.3
Large	20	18.5	85.2	20	18.2	95.5
Very large	16	14.8	100.0	5	4.5	100.0
Total	108			110		

SHACT: LIDBREE, Source: Table 11.15 in CSR PH-IUD-02.

Need for analgesics (rescue medication)
The need for oral analgesics was a secondary efficacy endpoint evaluated in two stages a) during the stay in the clinic and b) use of analgesics at home the first day and during the 3 subsequent post-procedural days.
During the approximately 1-hour long stay in the clinic additional analgesics were requested by 33/108 (30.5%) and 17/110 (15.4%) of women in the placebo and Lidbree treatment groups, respectively. For the follow-up period the patients were given 24 paracetamol 500 mg tablets as rescue medication to be used for pain relief at the discretion of the patient. The intake of these was reported in the patient diary.

In the placebo group 76.2 % of patients reported the intake of rescue medication on one or more of the follow-up days and in the Lidbree group the corresponding percentage was 72.0

%. Data was missing for 11 patients in the placebo and for 3 patients in the Lidbree group. The amount of rescue medication taken is described in Table 5.

Table 5: Number of tablets of rescue medication taken during follow-up

	Placebo, n=108		SHACT, n=110		Placebo-SHACT
Day number	Mean (SD)	No. of pts. with missing data	Mean (SD)	No. of pts. with missing data	Mean difference
1*)	2.0 (2.2)	13	1.7 (1.6)	7	0.3
2	1.6 (2.2)	13	1.4 (2.3)	3	0.2
3	0.8 (1.6)	15	0.8 (1.7)	4	0.0
4	0.6 (1.7)	18	0.6 (1.3)	11	0.0
Total	4.3 (6.1)	**)	4.2 (5.6)	***)	0.1

*) Day number 1 indicates the day of IUD insertion, but reported from home
**) Missing data – Placebo: All 4 days 11 patients, 1-3 days 10 patients
***) Missing data – SHACT: All 4 days 3 patients, 1-3 days 9 patients

In addition, other analgesics have occasionally been taken by the following number of patients, mostly ibuprofen as described in **Table 6**.

Table 6: Number of patients reporting alternative analgestics as rescue medication

	Day 1	Day 2	Day 3	Day 4
Placebo	6	3	8	3
SHACT	2	5	3	4

Neither penetration of the IUD through the uterine wall, malposition of IUD nor any other serious adverse events were reported.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application.

Table 7: Summary of efficacy for trial PH-UID-02

Title: PH-IUD-02	
Study identifier	PH-UID-02

Design	Double-blind randomized placebo-controlled study evaluating the pain relief of a single administration of Lidbree administered before insertion of an IUD in women of 18 years, or more of age. Patients were given 24 paracetamol tablets of 500mg, which could be used to alleviate pain in the days post treatment		
	Duration of main phase: Duration of Run-in phase: Duration of Follow-Up:		One visit Not applicable 5 – 10 days after IUD insertion
Hypothesis	Superiority of of a topical formulation of lidocaine administered over placebo for pain relieve caused by insertion of an Intra Uterine Device		
Treatments groups	Lidbree (topical formulation of lidocaine)		Single administration of up to 8.5ml 4% lidocaine gel.
	Placebo		Single administration of up to 8.5ml placebo gel.
Endpoints and definitions	Primary endpoint	Maximum VAS pain intensity	during and within 10 minutes after start of IUD insertion
	Secondary endpoint	VAS scale	Intensity of pain after 30 minutes, 1hour, 2hours and 1-3 days after IUD insertion
	Secondary endpoint	Safety & Tolerability	
	Secondary endpoint	Rescue medication	A maximum of 24 x500mg paracetamol tablets could be used during the 3 next consecutive days post treatment.
	Secondary endpoint	Application discomfort	degree of discomfort experienced by the patient
Database lock	<date>		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	218 patients were included in 3 clinics across Sweden.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Lidbree
	Number of subject	110	108
	Mean maximum VAS pain intensity	44.2	28.3

