ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

Lidbree™

1. NAME OF THE MEDICINAL PRODUCT

Lidbree 42 mg/mL intrauterine gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lidocaine 42 mg/mL

Excipients with known effect:
Each mL of gel contains 284 mg of macrogolglycerol ricinoleate (castor oil polyoxyl) and up to 28 microgram of butylated hydroxytoluene (E 321).
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Intrauterine gel. Sterile, clear to almost clear, slightly brown-yellow viscous liquid that is a gel at body temperature.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lidbree is indicated for topical anaesthesia for moderate acute pain during cervical and intrauterine procedures, in adults and adolescents from 15 years of age. See section 5.1.

4.2 Posology and method of administration

Posology

Cervical procedures
Apply 2 to 3 mL in a thick layer to the portio, and 3 mL into the cervical canal using the sterile applicator 5 minutes before start of procedure.

Intrauterine procedures
Using the sterile applicator, apply 1 to 2 mL to the anterior lip of the portio, and 2 to 3 mL into the cervical canal. Wait 2 minutes for the onset of effect at the inner meatus. Thereafter insert the applicator into the uterine cavity and introduce 3 to 5 mL, 5 minutes before the procedure. The applicator is marked with a centimetre scale. A smaller volume can be administered, e.g. in nulliparous patients, if the patient experiences discomfort before the whole volume has been given. A single intrauterine dose should not exceed a total of 10 mL.

Paediatric population from 15 years of age
In low-weight adolescents below 30 kg body weight the dose should be proportionally reduced, and a single dose should not exceed the maximum recommended parenteral dose (6 mg/kg lidocaine hydrochloride, corresponding to 5.2 mg/kg lidocaine base in Lidbree, i.e. 1.2 mL per 10 kg body weight). In adolescents with a body weight of 30 kg the maximum dose of Lidbree is 3.6 mL in total.

The safety and efficacy of Lidbree in infants and children below 15 years of age have not been established. Lidbree should not be used in children below 15 years of age because of safety concerns (see section 4.4 and 5.1).

Elderly
No dose reduction is necessary in elderly patients (see section 5.2).

Hepatic impairment
A reduction of a single dose is not necessary in patients with impaired hepatic function (see section 5.2).

Renal impairment
A dose reduction is not necessary in patients with impaired renal function.

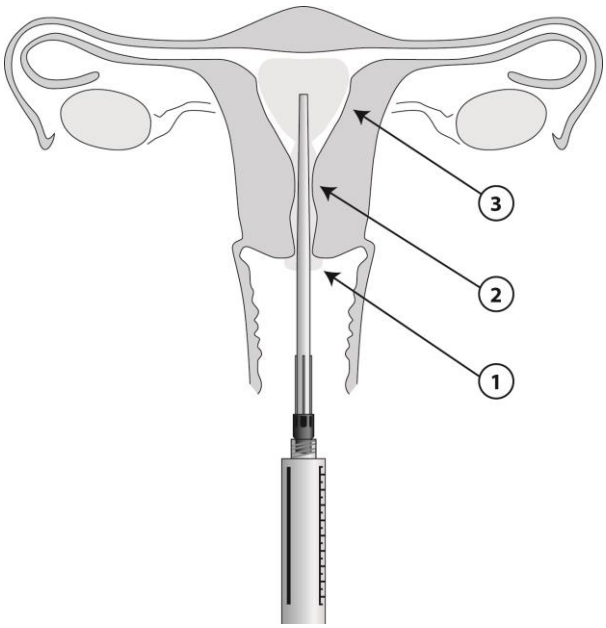
Method of administration
For cervical and intrauterine use only.
When administered, Lidbree should be a liquid. If it has formed a gel, it should be placed in a refrigerator until it becomes a liquid again. The air bubble visible in the syringe will then move if the syringe is tilted.

Assemble the product stepwise and apply the viscous liquid by use of the co-packed sterile applicator:

1) Check the appearance of the syringe while tilting it. The air bubble in the syringe will move when tilted if the product is in liquid state ready for use. If the air bubble does not move the product has formed a gel – then place in refrigerator until it becomes a liquid again.
2) Connect the plunger rod and applicator to the syringe and ensure they are tightly connected.

3) Extrude the air bubble and fill the applicator with gel by cautiously pushing the plunger of the syringe.
4) Use the applicator centimetre scale for positioning the Lidbree formulation.

With the applicator in place, 8.5 mL gel can be delivered from the syringe. One mL contains 42 mg lidocaine. Apply the gel stepwise (1 to 3) as illustrated in the figure.