	SD	26.0	24.6
	Rescue at Clinic	30.5% (33)	15.4% (17)
	Rescue during follow-up (4 days)	76.2%	72.0%
Effect estimate per comparison	Primary endpoint	Comparison groups	Lidbree vs Placebo
		Mean difference *	15.9
		CI (95%)	9.1;22.8
		P-value	P<0.0001
	Secondary endpoint VAS 30min	Comparison groups	Lidbree vs Placebo
		VAS (SD)	24.7 (21.9) vs 35.8 (24.1)
		P-value	P=0.0017
	Secondary endpoint VAS 60min	Comparison groups	Lidbree vs Placebo
		VAS (SD)	21.7 (21.2) vs 23.0 (19.2)
		P-value	Not significant
Notes	Both hormone and non-hormone IUDs could be used in this study, according to the wish of the patient. *mean difference is estimated from the ANOVA model Abbreviations: CI= Confidence Interval, IUD = Intra Uterine Device, Lidbree= a topical formulation of 4% lidocaine, VAS= Visual Analogue Scale		
Analysis description			

Exploratory study on hysteroscopy (study PH-HYS-01)

Objectives

The primary objective of the study was to obtain initial information regarding the feasibility of use for hysteroscopy, including the visibility for performing the hysteroscopy. Secondary objectives included the evaluation of the handling properties of Lidbree and the applicator, the evaluation of the Instructions for Use at hysteroscopy, and the collection of information about the safety and tolerability of the intrauterine gel in this procedure.

Methods

A non-comparative open label study was conducted in 10 patients to evaluate the feasibility of using the 4% lidocaine intrauterine gel formulation for hysteroscopy in women.
Women 18 years or older planned for hysteroscopy at the Department of Obstetrics and Gynaecology, Södersjukhuset, Stockholm, Sweden, who gave their informed consent were

included. A single dose of up to 8.5 mL containing 4% lidocaine was applied on the surface of the portio, in the cervix canal and in the uterus cavity with use of a special applicator. The hysteroscopy was carried out under general anaesthesia, and therefore no assessment of pain intensity during the procedure was made. Follow-up was conducted one day after hysteroscopy.

Results

The most important characteristic 'visibility during hysteroscopy' was rated as acceptable, good or very good in all 10 patients. It was found that the administered volume of 8.5 mL may be too large, in particular for 0-gravida. The results of other feasibility aspects such as ease of application and time required for use of the intrauterine gel constitute no hindrance for use in an outpatient setting. No safety or tolerability issues were recorded in this study. It was concluded that hysteroscopy can be carried out with Lidbree in an office setting from a feasibility point of view.

IV.5 Clinical safety

Patient exposure

In total, 244 women adult women were included in the clinical development programme, out of whom 136 were exposed to cervical and intrauterine administration of the active formulation, and 108 women were exposed to placebo gel consisting of the blinded vehicle of similar viscosity , see Table 9.The procedure for administering and dividing the total of up to 8.5 mL dose to the portio, into the cervical canal, and into the uterine cavity is for each study presented in the Study Narrative in the Summary of Efficacy.

Table 8: Clinical studies of the 4% lidocaine intrauterine gel formulation (Lidbree) involving assessment of safety

Development Stage*	Study Code	Number of Patients exposed		Objectives	Extent of exposure (total cervical and intrauterine)
		Active	Placebo gel		
Therapeutic exploratory	PH-IUD-01	16		PK, Safety, Local Tolerability, Efficacy,	8.5 ml gel
Therapeutic exploratory	PH-HYS-01	10		Feasibility, Safety, Local Tolerability	8.5 ml gel
Therapeutic confirmatory	PH-IUD-02	110	108	Efficacy, Safety, Local Tolerability	8.5 ml gel to 146 patients. In 72 patients the full dose could not be administered.
Total		**136**	**108**		

*Clinical development stage as defined in ICH guideline E8

Adverse events

Adverse events reported in the double-blind placebo-controlled study (PH-IUD-02) form the basis for the safety evaluation of LIDBREE 4% intrauterine gel. The number of patients with events are displayed in the table below.

Table 9: number of patients with adverse events in placebo and active treatment groups (study PH-IUD-02)

	Placebo (n=108)	LIDBREE (n=110)
Serious AE	0	0
No AE	72	78
≥AEs	36	32
Total	108	110

In the double-blind placebo-controlled study 68 patient reported 100 AEs. The number of non-serious AEs were almost identical in the two treatment groups. There was no uterine perforation as verified by ultrasound examination.

Severity of adverse events

Sixteen AEs were regarded with a "moderate" intensity and one (infection) was regarded as "severe" and this occurred 6 days after the insertion of IUD and lasted for 5 days. The remaining AEs were classified as "mild" severity.

Duration of adverse events

Most AEs lasted for a few hours and disappeared after the first day. Six patients with AE, did not report back any outcome of the AE, despite efforts from the midwives to get in touch with the patient. Those were appetite disorder (placebo), headache (Lidbree), abdominal pain (placebo), abdominal pain (Lidbree), stomach pain (placebo) and stomach pain (Lidbree).

Causality assessment

The causality assessments by the Principal Investigator were based on the complex complete procedure as causing the event and no differentiation could be done between a pharmacological influence of Lidbree, the stress situation around the insertion procedure or the patients´ tension in the gynaecological situation. Fifty-two AEs were judged to "probably/possibly" caused by this complex; 26 for Placebo and 26 for Lidbree. Forty-eight were regarded as "unlikely" related.

Common adverse events

The most common body organ system and adverse events with a frequency higher than 2% are proposed to be included in the SmPC as tabulated by Organ System, based on data presented below in the table below.

Table 10: Adverse events by system organ class in the placebo-controlled study reported in 2% or higher frequency following administration with Lidbree, but no difference in frequency as compared to placebo gel

System organ class	Frequency	Undesirable effect
Nervous system disorders	Common	Dizziness, headache, back pain
Gastrointestinal disorders	Very common	Nausea
	Common	Other gastrointestinal disorders

Source: Study PH-IUD-02

Table 11: Adverse events in the placebo-controlled study (PH-IUD-02) by MedDRA System Organ Class and preferred terms

SOC	MedDRA Term	Placebo (n=108)		SHACT (n=110)	
		Frequency	%	Frequen-cy	%
Infection and infestations	Influenza viral infections	1	0.93	1	0.91
	Common cold	0	0.00	1	0.91
	Infections - pathogen unspecified	0	0.00	1	0.91
Blood and lymphatic system disorders	Vasovagal reaction	1	0.93	0	0.00
Immune system disorder	Pollen allergy	0	0.00	1	0.91
Metabolism and nutrition disorders	Dehydration	0	0.00	1	0.91
Nervous system disorder	Dizziness	5	4.63	7	6.36
	Headaches	4	3.70	5	4.55
	Hypoaesthesia	0	0.00	1	0.91
Vascular disorders	Hypotension	0	0.00	1	0.91
	Syncope	1	0.93	1	0.91
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract infection	1	0.93	0	0.00
Gastrointestinal disorders	Abdominal distension	0	0.00	1	0.91
	Appetite disorder	1	0.93	0	0.00
	Diarrhoea	1	0.93	1	0.91
	Epigastric pain not food-related	0	0.00	1	0.91
	Gastrointestinal and abdominal pains (excl oral and throat)	3	2.78	1	0.91
	Gastric disorder	0	0.00	1	0.91
	Gastrointestinal disorders	2	1.85	0	0.00
	Nausea	14	12.96	14	12.73
	Nausea and dizziness	1	0.93	0	0.00

	Nausea and vomiting symptoms	1	0.93	4	3.64
	Swollen abdomen	2	1.85	1	0.91
Skin and subcutaneous tissue disorders	Pruritus	0	0.00	1	0.91
Musculoskeletal and conective tissue disorders	Back pain	3	2.78	1	0.91
	Musculoskeletal and connective tissue disorders	1	0.93	0	0.00
	Pain in thigh	1	0.93	0	0.00
	Pelvic pain	1	0.93	0	0.00
Reproductive system and breast disorders	Vaginal discharge	1	0.93	1	0.91
	Vulvovaginal pain	1	0.93	0	0.00
	Vulvovaginal burning sensation	0	0.00	1	0.91
	Vulvovaginal mycotic infection	0	0.00	1	0.91
General disorders and administration site conditions	Asthenic conditions	1	0.93	0	0.00
	Fatigue	2	1.85	0	0.00
	Pyrexia	2	1.85	1	0.91
Total number of AE:s		51		50	

SOC: System Organ Class. Table Programmed for MAA, Data from Study PH-IUD-02

Serious adverse events and deaths

No serious adverse events, deaths, or other significant adverse events have been reported in the clinical development program.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Lidbree.