4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

For cervical and intrauterine use only. Acute symptoms of local anaesthetic toxicity and life-threatening embolic complications may occur if the viscous thermogelling liquid is unintentionally injected intravascularly (for treatment of systemic toxic reactions see section 4.9). Other unintentional parenteral routes of administration may result in local tissue toxicity.

In case of difficult insertion of intrauterine contraceptives and/or exceptional pain or bleeding during or after insertion, physical examination and ultrasound should be performed immediately to exclude perforation of the uterine corpus or cervix, as with effective topical anaesthesia the patient might not react with pain in case of a perforation.

Some patients require special attention:
- Patients with partial or complete heart conduction block - due to the fact that local anaesthetics may depress myocardial conduction.
- Patients treated with antiarrhythmics of class III (e g amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be additive.
- Patients with acute porphyria. Lidocaine is probably porphyrinogenic and should only be prescribed to patients with acute porphyria on strong or urgent indications. Appropriate precautions should be taken for all porphyric patients.
- Patients in poor general condition.

Paediatric population
Lidbree should not be administered to mucous membranes of infants and children less than 15 years old as plasma concentrations of lidocaine may exceed the threshold for toxicity (see section 5.1).

Excipients
This medicinal product contains macrogolglycerol ricinoleate (castor oil polyoxyl) and butylated hydroxytoluene (E 321).
Macrogolglycerol ricinoleate may cause severe allergic reactions.
Butylated hydroxytoluene (E 321) may cause irritation to the mucous membranes.

4.5 Interaction with other medicinal products and other forms of interaction

In the case of concomitant use of Lidbree and other lidocaine-containing products, large doses of lidocaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics e.g. certain anti-arrhythmics, such as mexiletine, since the systemic toxic effects are additive. Specific interaction studies with lidocaine and anti-arrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution is advised (see also section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
No studies on reproductive and development toxicity have been conducted with Lidbree. Lidocaine crosses the placenta. It is reasonable to assume that lidocaine has been used in a great number of pregnant women and women of fertile age. There is no evidence that lidocaine causes disturbances in the reproductive process such as increased incidence of malformations. The risk to humans has, however, not been completely investigated. The reproduction toxicity of lidocaine has been investigated in non-clinical models that revealed no harm to the foetus.

Breast-feeding
Lidocaine may enter the mother's milk, but in such small amounts that there is generally no risk of this affecting the neonate. Breastfeeding may therefore continue in the case of treatment with Lidbree.

Fertility
There are no adequate data on the effect of Lidbree on fertility. No effect on fertility or early embryonic development is known for lidocaine.

4.7 Effects on ability to drive and use machines

Lidbree has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The adverse reactions reported in clinical studies were similar in type and frequency in women treated with Lidbree and women treated with placebo gel and were representative of transient undesirable effects seen in connection with placement of intrauterine contraceptive devices. No serious adverse events have been reported.

Tabulated list of adverse reactions
Adverse reactions are classified according to frequency and system organ class. Frequency categories are defined according to the following convention: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000); Not known (cannot be estimated from the available data). The following undesirable effects have been reported at 2% or higher frequency following administration of Lidbree.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Lidbree used as recommended is unlikely to cause toxic plasma concentrations of lidocaine. However, if other local anaesthetics are administered concomitantly the effects are additive and may cause an overdose, as may an unintentional intravascular injection (see section 4.4), with systemic toxic reactions.

Symptoms
Systemic toxic reactions primarily involve the central nervous system (CNS) and the cardiovascular system (CVS) and become increasingly apparent at increasing plasma concentration from 5,000 to 10,000 ng/mL. Signs of toxicity in the CNS generally precede cardiovascular toxic effects.

CNS toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are usually, circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis, tinnitus and visual disturbances. Dysarthria, muscular twitching or tremors are more serious and precede the onset of generalised convulsions. Unconsciousness and grand mal convulsions may follow which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly following convulsions due to the increased muscular activity, together with the interference with respiration and possible loss of functional airways. In severe cases apnoea may occur. Acidosis hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

Recovery is due to redistribution of the local anaesthetic drug from the central nervous system and subsequent metabolism and excretion.

Cardiovascular system toxicity may be seen in severe cases and is generally preceded by signs of toxicity in the central nervous system. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics, but in rare cases cardiac arrest has occurred without prodromal CNS effects.

Treatment
Severe CNS symptoms (convulsion, CNS depression) must promptly be treated with appropriate airway/respiratory support and the administration of anticonvulsants.

If cardiovascular depression occurs (hypotension, bradycardia), appropriate treatment with vasopressor, chronotropic and or inotropic agents should be considered.

If circulatory arrest should occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics; Anaesthetics, local, ATC code: N01BB02

Mechanism of action
Lidocaine is a local anaesthetic of the amide type. Lidocaine reversibly stabilises neuronal membranes and prevents initiation and conduction of nerve impulses, thus providing local anaesthesia. At high plasma concentrations, lidocaine may also decrease conduction of excitatory neural membranes in the brain and in heart muscle.

Pharmacodynamic effects
Lidbree is a thermogelling, preservative-free local anaesthetic viscous liquid. The formulation forms a gel when temperature increases to body temperature, and thereby remains adhered to the mucosal tissues in the cervical canal and the uterus (minimising leakage that would occur with a liquid formulation). The thermogelling formulation limits dilution with the mucus secretion and the local anaesthetic works as a buffering system.

Anaesthetic onset time of Lidbree after topical application to genital cervical mucous membranes is 2 minutes. Local anaesthesia of the corpus uteri for intrauterine procedures is achieved within 5 minutes after administration into the uterine cavity. The duration of effect is at least 30 minutes, while no effect on post-procedural pain compared to placebo gel remains after 60 minutes.

Visibility during hysteroscopy is not impaired.

Clinical efficacy and safety
The efficacy and safety of Lidbree as a topical anaesthetic for cervical and intrauterine procedures was demonstrated in a pain model: a placebo-controlled multicentre study in 218 nulliparous women requesting the placement of an intrauterine contraceptive device (IUD). This pain model is representative of the pain experienced from intrauterine procedures such as diagnostic hysteroscopy, and cervical and endometrial biopsies, which involve the same painful stimuli (grasping of the cervix with a tenaculum, cervical manipulation and uterine distension). In the placebo-controlled study gel was applied to the portio, into the cervical canal, and into the corpus uteri that was filled with gel 5 minutes before placement of IUD. The full volume of 8.5 mL could not be administered in 72 out of 218 women, nulliparous women often having a smaller uterus. The maximum pain intensity experienced during and within 10 minutes after the start of IUD placement, as rated on a 100 mm visual analogue scale (VAS), was significantly lower in women given Lidbree ($p<0.0001$) with an estimated effect size of 16 mm (mean difference) corresponding to a 36% lower mean VAS pain score, compared to women given placebo gel. The proportion of patients in the Lidbree and placebo group with close to pain-free scores (0-10), and the proportion with high scores indicating moderate or severe pain (51-100), was 31% vs. 9.7%, and 18% vs. 40%, respectively. The proportion of patients with

pain scores indicating severe pain (71-100) was 9.4 % vs. 19.4 %. The need for analgesics during the first hour after completion of the IUD placement was 15.4 % and 30.5 % in the Lidbree and placebo group, respectively. The proportion of patients in the Lidbree and placebo group with close to pain-free scores (VAS 0-10) after 30 min was 34.5 % and 16.1 % ($p < 0.01$), and after 60 min 38.7 % and 32.4 %, respectively.
In no case was uterine perforation observed on ultrasound examination. There were no serious adverse events.

Paediatric population
Lidbree has not been studied in paediatric patients below 18 years of age. Lidocaine is known to be an effective local anaesthetic in children, adolescents and adults. Posology for adolescents is provided based on the adult efficacy study (see Section 4.2). Administration of Lidbree to mucous membranes of infants and children below 15 years of age is not indicated (see Section 4.2) and may result in local anaesthetic systemic toxicity in individuals with body weight below 30 kg if the applied dose of lidocaine is larger than the maximum recommended parenteral dose (6 mg/kg bodyweight lidocaine hydrochloride, corresponding to 5.2 mg/kg lidocaine base in Lidbree, i.e. 1.2 mL Lidbree per 10 kg).

5.2 Pharmacokinetic properties

Absorption
The systemic absorption of lidocaine from Lidbree is dependent upon dose applied. In non-clinical studies plasma concentrations following intrauterine administration demonstrated less than dose proportional increases in peak concentration.
The high lidocaine concentration can temporarily increase the pH in the mucus secretion at the application site, which will increase the rate of absorption of the local anaesthetic.
The absorption of lidocaine was studied after a single cervical and intrauterine administration of 8.5 mL Lidbree in fifteen women 20 to 36 years of age, several in their menstrual cycle days 1 to 6, before placement of IUD. In all patients lidocaine was detected in plasma within 5 to 10 minutes after intrauterine administration of gel. Maximum plasma concentrations were observed at 30 to 180, mean 68 minutes. The mean (SD) peak plasma concentration (C_{max}) was 351 (205) ng/mL with a range of 65 to 725 ng/mL. Symptoms of local anaesthetic toxicity become increasingly apparent at increasing plasma concentration from 5,000 to 10,000 ng/mL and the observed mean C_{max} is less than 10 % of the ceiling for initial signs of CNS toxicity. At 3 hours concentrations had decreased to 30-50% of maximal values in most patients.

Biotransformation, elimination
The major elimination pathway of lidocaine is via hepatic metabolism involving CYP 1A2 and 3A4 forming monoetylglycinxylidid (MEGX) which has pharmacological activity similar to lidocaine. MEGX is further metabolised by CYP2A6 and the resulting metabolites are renally excreted. Following IV administration the systemic clearance of lidocaine is 10 to 20 mL/min/kg and the elimination half-life 1.5 to 2 hours. However, the rate of metabolism and elimination of the local anaesthetic after topical application of Lidbree are governed by the rate of absorption. Therefore, a decrease in clearance, such as in patients with severely impaired liver function, has limited effects on the systemic plasma concentrations after a single dose.

Special populations
Elderly patients
The clearance of lidocaine after epidural administration is decreased by approximately 40% in women with a mean age of 77 years as compared to women with a mean age of 42 years, whereas there are no significant differences in plasma concentrations of lidocaine. As the rate of metabolism and elimination of the local anaesthetic after topical application of Lidbree are governed by the rate of absorption, a decrease in clearance has limited effects on the plasma concentrations after a single dose.

No pharmacokinetic data is available on the intrauterine and cervical use of lidocaine in postmenopausal women. Safety data did not indicate an increased risk after a single dose of cervical and intrauterine lidocaine in postmenopausal women.

5.3 Preclinical safety data

Local and systemic toxicity of Lidbree containing 40 or 50 mg/mL of lidocaine were investigated up to the maximal intrauterine dose volume of 1mL/kg in female beagle dogs for up to 28 days. Due to the presence of macrogolglycerol ricinoleate in the formulation and minor changes indicating peripheral neuropathy in the 28-day study, a single dose study of Lidbree evaluating peripheral nerves was conducted at the maximal volume of 1 mL/kg of Lidbree. The dose of lidocaine at 40 or 50 mg/kg was 7 to 10 times the dose in humans at therapeutic use. Intrauterine application of Lidbree to female beagle dogs indicated rapid systemic uptake of lidocaine. There were no findings indicating systemic lidocaine toxicity or local reactions in vaginal, cervical or uterine membranes at this dose of Lidbree. No findings in the single dose study of 40 mg/kg lidocaine demonstrated a risk for systemic toxicity or peripheral nerurotoxicity following single dose in humans

Reproduction toxicology
No non-clinical studies on fertility, embryo-foetal development or pre- and postnatal toxicity have been conducted with Lidbree. In studies of lidocaine an impairment of the fertility of male or female rats was not observed.

Lidocaine crosses the placental barrier by means of simple diffusion. Embryotoxic or foetotoxic effects of lidocaine were detected in the rabbit, but only at maternally toxic doses which are higher than the clinical dose.

Genotoxicity and carcinogenicity
Studies on genotoxicity or carcinogenicity have not been conducted with Lidbree.
Genotoxicity tests with lidocaine showed no evidence of mutagenic potential. A metabolite of lidocaine, 2,6-dimethylaniline, showed weak evidence of activity in some genotoxicity tests. The metabolite 2,6-dimethylaniline has been shown to have carcinogenicity potential in preclinical toxicological studies evaluating chronic exposure. Risk assessments comparing the calculated maximum human exposure from intermittent use of lidocaine, with the exposure used in preclinical studies, indicate a wide margin of safety for clinical use. Cancer studies have not been performed with lidocaine, due to the area and duration of therapeutic use for this drug.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Lidbree 42 mg/mL intrauterine gel is provided 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 syringe is graduated in mL. A sterile (polypropylene) applicator with a Luer lock fitting compatible with the prefilled syringe is provided in a separate bag within the carton. 8.5 mL can be extruded from the syringe-applicator.

Pack size: 1×10 mL intrauterine gel in pre-filled syringe.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.
Gyömrői út 19-21.
Budapest H-1103
Hungary

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

10. DATE OF REVISION OF THE TEXT

08/07/2021