Table 12. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

Clinical efficacy

Lidocaine is a well-known local analgesic and is currently used in a 2% gel formulation up to a 10% spray for comparable indications, e.g. surface anaesthesia of the mucous membranes prior to obstruct procedures, etc.

The clinical development program of Lidbree included one double-blind randomized placebo-controlled confirmatory study (PH-IUD-02), one therapeutic exploratory study on IUD placement (Study PH-IUD-01) and one exploratory study on hysteroscopy (PH-HYS-01).

The selection of nulliparous population is agreed, as this population generally perceive pain following IUD insertion more severely than woman who have given birth. The exploratory trial (PH-HYS01) allowed assessment of the feasibility and visibility. These are important factors as the application of the product should not hamper the gynaecological procedures. Although the numbers are low, the MAH has demonstrated that the application of the gel does not lead to hindrance of the procedures.

In the pivotal study, PH-UID-02, a significant difference from placebo in VAS was reported, with a difference in VAS 10 minutes into the procedure of 15.9mm. However, no difference from placebo was observed one hour post procedure and in the efficacy outcome need for "rescue therapy".

Use of the product did not affect the procedure. There were no perforations or malposition of the IUD in any of the patients as confirmed by ultrasound.

The product is intended for less complicated intra-uterine and cervical procedures, such as IUD placement, diagnostic hysteroscopy and endometrial biopsies. These procedures involve to a large extent the same proceedings, i.e. grasping of the cervix with a tenaculum, cervical manipulation and uterine distension. Literature data showed that the average pain perceived for intrauterine outpatient procedures, i.e. IUD placement, diagnostic hysteroscopy and endometrial biopsies, fall within the same range. Moreover, the procedures can generally be completed within one hour, e.g. within the effective time window of 90 minutes. The lidocaine gel did not affect the visibility in hysteroscopy studies and literature data shows that the quality of the biopsies is not compromised by the use of lidocaine gel.
Therefore extrapolation to other intra-uterine and cervical procedures with moderate pain can be accepted based on the data from the IUD studies.

The lower age limit is 15 years of age. The applicator is suitable for this population.

Clinical safety
Lidocaine has a well-established safety profile. In the trials a total of 136 were exposed to the formulation and 108 patients to a placebo gel. There were no relevant differences observed in the treatment arm compared to the placebo arm regarding local tolerability.

The product is administered only once, in a low dose, resulting in a low systemic exposure, well below toxic levels.

Post-menopausal women generally have a thinner genital mucosal layer which is more vulnerable than compared to fertile population. The submitted safety data support that a

single dose of intrauterine and cervical lidocaine can be safely administered in post-menopausal women.
Risk management is adequately addressed.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL 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

Lidbree 42 mg/mL intrauterine gel a proven chemical-pharmaceutical quality and is a hybrid form of Xylocaine 20 mg/mL solution for injection. Xylocaine is a well-known medicinal product with an established favourable efficacy and safety profile.

Lidocaine has been in clinical use for 70 years and is a well-known local anaesthetic of the amide type with well-established pharmacokinetic and pharmacodynamics properties. The use of topical anaesthesia for gynaecological procedures has been investigated indicating a need for these products. Currently, the majority of these procedures are managed post procedure with paracetamol. For hysteroscopy even general anaesthesia is used. The pivotal trial showed a significant benefit of the product over placebo during IUD placement.

Literature data was submitted showing that the pain perceived during hysteroscopy, endometrial biopsies and IUD placements is comparable, therefore the efficacy can be extrapolated to other moderately painful intra-uterine and cervical procedures.

The benefit-risk for Lidbree for the proposed indication 'topical anaesthesia for moderate acute pain during cervical and intrauterine procedures, in adults and adolescents from 15 years of age' is considered positive.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that Lidbree 42 mg/mL intrauterine gel can be approved as a hybrid form of Xylocaine 20 mg/mL solution for injection, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 June 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse