COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Instillido 20 mg/ml gel
# (lidocaine hydrochloride monohydrate)

# NL/H/5080/001/DC

# Date: 29 March 2022

**This module reflects the scientific discussion for the approval of Instillido 20 mg/ml. The procedure was finalised at 3 November 2021. 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 |
| ATP | Adenosine tri-phosphate |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CHMP | Committee for Medicinal Products for Human Use |
| CKD | Chronic kidney disease |
| CL | Serum clearance |
| Cl(cr) | Creatinine clearance |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CMS | Concerned Member State |
| CNS | Central nervous system |
| CRF | Chronic renal failure |
| CYP | Cytochrome P450 |
| DNA | Desoxyribonucleic acid |
| ECG | Electrocardiographic |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| ED50 | Median effective concentration |
| EEA | European Economic Area |
| EMDA | Electromotive drug administration |
| EPA | Environmental protection agency |
| ERA | Environmental Risk Assessment |
| ESSIC | European Society for the Study of Interstitial Cystitis |
| Fr | Size of cystoscope using the French scale |
| IC | Interstitial cystitis |
| ICH | International Conference of Harmonisation |
| ICS | International Continence Society |
| igE | Immuno-globulin E |
| i.m. | Intramuscular |
| i.p. | Intraperitoneal |
| IRLA | Intrarectal local anaesthesia |
| i.v. | Intravenous |
| MAH | Marketing Authorisation Holder |
| NADH | Nictotinamide-adenine-dinucleotide |
| NaOH | Sodium hydroxide |
| NOAEL | no-observed-adverse-effect level |
| PBS | Painful bladder syndrome |
| PD | Pharmacodynamic |
| Ph.Eur. | European Pharmacopoeia |
| PK | Pharmacokinetic |
| pKa | Acidity constant |
| PL | Package Leaflet |

| | |
|---|---|
| PPNB | Periprostatic nerve block |
| RH | Relative Humidity |
| RMP | Risk Management Plan |
| SEM | Standard error of the mean |
| s.c. | Subcutaneous |
| SmPC | Summary of Product Characteristics |
| TRS | Transrectal sonography |
| TRUS | Transrectal ultrasound |
| TSE | Transmissible Spongiform Encephalopathy |
| $T_{1/2}\beta$ | Serum elimination half-life |
| UV | Ultraviolet |
| VAS | Visual analogue scale |
| $V_d$ | Volume of distribution |

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Instillido 20 mg/ml gel, from Farco-Pharma GmbH.

The product is indicated for surface anaesthesia and lubrication for:

- The male and female urethra during cystoscopy, catheterisation, exploration by sound and other endourethral operations;
- Proctoscopy and rectoscopy;
- Symptomatic treatment of pain in connection with cystitis.

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

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC. For this type of application, MAHs need to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least ten years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature. For this procedure, reference is made to Xylocain 2% gel, which has been authorised since 1984. This complies with the requirement that the active substance needs to be authorised for at least ten years.

The concerned member states (CMS) involved in this procedure were Denmark, Germany, France, Sweden and the United Kingdom (Northern Ireland).

# II. QUALITY ASPECTS

## II.1 Introduction

Instillido 20 mg/ml is a clear, nearly colourless, sterile gel with a pH of 6.5.

The product contains as active substance 20.1 mg of lidocaine hydrochloride monohydrate equivalent to 18,9 mg lidocaine hydrochloride per ml gel. Furthermore, each pre-filled syringe with 6 mL or 11 mL gel contains 120.6 mg or 221.1 mg lidocaine hydrochloride monohydrate respectively.

The gel is packed in sterile pre-filled syringes containing 6 mL or 11 mL gel. The syringes are composed of a syringe cylinder and plunger made of polypropylene (PP) and a plunger stopper and sealing tip-cap made of bromobutyl rubber. The syringe tip does not support needle attachment. Each pre-filled syringe is packaged in a sterile blister pack consisting of a polypropylene film and an uncoated medical paper sheet.

The excipients are hypromellose, sodium hydroxide (for pH adjustment) and purified water.

## II.2 Drug Substance

The active substance is lidocaine hydrochloride monohydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white crystalline powder and is very soluble in water. The active substance has no chiral centre and does not display polymorphism.

The CEP procedure is used for the active substance. 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

A CEP has 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 meets the requirements of the monograph in the Ph.Eur. Drug substance specification includes all parameters included in the Ph. Eur. monograph of the substance, plus additional controls for solvent content (with different limits depending on the supplier, in line with the CEPs) and for microbial quality control. Skip policy of the microbial controls and suitability of the method in presence of the drug substance are adequately justified. The information about reference standards in use at the Drug product manufacturing site is adequate. Batch analytical data demonstrating compliance with this specification have been provided for three full scale batches.

Stability of drug substance

The active substance is stable for five years with no special storage conditions for the Active substance, when stored as described in the CEP. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

## II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The development of the product has been described, the choice of excipients is justified and their functions explained. The application for well-established use refers to several lidocaine gels on the market in the EU and outside. The physico-chemical characteristics (pH, density and viscosity/ rheology) of the drug product subject of this application and of the three similar products referred to in the clinical part of the application have been adequately characterized and have been found to be sufficiently similar to sustain the well-established use application from a quality point of view. All these products are confirmed to be non-newtonian fluids.
The choice of grade and quantity of hypromellose has been discussed.

The manufacturing process is developed based on the experience of the manufacturer with similar products, the information provided is sufficient for an established process. Selection of the container closure system is discussed. The suitability of the syringe gradation for dosage in young children and the accuracy of dosing have been adequately demonstrated. Extractables studies have been performed with the same combination of syringes and stoppers and showed no extractables at concerning levels. Container closure integrity studies have been performed with the packaging materials intended for commercial use. Further, integrity of the blisters after sterilisation is routinely controlled. The chosen sterilisation process is a steam process in non-standard conditions. An adequate justification is provided for the selection of this sterilisation process.

Manufacturing process

The batch formula for both fill volumes at minimal and maximal batch size is provided, as are the formulas for calculation of exact quantity of the components to introduce. The manufacturing process consists of dissolving the active substance in water, pH adjustment, addition of gelling agent Hypromellose and homogenization. The syringes and the outer packaging are assembled (syringes in PP/paper blister in carton boxes) and then sterilized by steam. The manufacturing process, in-process controls and control of critical steps are described with sufficient details. Bioburden control before sterilisation is performed non-routinely. Limits and frequency are stated in the dossier and are acceptable.

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scaled batches of each fill volume. Validation of the sterilisation process is provided for both fill volumes. The provided reports show that the process is capable of effectively and reproducibly sterilize the load.

Control of excipients

The excipients comply with Ph. Eur. requirements, except the sodium hydroxide 5N solution, when purchased ready for use. For this excipient specifications, analytical methods, validation and batch analysis are provided. For hypromellose, sufficient information, including substitution type and viscosity, is provided. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, filling quantity, density, pH,

viscosity, identity, assay, related substances, sterility of the gel and microbiological packaging control. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Release and shelf-life specifications are identical. The drug product specification is acceptable. The limits for viscosity have been established based on results obtained in drug product subject of this application and in the products to which reference is made in the well-established use application and are acceptable. The analytical methods are described with sufficient details and are adequately validated. Forced degradation studies have been performed, showing some degradation after oxidative and light stress. Mass balance and peak purity have been confirmed in the forced degradation studies, therefore the stability indicating nature of the method for assay and related substances is considered demonstrated. All batches included have adequate batch size and all results comply to the proposed specifications.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from five batches of the 11 ml fill presentation and six of the 6 ml fill presentation from the proposed production sites have been provided, demonstrating compliance with the specification.

Container closure system

For all components of primary and secondary packaging the composition, detailed technical drawings, statements of conformance to relevant regulations and Ph. Eur. monographs and the specifications are provided. The polypropylene components comply to Ph. Eur. 3.1.3 and 3.1.6 and the rubber components comply to Ph. Eur. 3.2.9. The graduation is printed during the manufacturing process. Adequate graduation is also confirmed during stability studies as part of the control for appearance.

Stability of drug product

Stability data on the product have been provided for four batches of each fill presentation stored at 25°C/60%RH (up to 60 months), 30°C/65%RH (up to 12 months) and 40°C/75%RH (up to 6 months) in accordance with applicable European guidelines demonstrating the stability of the product for 36 months. The batches were packaged as proposed for commercial use. Photostability studies in accordance with ICH recommendations have been performed, it is concluded that the drug product is sensitive to light and a suitable warning is included in the SmPC. On basis of the data submitted, a shelf life was granted of 36 months with no special temperature storage conditions.

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 Instillido 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

### III.1.1 Primary pharmacodynamics

Lidocaine is a local anaesthetic agent. Its mode of action is the use dependent block of neuronal sodium channels (Hille, 1977), Lidocaine has limited selectivity for different sodium channel subtypes. It blocks tetrodotoxin sensitive and insensitive channels (Colatsky, 1982). It also blocks cardiac sodium channels, resulting in antiarrhythmic, and at toxic concentrations, in cardiotoxic effects. For analgesia especially in neuropathic pain, not a complete sodium channel block is required. Lidocaine reversibly suppresses tonic action potential discharges at therapeutically relevant concentrations, while a complete nerve conductance block required much higher concentrations. The median effective concentration in vitro (ED50) (5.7 µg/ml) corresponds to clinically effective plasma concentrations for analgesia (Tanelian et al. 1991).

Lidocaine gel is intended for the topical use on mucosal surfaces of the urogenital tract, the gastrointestinal tract including nasopharynx, aiming at local anaesthesia at the site of application (Hung et al. 2010, Vaughan et al. 2005, Van der Burght et al. 1994). It may be also used for local anaesthesia following topical administration to the skin. In addition, it is foreseen for the administration into the bladder as transurethral administration for the symptomatic treatment of pain in connection with cystitis and urethritis (Avelino et al. 1998, Guerios et al. 2009). Upon subcutaneous administration, the anaesthetic effect is rapidly reached within few minutes. The effect declines thereafter in line with the clearance of the drug from the exposed tissue. The extend of anaesthesia is dependent on the concentration in the affected tissue. With a 0.5% solution, complete local anaesthesia could be reached which had mostly vanished after 60 min. Following dermal application, higher concentrations are needed for local anaesthesia, since skin penetration is required for drug action (Chen et al. 2007, Chen et al. 2012).

Mucosal administration can reach high bioavailability, resulting in potent local anaesthesia at the site of administration. Lidocaine was shown to be also active following intravesical administration. Application of a 2% solution at a dose of 35-40 mg/kg resulted in suppression of cystitis related pain in rats. In addition, symptoms of overactive bladder were alleviated with instillation of 2% lidocaine solution in the same dose range. These data indicate that lidocaine is a potent local anaesthetic, which is active following dermal, mucosal, and

intravesical administration. The local anaesthetic effect has a rapid onset, and vanishes upon tissue clearance (Juszczak et al. 2009).

### III.1.2 Secondary pharmacodynamics

Multiple secondary pharmacology effects are reported for lidocaine. An antibacterial activity of lidocaine against a wide spectrum of human pathogens has been demonstrated following topical administration. Based on these effects, local anaesthetics can be considered as an adjunct to traditional antimicrobial use in the clinical setting (Johnson et al. 2008). In addition to analgesia following topical administration as applicable for gels, analgesic effects following other routes of administration including local injection for regional anaesthesia such as brachial plexus anaesthesia or intrathecal administration have been demonstrated and are in clinical use with parenteral lidocaine preparations (Wenger et al. 2005). Lidocaine was shown to exert also strong analgesic effects if directly administered to specific brain structures. Systemic administration of lidocaine has been shown to result in clinically useful antiarrhythmic effects (Anonymous, 2019). Parenteral formulations are approved for the treatment of ventricular arrhythmias or pulseless ventricular tachycardia (after defibrillation attempts, cardiopulmonary resuscitation, and vasopressor administration) (Bergey et al. 1982). However, due to the short half-life, a bolus exerts only short effects. For longer lasting effects, lidocaine has to be infused at a rate of 1-4 mg/min. Systemic lidocaine administration has been also shown to result in neuroprotective effects, resulting in reduced lesion related deficits after focal cerebral ischemia (Wright et al. 2008).

### III.1.3 Safety pharmacology

Safety pharmacology studies indicate that the central nervous system (CNS) and the cardiovascular system are the prime organ systems for adverse drug effects. CNS effects, leading into convulsive seizures and ultimately death due to respiratory depression have been reported (Blumer et al. 1973, Chadwick 1985, Seo et al. 1982). Cardiovascular toxicity following administration of doses exceeding antiarrhythmic doses lead to cardio-depression and ultimately cardiovascular collapse dose dependently. No QTc prolongation is reported for lidocaine (Heavner, 2002). The cumulative lethal dose in dogs was 76.2 mg/kg (Liu et al. 1982). In cats, doses exceeding the convulsive dose by a factor of four were required to induce cardiovascular collapse (Chadwick, 1985).

### III.1.4 Pharmacodynamic drug interactions

Analgesic interaction (potentiation) has been demonstrated with opioids and with locally administered monoamines (Sánchez-Chapula 1985, Chen et al. 2017, Kolesnikov et al. 2000, Hung et al. 2017). Systemic cocaine was shown to aggravate lidocaine toxicity (Derlet et al. 1991). Based on the mechanism of action of lidocaine, pharmacodynamic interaction can be expected with other antiarrhythmic agents.

## III.2 Pharmacokinetics

### III.2.1 Absorption

Lidocaine gel is foreseen for the topical administration. Upon dermal application, the skin absorption was found to be low, but sufficient to induce local anaesthesia. The absolute bioavailability following dermal administration was not determined, but was found to be dependent on the formulation used and on the condition of the skin, i.e. scared skin had higher bioavailability (Berton et al. 2017, Weiland et al. 2006, Joudrey et al. 2015). Following mucosal (rectal) administration, rapid absorption and high bioavailability could be demonstrated, reaching 100% (De Boer et al. 1980). In contrast, the bioavailability following local application into the urinary bladder was found to be low, and was not largely increased in case of active cystitis (Henry et al. 2001). While systemic therapeutic plasma levels leading to antiarrhythmic or analgesic activity in man are reported in man to be in the range of 1 – 5 µg/ml, plasma levels reached after instillation of 40 ml of a 1% solution, i.e. 400 mg in man resulted only in systemic peak plasma levels of 0.12 µg/ml (Birch et al. 1994). Upon alkalization of the urine, peak levels of 1.06 µg/ml were reached (Henry et al. 2001). Lidocaine is a high clearance drug. The half-life of lidocaine was found to be 33 min after intravenous dosing in rats. Therefore, the peak plasma level and exposure is highly dependent on the balance between influx and elimination. Only in conditions, where the rate of absorption exceeds the elimination, plasma levels can build up (De Boer et al. 1980).

### III.2.2 Distribution

Following oral or intravenous administration of radioactively labelled lidocaine in rats, the radioactivity is widely distributed in the whole body, but is represented primarily by metabolites (Keenaghan et al. 1972). A high percentage of radioactivity was found in the carcase and the liver as well as in the gut wall early after dosing, while at later time points, due to urinary excretion, the majority is found in urine and in the gut wall, indicating enteral re-absorption of biliary excreted metabolites. Lidocaine crosses readily the placenta and is also excreted in milk (Berggren et al. 2004, Lincir et al. 2001).

### III.2.3 Metabolism

Lidocaine undergoes extensive first pass metabolism, with some species differences with regard to the relative contribution of individual metabolites (De Boer et al. 1980). It is primarily metabolized in the liver, but other tissues including the lung also contribute to systemic clearance. The potentially critical metabolite 2,6-xylidine was found to contribute 1.5% of total urinary excreted radioactivity in rats and 1% in man, indicating that this is a minor metabolite (Keenaghan et al. 1972). Multiple cytochrome P450 (CYP) isoenzymes are involved in the metabolism of lidocaine, however, CYP1A2 and CYP3A4 represent the most relevant enzymes for the metabolic clearance of lidocaine in man (Wang et al. 2000).

### III.2.4 Excretion

Lidocaine and its metabolites are primarily excreted in urine. Hepatobiliary clearance can be demonstrated using bile duct cannulated rats. All biliary excreted material is reabsorbed, leading to the observation that no radioactivity is excreted via the faecal route following dosing of 3H labelled lidocaine. In rats, at the time point 24 h after an oral dose of 10 mg/kg, 73% of radioactivity was found in urine, but only 0.3% reflected parent compound. Similar

excretion patterns were found in dogs and guinea pigs (Keenaghan et al. 1972). Lidocaine and its metabolites are also excreted in milk (Hoogenboom et al. 2015).

#### III.2.5 Pharmacokinetic drug interactions

The combination of lidocaine with adrenergic compounds leading to vasoconstriction results in reduced tissue clearance following local administration, and this can be considered as pharmacokinetic interaction (Brown et al. 2005). Pharmacokinetic drug interaction has been also demonstrated for strong inhibitors of CYP1A2 and CYP3A4, as such agents can reduce the metabolic clearance of lidocaine. Such interaction has been demonstrated in for midazolam and thiamylal as well as for propofol (Nagashima et al. 2005, Inomata et al. 2003, Bill et al. 2004).

### III.3 Toxicology

#### III.3.1 Single dose toxicity

The acute toxicity of lidocaine has been tested in mice, rats, rabbits, lambs and dogs. Lidocaine has a low to moderate acute toxicity, depending on the route of administration. Early signs of intoxication are convulsions, while cardiac and CNS depression leading to respiratory arrest leads into death. In dogs, the convulsive plasma concentration was determined to be 47.2 µg/ml, which is more than 9-fold the reported upper limit of the therapeutic plasma level range of 1 to 5 mg/ml in man (Feldman et al. 1989). Prolonged exposure to high local concentrations of lidocaine can induce local neurotoxic and myotoxic effects (Byrne et al. 2013).

#### III.3.2 Repeat-dose toxicity

Following repeated administration, cumulation of toxicity occurs only if the spacing of the doses is very short, i.e. every 30-40 min in rats (Lawrence et al. 1966). In all repeat-dose toxicity studies, no specific target organ of toxicity could be identified. Doses up to 100 mg/kg oral for 30 days (Wiedling, 1952), 250 and 500 mg/kg/day as continuous infusion for 30 and 14 days (Fujinaga et al. 1986), 30 mg/kg subcutaneously for 8 months (Wiedling, 1965), and 30 mg/kg as ear drops for 28 days were tolerated with no specific sign of systemic toxicity reported. For local application in the ear, the local concentration was 10%, which was without toxicity. The plasma lidocaine levels that were achieved with continuous infusion of 100 to 500 mg/kg/d were in the same range or higher than those, which occur in humans (Zou et al. 2019). Based on the comparison of single and repeat dose toxicity it can be concluded that the toxicity of lidocaine is peak plasma level associated, with CNS effects representing the first signs of systemic toxicity, and without any accumulation of toxicity, if the doses are sufficiently spaced.

#### III.3.3 Genotoxicity

The genotoxic potential of lidocaine and one metabolite of lidocaine was evaluated in different studies. According to a review of publicly available data, lidocaine hydrochloride was negative in the bacterial genotoxicity test in salmonella strains (Ames test), in the in vitro chromosome aberration test, and in the in vivo micronucleus or chromosome aberration test.

However, details of the studies or references for the reports were not provided (Snyder et al. 2001).

Other studies were summarized by (Carson, 2000) in an extensive report on local anaesthetics that metabolize to 2,6-xylidine or o-toluidine, as prepared on request of the National Institute of Environmental Health Sciences (USA). In the absence of metabolic activation (S9), lidocaine (dose not provided) was negative in the Escherichia coli desoxyribonucleic acid (DNA)-polymerase-deficient assay system. In ultraviolet (UV)-irradiated cells of E. coli, lidocaine inhibited the excision-repair process. In Salmonella typhimurium strains TA98 and TA1900, lidocaine (8 mg/plate), in the presence and absence of S9, was not mutagenic. However, when the study was reviewed by the Salmonella Work Group for the U.S. environmental protection agency (EPA)'s Gene-Tox program, the mutagenicity of the drug was determined to be inconclusive. In intact murine L1210 cells, lidocaine (8 mM) produced no significant DNA damage compared to control cells; however, its addition to bleomycine A2-pretreated cells significantly increased DNA breakage by 4.4-fold. In summary, there was no evidence for direct genotoxicity of lidocaine. However, in a non-standard study, lidocaine inhibited the excision-repair process in E. coli, an effect of unknown relevance for human genotoxicity. In addition, in intact murine L1210 cells, the genotoxicity of bleomycin was aggravated, again, with unknown relevance for human genotoxicity.

### III.3.4 Carcinogenicity

While no carcinogenicity studies have been reported for lidocaine, respective studies conducted with 2,6-xylidine were clearly positive (Carson, 2000). The primary target organ for carcinogenesis was the nasal cavity, but tumors were also found in other tissues (NTP, 1990). The data indicate that 2,6-xylidine is a carcinogen in rodents. No no-observed-adverse-effect level (NOAEL) for carcinogenicity could be determined. (European Medicines Agency CVMP, 2015).

### III.3.5 Reproductive and developmental toxicity

*Fertility and early embryonic development*

Lidocaine was found to have no effect in vivo on fertility and early embryonic development (Wiedling, 1965). Even upon continuous infusion of 250 mg/d in rats prior to mating and throughout gestation, no effect on fertility and early embryonic development was noted (Fujinaga et al. 1986). If mice embryos were ex vivo exposed to lidocaine, retarded development and embryotoxicity was observed (Del Valle et al. 1996), but such findings could not be verified in man (Wikland et al. 1990).

*Embryo- fetal development*

In vitro exposure of rat embryos to lidocaine lead to embryotoxic effects including unspecific teratogenicity, but respective findings were only seen at 117 µg/ml, which is more than 23 times higher than the upper limit of the therapeutic plasma concentration range for lidocaine reported to be 1-5 µg/ml in man (Fujinaga, 1998). No teratogenicity or embryotoxicity was seen following chronic sub-cutaneous (s.c.) dosing of 30 mg/kg s.c., intraperitoneal (i.p.) dosing with 56 mg/kg during critical days of gestation, and following

continuous infusion of 500 mg/d throughout gestation (Wiedling, 1965, Ramazzotto et al. 1985).

*Prenatal and postnatal development, including maternal function*
Chronic infusion of 500 mg/kg/d in rats during late gestation, delivery and during nursing had no clinically relevant effect on pre-and postnatal development. While at this high dose the delivery was significantly delayed by seven hours, this had no visible effects on postnatal development (Fujinaga, 1986). While one author reports that a single dose exposure in rats during mid-gestation caused multiple behavioural alterations in the offspring (Smith et al. 1989), these findings could not be verified by two other groups, even following higher and longer exposure (Holson et al. 1988, Teiling et al. 1988, Teiling et al. 1987). In baboons and sheep, single exposure to lidocaine prior to or during delivery at clinically relevant doses had only minor effects on the fetus, in that its ability to compensate asphyxia was reduced (Morishima et al. 1981, Morishima et al. 1989).

### III.3.6 Local tolerance
Lidocaine is very well tolerated if administered locally and no local irritation potential has been demonstrated if administered topically (Patel et al. 1965, Wiedling et al. 1963). While lidocaine in general is considered to have a low sensitizing potential and no allergic sensitization has been seen in animal experiments, allergic drug reactions have been reported in man.

### III.3.7 Immunotoxicity
A series of studies have demonstrated some effects on immune cells. While repeated intramuscular (i.m.) dosing of about 5 mg/kg in rabbits resulted in a 30% lower antibody response upon re-exposure with an antigen, this effect was considered to be within the variability of the method (Margaria et al. 1966). The exposure of isolated immune cells resulted in reduced activity of cells of the innate and the adaptive immune system at high concentration exposure. In summary, local administration of lidocaine seems to have no or only transient and minor effects on human immune function (Takagi et al. 1983, Procopio et al. 2001).

## III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Instillido is intended for substitution by well-established use, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

## III.5 Discussion on the non-clinical aspects

The submission is intended for well-established use. As such, the MAH has not provided additional non-clinical studies and further studies are not required. An overview based on literature review is, thus, appropriate. The effects of lidocaine hydrochloride monohydrate are well known, and the literature on pharmacology, pharmacokinetics and toxicology has been adequately reviewed in the MAH's non-clinical overview.

# IV. CLINICAL ASPECTS

## IV.1 Introduction

Lidocaine hydrochloride monohydrate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided for this well-established use application, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

## IV.2 Pharmacokinetics

### IV.2.1 Absorption

The rate and extent of absorption of lidocaine depends on the concentration and total dose administered, the specific site of application and duration of exposure. In general, the rate of absorption of local anaesthetic agents following topical application to wound surfaces and mucous membranes is high, and occurs most rapidly after intratracheal and bronchial administration. The absorption of lidocaine gel formulations from the nasopharynx is usually lower than with other lidocaine products (Pendopharm, 2017).

It has been shown that upon injection of lidocaine 400 mg, serum levels were highest following infiltration of vaginal mucosa and lowest following subcutaneous abdominal infiltration. Major nerve blocks and epidurals result in intermediate peak plasma levels.
Irrespective of the administration site, peak serum levels occurred 20 to 30 min following injection. The addition of adrenalin (1:200000) to the local anaesthetic solution reduced peak levels and delayed the rate of absorption (Weinberg et al. 2015).

Blood concentrations of lidocaine after instillation of lidocaine gel in the intact urethra and bladder in doses up to 800 mg are well below toxic levels. Lidocaine is also well absorbed from the gastrointestinal tract, although little intact drug may appear in the circulation because of biotransformation in the liver (Pendopharm, 2017).

### IV.2.2 Bridging to products used in literature

No bioequivalence studies have been conducted between products used in literature and the product at stake. The MAH provided data to indicate that qualitative composition of registered lidocaine gel formulations and Instillido are comparable to a large extent. Further, the MAH provided information on the products were used in literature supporting efficacy and safety of the product. Overall, all relevant lidocaine products (both test and those used in literature) are watery solutions, with sodium hydroxide (NaOH) added in order to adjust the pH. There are differences in the gelling agents, with agents containing either hypromellose (hydroprophylcellulose), sodium carboxymethylcellulose or hydroxyethylcellulose; the latter either alone or in combination with propylenglycol. From a pharmacokinetic (PK) point of

view, this is not considered a critical issue affecting systemic exposure to lidocaine. Density, pH, rheological characteristics and viscosity of the referenced lidocaine products do not appear to be markedly different and from a PK point of view, the products may be considered comparable to the test product.

### IV.2.3 Distribution

When lidocaine is given intravenously to normal subjects, the volume of distribution is 0.6 to 4.5 L/kg. The plasma binding of lidocaine is inversely proportional to the drug concentration. It is 60% to 80% protein-bound at concentrations of between 1 and 4 µg/mL. Binding fraction also depends on the plasma levels of the acute phase reactant alpha-1-glycoprotein. A paediatric PK study revealed that children older than 6 months of age distribute and eliminate intravenous lidocaine in the same manner as adults (Finholt et al. 1986).

Lidocaine is a weak base with an acidity constant (pKa) of 7.9 and at tissue pH can diffuse through connective tissue and cellular membranes to reach the nerve fibres where ionisation can occur. Lidocaine is bound to plasma proteins to an extent of approximately 64% (Monographie Lidocain, 1993, Hohenfeller, 1994, Mehra et al. 1998, Sökeland et al. 1985).

Lidocaine has been shown to cross the placenta and blood-brain barrier by simple passive diffusion. Because the degree of plasma protein binding in the foetus is less than in the mother, the total plasma concentration will be greater in the mother, but the free concentrations will be the same. As mentioned above, as a weak base, lidocaine tends to be more unionised and able to cross cell membranes in basic media. In foetal acidosis lidocaine crosses the placenta in unionised form, becomes ionised given the acidic environment of the foetal circulation and becomes “trapped”, thus increasing foetal lidocaine concentration (Weinberg et al. 2015).

### IV.2.4 Excretion

Lidocaine has an elimination half-life of 1.6 hours and an estimated hepatic extraction ratio of 0.65. The clearance of lidocaine is almost entirely due to liver metabolism, and depends both on liver blood flow and the activity of metabolizing enzymes. Approximately 90% of the lidocaine administrated intravenously is excreted in the form of various metabolites, and less than 10% is excreted unchanged in the urine. The primary metabolite in urine is a conjugate of 4-hydroxy-2,6-xylidine, accounting for about 70-80% of the dose excreted in the urine (Pendopharm, 2017).

The elimination half-life of lidocaine following an intravenous bolus injection is typically 1.5 to 2.0 hours. The elimination half-life in neonates (3.2 hours) is approximately twice that of adults. The half-life may be prolonged two-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites (Pendopharm, 2017).

### IV.2.5 Metabolism

Lidocaine exerts a pronounced first-pass metabolism. It is dealkylated in the liver by the cytochrome P450 system resulting in numerous metabolites. Monoethylglycine xylidide and

glycine xylidide are the key active metabolites, both of which have reduced potency but their pharmacologic activity is comparable to lidocaine. The only reported metabolite of lidocaine found to be carcinogenic in a rat model is 2, 6-xylidine. Its pharmacologic activity is unknown. Upon intravenous administration of lidocaine, monoethylglycine xylidide and glycine xylidide concentrations equate to approximately 11% to 36%, and 5% to 11%, respectively, of the total plasma lidocaine concentrations (Weinberg et al. 2015).

Lidocaine and its metabolites are predominantly excreted via the kidney. Less than 10% of lidocaine is excreted without being metabolised. The total body plasma clearance of lignocaine in healthy volunteers has been reported to be approximately 10-20 mL/min/kg. The majority of lignocaine elimination occurs in the liver, and since the total body plasma clearance of lignocaine is about 800 mL/min and hepatic blood flow is about 1.38 L/min, up to 60% of an oral dose is metabolised before entry into the systemic circulation (Weinberg et al. 2015).

Upon infusion lasting <12 hours or bolus injection, the plasma half-life of lidocaine has been shown to be approximately 100 min with linear pharmacokinetics. In contrast, following an intravenous infusion >12 hours, lidocaine exhibits non-linear or time-dependent pharmacokinetics. Patients receiving prolonged lidocaine infusions following myocardial infarction, lidocaine concentrations raised for approximately 48 hours, with the half-life extending up to four hours (Weinberg et al. 2015).

### IV.2.6 Pharmacokinetics in target population

Systemic exposure to lidocaine upon intraurethral application, intravesical application, intrarectal application, intravaginal/intrauterine application, nasopharyngeal/oropharyngeal application generally is low, and well below the toxic levels of 5 µg/ml. PK in patients has been published and discussed in the previous sections of this AR. As indicated earlier, although exposure in many cases may be below the expected toxic levels, this may not always be the case, since e.g., absorption from wound surfaces and mucous membranes can be relatively high, especially in the bronchial tree. This is included as a warning in the SmPC, which is agreed. In the SmPC it is also stated that debilitated, elderly, acutely ill patients and patients with sepsis should be given reduced doses commensurate with their age, weight and physical condition, because they may be more sensitive to systemic effects due to increased blood levels of lidocaine following repeated doses.

### IV.2.7 Pharmacokinetics in special populations

<u>Impaired renal or hepatic function</u>

Lidocaine is metabolised in the liver by cytochrome P450 isoenzymes. In patients with hepatic impairment, it has been shown that lidocaine clearance is markedly decreased and the elimination half-life is significantly prolonged. Therefore, dose reductions should be taken into consideration, at least in patients with severe hepatic impairment.

In 2002, Wojcicki et al. published the results of a study evaluating the lidocaine elimination and the rate of formation of its main metabolite MEGX in patients with various stages of liver

dysfunction due to cirrhosis (Wojcicki et al. 2002). The study was carried out in 44 subjects allocated into the following groups: A control group consisting of 14 healthy volunteers as well as 30 patients with liver cirrhosis. All subjects were administered lidocaine, intravenously, at a dose of 1 mg/kg (Xylocaine, Astra) over approximately 2 min. Lidocaine blood concentrations were more elevated in patients with more advanced stages of liver dysfunction, i.e. proceeding from Child-Pugh's stage A to C. The reduced ability of liver to metabolise lidocaine is confirmed by significant prolongation of lidocaine half-live in patients with more advanced liver disease according to Child-Pugh's staging. It was found that in patients at stage C, elimination half-life of lidocaine was prolonged by more that 3.5-fold ($P<0.001$), and in patients at stage B more than 2.5-fold ($P<0.01$) as compared to patients at stage A, respectively (Wojcicki et al. 2002).

In the PK study published by Axelsson et al., up to 800 mg lidocaine were instilled intraurethrally resulting in low systemic plasma levels in subjects without known hepatic dysfunction. Intraurethrally, a maximum single dose of up to 800 mg is proposed for the proposed medicinal product, which is not to be expected to result in toxic plasma concentrations (Axelsson et al. 1983). Following intraurethral administration of 400 mg or 800 mg lidocaine to patient without known impairment in renal or hepatic function, mean peak plasma levels reached 0.06 µg/mL and 0.15 µg/mL, respectively (Axelsson et al. 1983). The concentration remained constant in the time interval 30 to 60 min and then decreased to 0.04 µg/mL 3 h after administration of 400 mg lidocaine. In the 800 mg-group, the blood concentration curve rose almost linearly up to 45 min and then remained fairly constant in the interval between 45 and 180 min with concentrations between 0.13 and 0.15 µg/mL (Axelsson et al. 1983). However, as shown in Figure 1 below, high deviations standard error of the mean (SEM) apply.

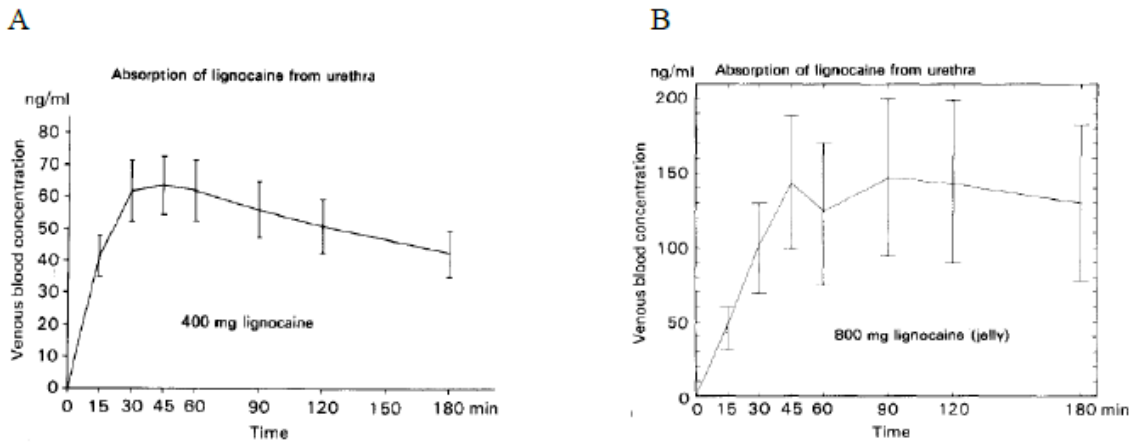


*Figure 1. Venous blood concentration of lidocaine after intraurethral administration of 400 mg (A) and 800 mg (B) lidocaine (2% lidocaine gel. Mean values +/- SEM for all patients. (Source: Axelsson et al. 1983)*

Upon intravenous administration of 1 mg/kg lidocaine (equating to 75 mg for an average body weight of 75 kg), plasma concentrations of up to 1.29 ± 1.89 µg/mL have been determined after 15 min in cirrhotic patients decreasing to 0.13 ± 0.15 µg/mL at 240 min after administration (Wojcicki et al. 2002). Both values are well below the toxic level of 5 µg/mL.

However, it was found that in cirrhotic patients at Child-Pugh's stage C, elimination half-life of lidocaine was prolonged by more than 3.5-fold, and in patients at stage B more than 2.5-fold (P<0.01) as compared to patients at stage A, respectively (Wojcicki et al. 2002). Thus, given an average plasma half-live of lidocaine of 1.6 h in normal subjects, plasma half-lives of up to 5 h or higher can be assumed in patients with severe liver cirrhosis. However, it is not expected that toxic lidocaine plasma levels will be reached as 800 mg lidocaine are the maximum daily dose as stated in the proposed SmPC.

Despite the plasma concentrations of the parent compound lidocaine, the blood levels of the main active metabolites MEGX and GX must be taken into considerations in patients with impaired renal or hepatic function.

Distribution and elimination kinetics of lidocaine and its metabolites MEGX and GX in patients with chronic kidney disease (CKD) undergoing haemodialysis have been investigated by Collinsworth and co-workers already in 1975 (Collinsworth et al. 1975). To that end, each patient received a loading dose of 75 mg of lidocaine, followed by a 30 µg /kg /min lidocaine infusion (Collinsworth et al. 1975). After the infusions were stopped, lidocaine plasma levels initially fell rapidly, then slowly, with a terminal elimination half-life of 118 to 170 min. Thus, the average terminal half-life of 148 min is higher than reported for normal subjects of approximately 1.6 hours. When the infusions were stopped, the fall in MEGX levels also generally paralleled the decline in lidocaine levels. On the other hand, GX levels did not reach a clear plateau during the 12-hour infusion period and were found in two patients to persist relatively unchanged for 12 hours after the lidocaine infusions were discontinued. It appears that accumulation of lidocaine and MEGX presents no greater hazard in patients with renal impairment compared to normal subjects. GX levels, however, may increase progressively for as long as 1.5 to 2.5 days in patients receiving continuous lidocaine infusions (Collinsworth et al. 1975).

Lidocaine PK has been reported in patients with chronic renal failure (CRF) receiving and not receiving haemodialysis in 2006 by De Martin and co-workers as well (De Martin et al. 2006). The kinetics of lidocaine and its metabolites MEGX and GX has been determined after intravenous injection of 1 mg/kg lidocaine in 15 healthy volunteers (creatinine clearance, CL(cr), >80 mL/min x 1.73 m-2), 10 subjects with moderate renal insufficiency (CL(cr) between 30 and 60 mL/min x 1.73 m-2), 10 subjects with severe renal insufficiency (CL(cr) <30 mL/min x 1.73 m-2), and 10 functionally anephric patients undergoing long-term haemodialysis. In patients not undergoing haemodialysis, lidocaine kinetic parameters were altered in proportion to the degree of renal function impairment, but only in patients with severe renal insufficiency were differences statistically significant: clearance was about half that of control subjects (mean ± SD, 6.01 ± 2.54 mL/min x kg vs. 11.87 ± 2.97 mL/min x kg; P <0.001), and half-life was approximately doubled (4.55 ± 1.71 h vs. 2.24 ± 0.55 h, P <0.001). No such alterations were observed in patients undergoing regular haemodialysis, whose values were similar to those of the control group. The steady-state volume of distribution and MEGX levels were independent of renal function, whereas GX levels were more than double those of control subjects (P <0.05) in all CRF groups (De Martin et al. 2006). The data obtained in this study indicate that lidocaine metabolites may accumulate in patients with renal impairment. It must

be noted that toxic side effects have not been observed. However, only four patients have been analysed in the course of this study.

In general, the minimum change in kidney function that necessitates drug dose adjustments is not well defined. Usually, dose adjustments are not deemed required if PK parameters changes are below <30% or when <30% of a dose is excreted via the kidneys. Lidocaine is extensively metabolised in the liver and the active metabolites are cleared via the kidneys. No accumulation of the parent compound lidocaine could be detected in PK investigations in CKD patients, however, accumulation of its active metabolites is considered possible, at least when lidocaine is administered as bolus injection or as high repeated topical doses.

<u>High/Low weight</u>

Lidocaine disposition in obese men and women has been investigated by Abernethy and Greenblatt in 1984 (Abernethy et al. 1984). To that end, each subject received a single 25-mg intravenous (i.v.) infusion of lidocaine hydrochloride over 30 seconds. Venous blood samples were drawn before lidocaine dosage and after the dose at 5, 15, 30, 45, 60 min, 1.5, 2.0, 2.5, 3, 4, 5, 6, 7 and 8 hours. Actually, mean lidocaine elimination half-life was markedly prolonged in obesity for both men (2.69 vs. 1.62 h, P <0.001) and women (2.95 vs. 2.08 h, P <0.01) as shown in Figure 2 below (Abernethy et al. 1984).

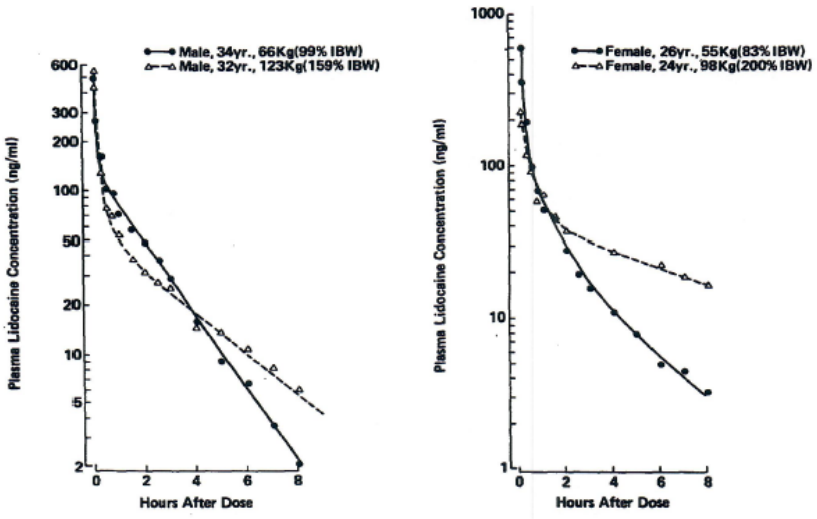


*Figure 2. Plasma lidocaine concentrations and pharmacokinetic functions in an obese man and control (left) and an obese woman and control (right). Obese and control subjects are age matched. (Source: Abernethy et al. 1984)*

The prolongation of lidocaine elimination half-life in obesity after a single dose was due to the marked increase in volume of distribution ($V_d$) (Table 1 below (Abernethy et al. 1984). In obese men, $V_d$ was nearly twice that seen in control subjects (325 vs. 186 L, P <0.001), with a similar, though less striking, finding for women (264 vs. 209 L, P <0.025).

| | Men | | Women | |
|---|---|---|---|---|
| | Obese | Control | Obese | Control |
| Subject characteristics | | | | |
| Number | 14 | 19 | 11 | 12 |
| Age (yr) | 35 ± 3 | 31 ± 2 | 32 ± 3 | 30 ± 1 |
| Weight (kg) | 124 ± 8 | 69 ± 1‡ | 96 ± 6 | 59 ± 2‡ |
| Percent IBW | 169 ± 10 | 93 ± 2‡ | 174 ± 11 | 102 ± 3‡ |
| Kinetic variables | | | | |
| Elimination half-life (hr) | 2.69 ± 0.20 | 1.62 ± 0.06‡ | 2.95 ± 0.31 | 2.08 ± 0.06† |
| Vd (liters) | 325 ± 29 | 186 ± 12‡ | 264 ± 20 | 209 ± 15* |
| Vd/kg body weight (liters/kg) | 2.67 ± 0.22 | 2.71 ± 0.18 | 2.88 ± 0.31 | 3.57 ± 0.25 |
| Clearance (ml/min) | 1,427 ± 117 | 1,346 ± 86 | 1,089 ± 83 | 1,162 ± 84 |

Student *t* test for obese vs control of the same sex: * $p < 0.025$; † $p < 0.01$; ‡ $p < 0.001$.
Values are mean ± standard error of the mean.
IBW = ideal body weight; Vd = volume of distribution.

*Table 1. Effect of obesity and sex on lidocaine pharmacokinetics. (Source: Abernethy et al. 1984)*

Furthermore, increases in lidocaine half-life were highly correlated with $V_d$ in both men and women (data not shown). When lidocaine $V_d$ was corrected for total body weight, differences between control and obese groups were no longer significant. Therefore, lidocaine distributes into excess body weight over ideal body weight (IBW) to a similar extent as into IBW. Actually, in obese subjects, lipophilic drugs may have marked increases in $V_d$ and minimal changes in clearance, resulting in a prolonged elimination half-life after single doses and a prolonged time to reach steady-state plasma drug concentrations during chronic dosing. The authors concluded that distribution of a drug such as lidocaine is markedly increased in obesity, similar to that seen for restrictively cleared drugs. However, lidocaine clearance, which closely parallels hepatic blood flow, was not influenced by obesity in these otherwise healthy subjects. The pharmacokinetic result of such a finding is prolongation of lidocaine elimination half-life (Abernethy et al. 1984).

In the above-mentioned study, the prolonged elimination half-life of lidocaine in obese subjects has been described after single intravenous administration of 25 mg lidocaine hydrochloride. However, clearance of lidocaine was not affected. Unfortunately, PK of the active metabolites MEGX and GX have not been established by the authors. However, in contrast to patients with impaired renal or hepatic function, it is not to be expected that the active metabolites may accumulate in obese, but otherwise healthy subjects. Therefore, the MAH is of the opinion that the lidocaine half-life prolongation described by Abernethy and Greenblatt are not considered to constitute a safety issue for obese subjects in general, given that the recommended maximum doses stated in the proposed SmPC will not be exceeded.

Race

The potential effect of race on lidocaine PK has been investigated by Goldberg and co-workers in 1982 (Goldberg et al. 1982). Seventeen subjects received 1 mg/kg lidocaine hydrochloride intravenously. Blood samples were drawn at 0, 2, 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, and 420 min after administration.

| Parameter | Caucasian | Oriental | Black |
|---|---|---|---|
| Number of subjects | 7 | 5 | 5 |
| Sex (M : F) | 3 : 4 | 3 : 2 | 1 : 4 |
| Age (yrs) | 23.4 ± 1.0 | 22.8 ± 1.9 | 22.6 ± 1.0 |
| Weight (kg) | 66.2 ± 3.9 | 60.1 ± 3.4 | 63.0 ± 5.8 |
| $V_d$ (liters/kg) | 2.13 ± 0.36 | 2.13 ± 0.11 | 2.28 ± 0.53 |
| $CL$ (ml/min · kg) | 26.2 ± 2.9 | 25.7 ± 3.1 | 20.8 ± 3.4 |
| $t_{1/2}\beta$ (min) | 58.2 ± 10.0 | 62.7 ± 11.3 | 94.5 ± 40.6 |
| Unbound fraction (%) | 26.5 ± 1.4 | 26.8 ± 2.6 | 30.1 ± 2.4 |

* Values are means ± S.E.M.

*Table 2. PK parameters in young adults of different ethnic origin after i.v. lidocaine administration.*

As shown in Table 2 above, there were no significant differences in PK parameters such as $V_d$, serum clearance (CL), serum elimination half-life ($t_{1/2}\beta$) and unbound fraction of lidocaine demonstrated among Caucasians, Blacks and Orientals. It should be noted that the elimination half-life in one black female was unusual high with a value of 257 min, resulting in a mean $t_{1/2}\beta$ value of 94.5 ± 40.6 min for black volunteers. The $t_{1/2}\beta$ in black volunteers without this subject was 54.0 ± 2.6 min (n=4).

Regarding efficacy, no effect of ethnic origin could be found upon intraurethral lidocaine use as reported by Goldfischer and co-workers (Goldfischer et al. 1997). Study subjects of different ethnic origin have also been enrolled in the study published by Tanabe et al., 2004 with no significant differences found in pain ratings between ethnic groups (Tanabe et al. 2004).

Thus, there is no evidence from published clinical literature that PK or pharmacodynamic (PD) of lidocaine hydrochloride is influenced by ethnic origin.

Elderly

The terminal half-life of lidocaine may be prolonged from approximately 1.5 hours up to 2.3 hours in elderly patients. Following repeated doses, elderly patients may be more sensitive to systemic effects due to the increased blood levels of lidocaine (Pendopharm, 2017). A warning is provided in the SmPC, which is considered adequate.

Children

The proposed medicinal product is not indicated for use in children below the age of two years. Results from PK studies indicate that higher peak plasma levels are reached when lidocaine is applied topically on mucous membranes (nose, upper airways) to children aged between zero and three years when compared to older children and adults. Thus, children may be more sensitive to systemic effects due to increased blood levels of lidocaine.

Studies published by Whittet and co-workers as well as Leopold and colleagues demonstrated significantly higher lidocaine plasma levels compared to adults and/or older children. In the study published by Whittet and co-workers, 30 children were studied, with ages which ranged from eight months to ten years and weights from 7 to 24 kg. An anaesthetist then sprayed the upper airway with lidocaine via a metered spray (Xylocaine aerosol spray, Astra); each puff

delivered 10 mg of lidocaine base. A dose of 4 mg/kg was directed in equal proportions to the supraglottic, glottic and subglottic regions resulting in total doses from 28 to 96 mg lidocaine base. None of the children in this study showed signs of systemic toxicity. However, plasma levels of up to 5.6 µg/mL, which is above the toxic level, have been observed. These findings could be confirmed by Leopold and co-workers (Whittet et al. 1988). In this study, 11 children aged 25-85 months (body weight: 12.6-26.3 kg) requiring general anaesthesia for comprehensive dental care received a lidocaine DentiPatch (46.1 mg lidocaine, 20%), which was placed on the buccal mucosa above the maxillary incisors for 5 min. Blood samples were drawn after 1, 5, 10, 15, and 45 min after patch removal.

The mean peak plasma lidocaine concentration was 82 ± 26 ng/mL, ranging from 41 to 128 ng/mL. The mean time at which peak plasma lidocaine concentration was attained was 9 ± 1 min, ranging from 1 to 15 min. The mean maximum plasma MEGX concentration was 11.98 + 1.44 ng/mL, ranging from 5.4 to 18.98 ng/mL. All subjects demonstrated a maximum MEGX level at the latest time point (45 min); higher MEGX concentrations at time points later than 45 min must therefore be considered. The local tolerability of the patch was good and no adverse events were reported. These results indicated that lidocaine absorbed from a 5-min application of a single 20% lidocaine (46.1 mg) oral patch did not reach toxic plasma concentrations of 5 µg/mL. This is consistent with studies measuring plasma lidocaine concentrations after lidocaine patch application in adults. However, this study showed that the plasma concentrations were much higher (4-5 times) in children than reported for adults with 21.8-22.3 ng/mL after a 15-min application of the 20% lidocaine patch (Whittet et al. 1988). Furthermore, several factors may result in lidocaine toxicity being reached at normally safe dosages. Moreover, plasma levels could be significantly higher than the mean value due to the high inter-individual variability. For example, in this study, the investigators recorded a peak plasma lidocaine concentration of 128 ng/mL compared to a mean value of 82 ng/mL (Whittet et al. 1988).

Furthermore, in 2014, the US FDA reviewed more than 20 case reports of serious adverse reactions, also with fatal outcome, in infants and young children aged from five months to 3.5 years (FDA, 2014). Of the 22 cases, six were fatal, three were categorised as life-threatening, 11 cases required hospitalisation and two required ambulant medical intervention. Children received viscous 2% lidocaine solution orally for treatment of teething pain (n=5), oral stomatitis (n=6), fever blister (n=1), thrush (n=2), oral ulcer/lesion (n=3), and sore throat due to croup (n=1). For four cases, no reason for treatment has been specified. In 11 cases out of 22, repeated doses have been applied prior to onset of the adverse reaction. In six cases, lidocaine toxicity became apparent after a single accidental ingestion, whereas in five cases, it was not reported whether multiple or single doses were taken prior to manifestation of toxic symptoms. The FDA decided that these medicinal products should not be applied to children for treatment of teething pain (FDA, 2014).

Clinical data from well-controlled studies investigating the effect of intraurethral 2% lidocaine gel in children below two years of age are somewhat limited. Data from four randomised clinical trials (RCTs) comprising about 300 children are available (Vaughan et al. 2005, Mularoni et al. 2009, Poonai et al. 2015, Uspal et al. 2018). In these studies, no serious adverse

events have been reported. However, a meta-analysis of these clinical trials revealed no significant effect of local anaesthesia compared to plain lubricant in infants and very young children.

Interestingly, a subgroup analysis revealed that 2% lidocaine gel showed a favourable effect compared to placebo in children ≥ 4 years of age (Chua et al. 2017). The results from PK studies indicate that higher peak plasma levels are reached when lidocaine is applied topically on mucous membranes (nose, upper airways) to young children and infants when compared to older (school)children and adults. Although these data were obtained after oral or tracheal exposure, it cannot be excluded that comparable lidocaine plasma levels might be reached upon other topical routes of administration and could therefore potentially harmful to young children below the age of two years.

Altogether, given the potential risk of high systemic lidocaine levels and limited data on the efficacy in this age group, the MAH is of the opinion that there is insufficient clinical data available in infants and children below the age of two years so far and is therefore not considered recommendable for use in this vulnerable patient population. This is in line with other lidocaine gels, which are authorized and marketed as medicinal products in the EU.

## IV.3 Pharmacodynamics

### IV.3.1 Anaesthetic effect

Lidocaine has a rapid onset of action with 1 to 5 min after local infiltration, and 5 to 15 min after peripheral nerve blockade (Weinberg et al. 2015).

Thin and slow-conducting nerve fibres (pain and temperature, vessel regulation) are blocked first, followed by fibres for other senses and thick, fast-conducting motor neurons. Anaesthesia lasts longer at thin compared to thick neurons (Sweetman et al. 2009, Karzel 1981).

### IV.3.2 Lubricating effect

The proposed medicinal product is intended for surface anaesthesia and lubrication for:

- The male and female urethra during cystoscopy, catheterisation, exploration by sound and other endourethral operations;
- Proctoscopy and rectoscopy;

Symptomatic treatment of pain in connection with cystitis and urethritis.

In female patients, the effect of 2% lidocaine gel was found to be lesser pronounced than in male patients with a numerical but not significant advantage compared to plain lubricant. Thus, it seems that women do not necessarily take advantage from lidocaine treatment compared to men, which could be related to their anatomical differences. In contrast to men, the female urethra is very short and therefore, transurethral interventions can be considered more or less painless in most cases. It is therefore quite conceivable that the lack of significance in clinical trials with female patients is due to the fact that a lubricant sufficiently reduces pain in the majority of women undergoing cystoscopy. This is confirmed by the study

published by Goldfischer and co-workers in 1997 (Goldfischer et al. 1997). Whereas a significant reduction in pain could be found in men (P = 0.002), no significant effect could be observed in female patients (P = 0.823), even in rigid cystoscopy (Goldfischer et al. 1997).

Furthermore, lack of pronounced significance might be related to the type of cystoscope used in clinical trials investigating the pain reduction by lidocaine gels during cystoscopy. In published clinical trials, both types of cystoscopes have been used. Actually, flexible cystoscopes are quite comparable with catheters with regard to the possible complaints, whereas rigid cystoscopes are known from clinical practice to cause significantly more pain, at least in male patients. Therefore, lidocaine treatment might be more of relevance in patients undergoing rigid cystoscopy compared to those where a flexible cystoscope has been used, albeit there are too few clinical trials using rigid cystoscopes to draw a clear conclusion.

A further parameter influencing the lidocaine effect in patients undergoing transurethral interventions is the dose. Actually, the doses used differed substantially between the published clinical trials. Mainly, doses between 10 mL and 30 mL gel have been applied intraurethrally. In the study published by Holmes and co-workers in 2001, patient have either been treated with 10 mL or 20 mL 2% lidocaine gel prior to flexible cystoscopy (Holmes et al. 2001).

Besides the local anaesthetic effect related to the active substance lidocaine hydrochloride monohydrate, the proposed medicinal product exerts a supportive lubricant effect as well. As gelling agent for the proposed medicinal product, hydroxypropyl methylcellulose was selected considering technical aspects such as processability, viscosity, subjective slip as well as adhesion. Hydroxypropyl methylcellulose (hypromellose; CAS Registry Number 9004-65-3) is widely used in oral, ophthalmic, nasal, and topical formulations as an emulsifier, suspending agent, and stabilizer in topical gels and ointments. As a protective colloid, it can minimize or prevent coalescence or agglomeration of droplets or particles. Hypromellose is used as film-forming agent in the manufacture of hard-shell capsules, as an adhesive in plastic bandages, as a wetting agent for hard contact lenses and as a suspending and/or thickening agent in topical formulations. It is also commonly used in cosmetics and food products. Hypromellose is generally recognised as safe listed; accepted for use as a food additive in Europe; included in the FDA Inactive Ingredients Database (ophthalmic and nasal preparations; oral capsules, suspensions, syrups, and tablets; topical and vaginal preparations); included in non-parenteral medicines licensed in the UK; included in the Canadian Natural Health Products ingredients Database.

Hypromellose is considered to be the main ingredient of the proposed medicinal product. Lubrication is known to reduce the vulnerability of sensitive tissues during catheterisation or introduction of instruments prior to procedures and is therefore considered to further support the local anaesthetic effect of the proposed medicinal product.

### IV.3.3 Anti-inflammatory effect

Various anti-inflammatory actions of lidocaine have been demonstrated in vitro. For instance, pre-incubation of human polymorphonuclear granulocytes or monocytes with varying

concentrations of lignocaine have been reported to inhibit leukotriene B4 release. Both leukotriene B4 and prostaglandin E2 can induce oedema and therefore, the blockade of these cells may explain the beneficial effects of lidocaine on tissue inflammation and oedema prevention (Weinberg et al. 2015).

Furthermore, lidocaine has been shown to block interleukin-1 (IL-1) release, which in turn activates phagocytosis, respiratory burst, degranulation and chemotaxis of polymorphonuclear granulocytes. This reduction in the release of interleukins may also contribute to the anti-inflammatory effects of lidocaine. Moreover, early studies demonstrate that lidocaine at low concentrations can inhibit histamine release from activated mast cells. In in vitro studies, lidocaine has also been shown to inhibit spontaneous prostaglandin synthesis. Administration of lidocaine significantly inhibits prostanoid release and synthesis from human gastric mucosa after experimental damage. In an animal model, the inhibitory effect of lidocaine on prostaglandin release has also been shown to be beneficious in the treatment of burns. In addition, lidocaine also shows important effects on oxygen free radical production (such as superoxide anions). The inhibition of free oxygen radical formation by lidocaine has been demonstrated in clinical trials. The underlying mechanism of action can be explained by interaction of lidocaine with protein and phospholipid membranes, interference with mitochondrial radical formation and prevention of free radical production (Weinberg et al. 2015).

### IV.3.4 Antibacterial effect

Lidocaine has been shown to have significant inhibitory actions on various bacterial strains, including important Gram-positive cocci such as Staphylococcus aureus and Streptococcus pneumonia as well as Gram-negative bacteria such as Haemophilus influenzae and Pseudomonas aeruginosa. The anti-bactericidal effects are poorly understood, however complex interactions between the local anaesthetic solutions and the bacterial wall or with macromolecules at the surface of the bacterium have been implicated. Lidocaine may lead to alterations in the membrane proteins and to the reduction of membrane fluidity induced by electrostatic interactions between anionic membrane components and the cationic local anaesthetic. Consequently, various cell and membrane functions such as the DNA binding properties of the cell and membrane-bound adenosine tri-phosphate (ATP)ase activity may be inhibited (Weinberg et al. 2015).

### IV.3.5 Pharmacodynamic interactions with other medicinal products

<u>Local anaesthetics and agents structurally related to amide-type local anaesthetics</u>
Lidocaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, since the toxic effects are additive.

<u>Antiarrhythmic drugs</u>
*Class I Antiarrhythmic drugs:* Class I antiarrhythmic drugs (such as mexiletine) should be used with caution since toxic effects are additive and potentially synergistic.
*Class III Antiarrhythmic drugs:* Caution is advised when using Class III antiarrhythmic drugs (e.g. amiodarone) concomitantly with lidocaine due to potential pharmacodynamic or

pharmacokinetic interactions with lidocaine, or both. A drug interaction study has shown that the plasma concentration of lidocaine may be increased following administration of a therapeutic dose of intravenous lidocaine to patients treated with amiodarone (n=6). Case reports have described toxicity in patients treated concomitantly with lidocaine and amiodarone. Patients treated with Class III antiarrhythmic drugs (e.g., amiodarone) should be kept under close surveillance and electrocardiographic (ECG) monitoring should be considered, since cardiac effects of these drugs and lidocaine may be additive (Pendopharm, 2017).

Beta-blockers and cimetidine

Following a single intravenous dose of lidocaine administered to healthy volunteers, the clearance of lidocaine has been reported to be reduced up to 47% when co-administered with propranolol and up to 30% when co-administered with cimetidine. Reduced clearance of lidocaine, when co-administered with these drugs, is probably due to reduced liver blood flow and/or inhibition of microsomal liver enzymes. The potential for clinically significant interactions with these drugs should be considered during long-term treatment with high doses of lidocaine (Pendopharm, 2017).

Antiepileptics

Studies in healthy subjects and patients with epilepsy suggest that long-term use of drugs such as phenytoin or barbiturates may increase dosage requirements for lidocaine due to induction of drug-metabolising microsomal enzymes. Phenytoin can also increase plasma concentrations of α1-acid glycoprotein and thereby reduce the free fraction of lidocaine in plasma. The cardiac depressant effects of lidocaine may be dangerously enhanced by intravenous phenytoin (Sweetman et al. 2009).

Calcium channel antagonists

Additive cardiac effects may occur when lidocaine is used in patients receiving calcium channel antagonists such as diltiazem or verapamil. Lidocaine should therefore be used with caution in those patients.

Fluvoxamine

Strong inhibitors of CYP1A2, such as fluvoxamine, given during prolonged administration of lidocaine to areas with a high extent of systemic absorption (e.g., mucous membranes) may cause a metabolic interaction leading to an increased lidocaine plasma concentration. The plasma clearance of a single intravenous dose of lidocaine was reduced by 41 to 60% during co-administration of fluvoxamine, a selective and potent CYP1A2 inhibitor, to healthy volunteers. Therefore, prolonged administration of lidocaine should be avoided in patients treated with strong inhibitors of CYP1A2, such as fluvoxamine (Pendopharm, 2017).

Erythromycin and itraconazole

Erythromycin and itraconazole, which are strong inhibitors of CYP3A4, have been shown to reduce clearance of lidocaine by 9 to 18%, following a single intravenous dose of lidocaine to healthy volunteers. During combined co-administration with fluvoxamine and erythromycin, the plasma clearance of lidocaine was reduced by 53% (Pendopharm, 2017).

Protease-inhibitors
Ritonavir and cobicistat inhibit CYP3A4, resulting in an increased exposure (increased AUC), increased Cmax and increased t1/2 of antiretroviral drugs that are substrates of CYP3A4. Drug-drug interactions between ritonavir or cobicistat and lidocaine have been suggested to increase lidocaine exposure by more than three-fold (Dekkers et al. 2019).

Drugs for treatment of methaemoglobinaemia
Glucose-6-phosphate dehydrogenase is a major co-factor in the nicotinamide-adenine-dinucleotide (NADH)-methaemoglobin reductase system and therefore, patients with glucose-6-phosphate dehydrogenase deficiency are unable to respond to methylene blue, the current drug of choice for the management of methaemoglobinaemia (Barash et al. 2015).

## IV.4 Clinical efficacy

### IV.4.1 Efficacy of 20 mg/mL lidocaine hydrochloride monohydrate in intraurethral procedures

Numerous studies on the efficacy of lubricant gels containing lidocaine hydrochloride monohydrate at a concentration of 2% used in urethral catheterisation or cystoscopy in men, women and children have been published during the past decades.

In a randomised, prospective double-blind study published in 1997, Goldfischer et al. studied the effect of instillation of 30 ml 2% lidocaine gel compared to the same amount of plain lubricant in 189 male and female patients undergoing rigid cystoscopy. Pain during cystoscopy was assessed using a 10-point scale (1: least, 10: most painful). Mean pain levels were not significantly different between the 2% lidocaine gel group versus plain lubricant (mean 3.1 versus 3.9 points respectively, p=0.014). However, in the male sub-population (n=126) pain perception was significantly decreased when lidocaine gel was used (mean 3.00±0.21 versus 4.36±0.37 points, p=0.002). None of the male patients on lidocaine had extreme pain scores of 9 or 10 compared with eight men (15%) who had received plain lubricant. The overall incidence of severe pain scores of six or greater was also significantly lower in the lidocaine group. Analysis of the female subpopulation (n=63) could not find any advantage of intraurethral lidocaine 2% gel over plain lubricant with regard to pain control (mean 3.21±0.38 versus 3.11±0.30 points, p=0.823). Patient race, a history of cystoscopy, performance of an additional procedure during cystoscopy and/or cystoscope size did not affect patient pain perception. In summary, the authors concluded that the decreased mean pain scores in men as well as the strikingly low incidence of severe pain justifies the routine use of lidocaine gel in men undergoing rigid cystoscopy (Goldfischer et al. 1997).

The results reported by Goldfischer et al. are in contrast to Stein et al. who were unable to detect any advantage of lidocaine 2% gel (the quantity of lidocaine was not stated in the publication) over plain lubricant in routine rigid cystoscopy. In this study involving 236 patients, neither stratification for gender nor for lengths of indwelling time (5 vs. 10 minutes) resulted in any differences between the treatments. The disparity between these study results may be related to the volume of lubricant and/or the time that lidocaine was allowed to dwell

in the urethra before cystoscopy (Stein et al. 1994).

Lidocaine gel is frequently used during flexible and rigid cystoscopy. In a randomised trial, Borch et al. compared the use of urethral lidocaine versus a plain lubricating gel for pain reduction in men undergoing flexible cystoscopy. Overall, 50 male patients were recruited to receive either a 2% lidocaine gel or a plain gel before cystoscopy. The mean pain scores were 3.38 in the plain gel group and 2.04 in the lidocaine group, equalling a difference of 1.34 points (95% CI: 0.63 to 2.04; p <0.001). Median pain scores were 4.0 in the plain gel group and 2.0 in the lidocaine group, a difference of 2.0 points (95% CI: 0.94 to 3.06; p <0.001). Therefore, the use of 2% lidocaine gel resulted in significantly less pain compared with plain lubricating gel in men undergoing flexible cystoscopy (Borch et al. 2013).

In 2009, Tzortzis et al. conducted a formal literature search of the major citation databases including all related articles between 1949 and September 2008 to review critically the body of evidence on the effectiveness of intraurethral lidocaine gel and to define evidence based indications for its use (Tzortzis at al. 2009). The authors summarised that the evaluated data suggested that anaesthetic lubricants are needed during catheterisation in men and children older than four years. In women, plain lubricants were sufficient during catheterisation. In this context, Tanabe et al. reported no significant difference in the severity of pain when comparing instillation of lidocaine gel with plain lubricant for urethral catheterisation in women (Tanabe et al. 2004). Similarly, plain lubricants were sufficient in flexible cystoscopy in men based on the results by Patel et al. and Chitale et al. in 2008 (Chitale et al. 2008, Patel et al. 2008). In contrast to the results for flexible cystoscopy, Tzortzis et al. summarised that a slow instillation rate of more than 20 mL of cooled anaesthetic gel, with an exposure time of 10 to 20 minutes decreased initial pain perception and increased patient tolerance during rigid cystoscopy. In addition, Choe et al. found a statistically significant reduction in pain score after application of anaesthetic gel in women during rigid cystoscopy (visual analogue scale (VAS) score: 1.6 ± 1.3 lidocaine gel group, n = 48 vs. 3.9 ± 2.2 plain gel control group n = 48; p <0.001). As an overall conclusion, Tzortzis et al. state that - while the available evidence for best practice in terms of treatment is continuously evolving - the important issues regarding the correct use of intraurethral gels are mostly left to individual preference (Tzortzis at al. 2009).

Similar results were reported by the authors Schede and Thüroff in their literature overview in 2006. The authors concluded that the need to add an anaesthetic to a lubricant can be questioned for cystoscopy in women and if flexible cystoscopy is done by an experienced urologist. They added that in men, a pain-relieving effect of lidocaine gel was reported for 21 Fr (size of cystoscope using the French scale; refers to the outside diameter of the instrument
in millimetres; 1 Fr = 0.3 mm) rigid cystoscopy. In addition, they emphasised that for reliable anaesthetic efficacy, larger volumes (20-30 mL) and longer urethral exposure times (≥10 min) must be used (Schede et al. 2006).

In 2009, a meta-analysis by Aaronson et al. (Aaronson et al. 2009) on the efficacy of the instillation of lidocaine gel before flexible cystoscopy yielded 14 studies, but only four met the inclusion criteria, two double-blind and two single-blind trials, including a total of 414 male

patients (McFarlane et al. 2001, Rodriguez-Rubio et al. 2004, Chen et al. 2005, Choong et al. 1997). The analysed studies varied in the quantity of gel instilled and in the dwell time of gel before cystoscopy. Three of them found no statistical improvement and one study found a statistically significant improvement in pain relief using lidocaine gel. However, the meta-analysis over all available data found that subjects who received plain lubricant were 1.7 times more likely to experience moderate to severe pain (odds ratio 1.7, 95% confidence interval 1.1 to 2.8) than subjects who received intraurethral instillation of lidocaine gel. The authors therefore concluded that instillation of lidocaine gel provides control of moderate to severe pain and benefit to male patients undergoing flexible cystoscopy (Aaronson et al. 2009).

### IV.4.2 Efficacy of lidocaine hydrochloride monohydrate 20 mg/mL in cystitis

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a chronic condition characterised by pelvic pain and urinary storage symptoms such as persistent urge to void, nocturia and urinary frequency. Its aetiology is unknown and a multitude of therapies are currently available for its treatment. Estimates of the prevalence of the disease vary widely based on the methods used to define the condition. Estimates from patient self-reports are 500-865 per 100000, from physician diagnosis, which probably underestimates the true prevalence rate, 52-197 per 100000 women, while the prevalence of patients with symptoms of IC is 450-11 200 per 100000, depending on the definition and geographical location (Nickel et al. 2009). The underlying pathophysiology of PBS/IC is poorly understood because there is no general consensus on defining and classifying the condition (Davis et al. 2014). The European Society for the Study of IC/PBS proposes that the diagnosis of IC/PBS is based on the following symptoms and signs:

- Pelvic pain > six months duration
- pressure/discomfort accompanied by at least one other urinary symptom such as urgency or frequency
- conditions with similar presenting symptoms should be excluded with appropriate investigations before a diagnosis is made.

A thorough history is important for patients presenting with pelvic discomfort, urinary frequency and urgency. Typically, patients with IC/PBS present with pain on bladder filling that is relieved upon voiding (Davis et al. 2014). Because the term ‘‘interstitial cystitis’’ (IC) has different meanings in different centres and different parts of the world, the European Society for the Study of Interstitial Cystitis (ESSIC) has worked to create a consensus on definitions, diagnosis, and classification in an attempt to overcome the lack of international agreement on various aspects of IC. The International Continence Society (ICS) defined the term ‘‘painful bladder syndrome’’ (PBS) as ‘‘the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology’’. The name IC is reserved for PBS with typical cystoscopic and histologic features. Logically IC should include some form of inflammation in the deeper layers of the bladder wall, whereas PBS should include pain in the region of the bladder. Although BPS is the name of choice, ESSIC agrees that including IC in the overall term (BPS/IC) could be used in parallel to BPS during a transition period (van der Merwe et al. 2008). Lidocaine is known to reduce pain by briefly blocking sensory nerve fibres.

Besides its analgesic properties, lidocaine has been discussed as suitable option for symptomatic treatment in BPS/IC due to its local analgesic as well as potential anti-inflammatory action (Henry et al. 2001). According to the pertinent literature, lidocaine has a potential as an anti-inflammatory agent (Caracas et al. 2009). However, well-designed studies to support its clinical use as anti-inflammatory drug are still lacking and corresponding effects on a mucous epithelium have not been studied at all. According to the guidelines on chronic pelvic pain, lidocaine may be applied intravesically to improve bladder symptoms (European Association of Urology, 2016). Furthermore, according to the Canadian Urological Association guideline on diagnosis and treatment of interstitial cystitis/bladder pain syndrome, anaesthetic bladder challenge with lidocaine may be considered when there is uncertainty as to whether the pain is originating from the bladder (OPTIONAL, select patients, Grade C, Level 3 evidence) (Cox et al. 2016).

### IV.4.3 Efficacy of lidocaine hydrochloride monohydrate 20 mg/mL in intrarectal procedures

According to the published data, anaesthetic lubricants are frequently used for rectal procedures such as endoscopy and biopsy. The efficient reduction of pain experienced upon probe insertion and anaesthesia infiltration by intrarectal application of 2% lidocaine gel has been demonstrated in several studies. These studies demonstrated that 2% lidocaine gel is effective in pain reduction in the rectum. Interestingly, although lidocaine-containing gels such as Xylocaine and Instillagel are authorised in these particular indications (Aspen, 2017; Farco, UK), well-controlled clinical trials investigating the efficacy of 2% lidocaine gels in pain reduction during rectoscopy and proctoscopy could not been identified in current published literature. Actually, several underlying reasons, why there is no clinical data available, are conceivable. First of all, procedures such as proctoscopy and rectoscopy are highly established in daily clinical practice for decades and therefore, there might be no need considered by potential investigators for clinical trials on the efficacy and safety of already well-established medicinal products. Furthermore, patients might not be willing to participate in randomised controlled clinical trials, in which placebo treatment must be considered due to the expectable discomfort during the procedure. According to London et al., 2% lidocaine gel is used routinely in anoscopy as well (London et al. 2020), while well-controlled clinical trials are lacking here either.

### IV.4.4 Intrarectal lidocaine use for pain prevention

Although the use of intrarectal anaesthetic lubricants has not been universally confirmed, many authors recommend it for prostate biopsy and it is regularly used by urologists. Especially the efficacy of intrarectal lidocaine gel in reducing pain experienced upon probe insertion has been shown in several studies. Compared to other analgesic methods, it is considered safe, cost-effective and easy to handle so that it can be used in an office setting without the need for further monitoring.

Efficacy of intrarectal lidocaine gel on overall biopsy related pain was also reported in a prospective randomised study by Issa et al in 2000. Fifty men undergoing transrectal prostate biopsy qualified for this study. Group one received 10 ml of 2% intrarectal lidocaine gel ten minutes before the procedure, while group two underwent biopsy without anaesthesia and served as controls. The pain score was assessed using a ten-point linear VAS. During

transrectal prostate biopsy, a significant difference in median pain score was reported: a median score of two in group one (range one to five) and of five in group two (range one to seven) (p=0.00001). No adverse events were noted. The authors concluded that intrarectal lidocaine gel is a simple, safe and efficacious method and recommend its routine administration during transrectal prostate biopsy (Issa et al. 2000).
The efficacy of lidocaine 2% gel in transrectal prostate biopsy was shown by Saad et al. in 2002 in a large prospective randomised study. Three hundred and sixty men were randomised into two groups, receiving either 10 mL of 2% intrarectal lidocaine gel five to ten minutes before the procedure or 10 mL of plain lubricating gel. The experienced pain level was assessed by the patients on a ten-point linear VAS. An average of eight (six-11) biopsy scores were obtained. The mean pain score during transrectal prostate biopsy was significantly different between the two groups: 2.62 (2% lidocaine gel group) and 3.32 (lubricating gel group), p=0.0001. Only minor complications occurred and complication rates were not significantly different between the groups. The authors concluded that rectal administration of lidocaine gel is safe, simple and effective for reducing the pain level associated with transrectal prostate biopsy (Saad et al. 2002).
Minimal effects on patients' tolerance to pain on transrectal prostate biopsy were reported by Antunes et al. in 2004. In a prospective randomised study, 72 patients underwent six-core transrectal prostate biopsy at an outpatient service. 20 mL of 2% lidocaine gel intrarectally 15 minutes before biopsy (group one) were compared to 20 ml of ultrasound gel under the same conditions (group two). Pain was rated on a three-point VAS. Although no significant difference was reported, a trend towards reduced pain after administration of lidocaine gel was seen. More patients reported no or slight pain (76.4% in the lidocaine group versus 68.3% in the placebo group). In addition, fewer patients experienced moderate or intense pain (23.4% in the lidocaine group versus 31.5% in the placebo group). Here, the low numbers of patients and biopsies as well as the limited resolution of an only three-point VAS are possible reasons for not obtaining significant results (Antunes et al. 2004).

### IV.4.5 Efficacy of intrarectal lidocaine gel on reducing probe related pain during TRUS-guided biopsy

The efficacy of intrarectal lidocaine gel on reducing probe related pain during TRUS-guided biopsy has been assessed by several investigators. The discomfort of probe insertion results from the somatic sensation caused by stretching the anal canal distal to the dentate line, which is full of sensory fibres (Maccagnano et al. 2011, Nazir. 2014). This has been shown to be the most uncomfortable act of the prostate biopsy. In addition, an influence of the patient's age has been reported where younger men experience higher levels of pain (Philip et al. 2006). In a larger prospective randomised study, Stirling et al. showed a significant reduction of pain experienced during probe insertion using intrarectal lidocaine gel. Hundred and fifty patients were assigned to three groups: no anaesthetic (group one), 10 mL of 2% lidocaine gel intrarectally (group two), and periprostatic injection of 5 mL of 1% lidocaine solution (group three) before undergoing prostate biopsy. Pain was assessed for different time points using a 10- point visual analogue scale. The authors showed a significant reduction of the pain levels associated with probe insertion for the topical lidocaine group. While periprostatic nerve blockade appears to be more specific in reducing pain during the biopsy portion of the

procedure, both techniques of local anaesthesia are effective in reducing patient discomfort (Stirling et al. 2002).
In 2004, Mallick et al. compared the analgesic efficacy of the rectal administration of lidocaine gel and lidocaine periprostatic infiltration with regard to different time points during the biopsy procedure. Three hundred and twenty-eight men were enrolled in this prospective, randomised study. Group one received 15 mL 2% lidocaine gel intrarectally ten minutes before prostate biopsy. Results were compared to group two, which received two periprostatic injections of 5 mL 1% lidocaine each five minutes prior to biopsy. Pain was assessed using a ten-point VAS for three different time points: during anaesthesia, during biopsy and 30 minutes later. Intrarectal application of lidocaine significantly reduced the pain experienced during anaesthesia. No difference was seen during biopsy, while 30 minutes after biopsy patients assessed their pain level significantly lower in the lidocaine gel group. No major morbidity was reported with either anaesthesia. The authors concluded that rectal administration of lidocaine gel is safe, simple and effective. They provide evidence that this method is especially useful in reducing probe-related pain. Furthermore, the study shows that a periprostatic block is accompanied by higher levels of pain 30 minutes after the procedure (Mallick et al. 2004).
In 2009, Skriapas et al. evaluated anaesthesia for prostate biopsy especially in younger patients (<65 years of age) (Skriapas et al. 2009). The study enrolled 147 patients. Group one received perianal local anaesthesia with lidocaine cream 2%, while group two received only lubricant gel prior to the insertion of ultrasound probe. Patients in both groups received additional periprostatic anaesthesia before the 12-core biopsy portion of the procedure. A significant difference in the mean pain score for pain and anal discomfort during probe insertion was reported on a ten-point VAS (1.7 versus 5.7 for group one and two, respectively; p <0.001). During biopsy, patients in the first group reported also less pain, but there was no significant difference. These results are especially important, as the patient's age has been reported to influence the experienced pain level. In addition, it has to be considered that young patients could undergo repeated biopsies and thus discomfort during the initial biopsy has to be kept to a minimum.

### IV.4.6 Combined use of intrarectal lidocaine gel and periprostatic nerve block

Several studies have shown that periprostatic nerve block (PPNB) is effective and safe in alleviating pain from prostate biopsy. Due to the time schedule for the biopsy procedure, however, PPNB can have little effect on probe-related pain. In a large prospective randomised study, Otunctemur et al. compared pain upon probe insertion and biopsy pain after administration of perianal-intrarectal lidocaine gel (n=159) and after combined treatment with intrarectal lidocaine gel and periprostatic nerve blockade (two injections of 5 mL 2% lidocaine each) (n=314). Pain upon probe insertion was not significantly different (2.19±0.9 intrarectal lidocaine gel vs. 2.18±0.9 combined treatment, p=0.904). The combined treatment, however, significantly reduced pain caused by the biopsy needle (4.54±1.02 intrarectal lidocaine vs. 2.06±0.79 combined treatment, p=0.001). However, this study does not include a group with periprostatic nerve block alone. Thus, whether infiltration pain is reduced by intrarectal lidocaine gel is not assessable in this study (Otunctemur et al. 2013).
Similarly, Siddiqui et al. compared probe- and biopsy-related pain in a control group with only aqueous gel (n=60) with pain in another group after administration of 11 mL 2% lidocaine and

periprostatic infiltration of 5 ml 1% lidocaine (n=60). This study was a non- randomised study, consisting of a retrospective element (group one) and a prospective element (group two). Patients assessed their discomfort on a four-point scale from no, mild, moderate to severe pain. The Chi-squared test for trend showed a highly significant association between the use of local anaesthetic gel and a reduction in pain on probe insertion (p=0.0001) and on biopsy procedure (p<0.0001). Reduction of infiltration pain is again not assessable (Siddiqui et al. 2006).

### IV.4.7 Lidocaine use for other rectal procedures

Another example for rectal application is its use during anal dilatation using a rectal balloon catheter for treatment of anal fissures and rectal strictures.

The efficacy of 2% lidocaine gel as an adjunct to general anaesthesia for anal stretch was assessed by Kumar in a prospective randomised double-blind study. All patients (n=20) received 2 mg lorazepam two hours before the operation. The control group received 20 mL lubricant, the other group received 20 mL 2% lidocaine gel intrarectally 15 minutes before anaesthesia. Anaesthesia was induced with propofol, alfentanil and metoclopramide. In the control group, all patients had features of inadequate anaesthesia and surgery was interrupted. Heart rate, respiratory rate and blood pressure were significantly increased. All patients moved and there was a high incidence of inspiratory stridor. Laryngospasm occurred in one case. Patients of the lidocaine group showed an increase in heart rate, respiratory rate and blood pressure but this was not significant. Minor movements were recorded but surgery was not interrupted. One case of inspiratory stridor occurred and no case of laryngospasm. The authors concluded that additional administration of intrarectal lidocaine reduced the need for deep general anaesthesia and decreased the severe reflex responses seen during anal stretch procedures. However, it is to be noted that this study comprises only a small sample size and statistical data is lacking (Kumar, 1988).

In 2017, Nam et al. published the results of a randomised controlled trial comparing the efficacy and safety of lidocaine gel and plain lubricating gel in relieving pain during transrectal sonography (TRS) in patients with gynaecologic problems. Eighty participants were allocated into the lidocaine gel group and the aqueous gel group at a 1:1 ratio. The intensity of pain during TRS based on the VAS (zero-ten points). The two groups had similar demographic characteristics. Between the lidocaine and aqueous gel groups, there was no significant difference in the pain score at probe manipulation (4.04±2.14 vs. 4.21±2.79; P=0.868), as well as at baseline, probe insertion, and five minutes after probe removal. The degree of acceptability of the sonographer also did not differ between the two groups. No acute and delayed adverse events were occurred. The authors concluded that intrarectal lidocaine gel for TRS provides no analgesic benefit compared with aqueous gel in female patients undergoing TRS (Nam et al. 2017).

No additional efficacy studies for these specific applications have been identified in the literature search. However, it has been reported that 4.3% of patients undergoing intensity-modulated radiation therapy for prostate cancer needed the application of lidocaine gel for the insertion of a rectal balloon that is used to immobilise the prostate before treatment (Bastasch et al. 2006). Based on the study published by Kumar (Kumar, 1988) and the discussed efficient reduction of pain experienced upon probe insertion and anaesthesia infiltration during prostate biopsy, topical application of lidocaine gel can thus be

recommended for insertion of instruments and catheters such as rectal balloon catheters used for example in the treatment of anal fissures and rectal strictures.

### IV.4.8 Dose-response studies

Lidocaine has a fast onset of action with one to five min after local infiltration, and five to 15 min after peripheral nerve blockade (Weinberg et al. 2015). Therefore, to ensure a sufficient grade of local anaesthesia, the gel should be allowed to act on the mucous membrane for at least five min after administration.

Single doses of up to 40 mL (800 mg) 2% lidocaine gel have been administered intraurethrally without toxic reactions. In a study published by Riedl and co-workers, 100-150 mL of a 2% lidocaine solution (corresponding to 2000-3000 mg lidocaine) have been applied to patients with IC/BPS via intravesical electromotive drug administration (EMDA). These doses seem to be quite high as in other studies, 8 to 20 mL of 2% lidocaine hydrochloride monohydrate have been used for pain control in IC/BPS (Riedl et al. 1998). In a clinical study investigating the safety of lidocaine infusions at different sites of administration, doses ranging from 300-3200 mg could be safely applied without exceeding the toxic plasma level of 5 µg/mL (Glowacka et al. 2009). Intraurethrally, a maximum single dose of 800 mg lidocaine hydrochloride monohydrate in adults apply. This amount should also not be exceeded within 24 hours. To allow adequate anaesthesia, lidocaine hydrochloride monohydrate 2% gel has been applied five to 15 min before start of the procedure. Doses applied in the course of published clinical studies are summarised in the table below.

*Table 3: Doses applied in the course of published clinical studies investing the efficacy of 2% lidocaine hydrochloride monohydrate*

| Indication | Range of doses applied |
|---|---|
| Intraurethral anaesthesia | 5 – 40 mL |
| Intravesical use (Pain control in cystitis) | 8 – 150 mL (most studies 8 – 20 mL) |
| Intrarectal anaesthesia | 10 – 20 mL |

Due to differences in the absorption of lidocaine between the different application areas, lidocaine doses vary and depend on the site of administration. Taken this into account, the following dose recommendations apply for adults and adolescents from 12 years of age:

*Table 4: Dose recommendations for Lidocaine hydrochloride monohydrate 20 mg/mL gel in adults and adolescents*

| Clinical use | Recommended dose range |
|---|---|
| Intraurethral anaesthesia | |
| – Endoscopy | 10 – 40 mL |
| – Catheterisation | 5 – 10 mL |
| – Female adults | 5 – 10 mL |
| Intravesical use | 10 – 20 mL |
| Intrarectal anaesthesia | 10 – 20 mL |

Generally, the lowest concentration and smallest dose producing the required effect should be administered.

## IV.5 Clinical safety

### IV.5.1 Safety of lidocaine hydrochloride monohydrate after intraurethral/intravesical administration

For some studies, adverse events have been reported, albeit not necessarily related to the active substance lidocaine hydrochloride monohydrate, but rather to the intervention itself (e.g. bleeding or haematuria) or to other ingredients of the gels such as chlorhexidine or parabens (anaphylaxis). Furthermore, more detailed information regarding the adverse events, e.g. severity, is frequently lacking. Moreover, many studies did not include any control group. Thus, a safe determination of severity and frequency of expected adverse reactions upon intraurethral and intravesical treatment with 2% lidocaine gel can be considered difficult. Some authors stated that adverse events were only mild in nature and resolved without treatment. Urinary tract infections and bacteriuria were treated with antibiotics accordingly. In some cases, serious adverse reactions such as confusion and anaphylaxis have been reported. One patient was found unresponsive and showed persistent disorientation and confusion (Panacek et al. 1984). This adverse event has been related to lidocaine administration. This elderly patient received a total dose of 1200 mg lidocaine intraurethrally, which can be considered a high dose (Panacek et al. 1984). Confusional state and disorientation are known signs of lidocaine neurotoxicity, which may occur at least at high doses and especially in vulnerable patient populations.

One case of seizure occurred in one elderly patient after intraurethral administration of 20 mL 2% lidocaine gel corresponding to approx. 400 mg lidocaine hydrochloride monohydrate (Sundaram, 1987). Several minutes after the lidocaine instillation the patient had a generalized tonic-clonic seizure and injured his tongue. One week later cystoscopy was attempted again to rule out any other cause of the haematuria. A few minutes after the administration of 10 mL of 2% lidocaine gel intraurethrally the patient had another convulsion. There were no abnormalities diagnosed. The patient has remained free of seizures without anticonvulsant therapy (Sundaram. 1987). Hypersensitivity reactions, including anaphylaxis, have been reported for several cases upon administration of lidocaine gels (Dyer et al. 2013, Parkes et al. 2009, Carr. 1990). However, these reactions were related to chlorhexidine and/or parabens which are included in the preparations used (mainly Instillagel). Although these particular cases were not related to lidocaine itself, hypersensitivity reactions (incl. anaphylaxis) in relation to the local administration of the proposed medicinal product cannot be excluded as hypersensitivity to lidocaine has been described (Duque et al. 2004), albeit for another route of administration. Lidocaine belongs to the amide-type local anaesthetics, which are known to cause hypersensitivity reactions, including contact dermatitis and anaphylaxis (Duque et al. 2004, Sweetman. 2009). However, they can be considered rare and true allergic, immuno-globulin E (IgE)-mediated anaphylaxis caused by these compounds is a matter of debate (Lukawska et al. 2009).

Hypotension has been observed in the study published by Axelsson and co-workers (Axelsson et al. 1983). The blood pressure decreased by more than 30% of the initial systolic value or a short period in two out of ten patients, who received 20 mL of 2% Xylocaine gel intraurethrally additional to spinal anaesthesia using 2 mL of 5% lidocaine (Axelsson et al. 1983). These patients (group III) received a total lidocaine dose of 500 mg compared to 800 mg in group I. However, in group I, 800 mg lidocaine were given only intraurethrally (Axelsson et al. 1983). From these cases, it is not possible to clearly ascribe this side effect to a specific route of administration. However, at least an increased risk for neurotoxic adverse reactions must be considered to be associated with lidocaine spinal anaesthesia (Sweetman. 2009), albeit a possible association with the intraurethral use in the reported cases cannot completely be excluded.

Risk of cardiac and neurotoxicity upon intraurethral/intravesical administration

Upon intraurethral administration of 400 mg and 800 mg lidocaine, mean blood concentrations of 0.06 µg/mL and 0.15 µg/mL have been determined by Axelsson and co-workers (Axelsson et al. 1983). These values are significantly lower than the therapeutically relevant plasma concentrations for antiarrhythmic effects, which ranges from 1.5 to 5.5 µg/mL. Furthermore, these values are far below the toxic lidocaine plasma level of 5 µg/mL. Therefore, under normal conditions, cardiac and CNS side effects should not occur when the proposed medicinal product is administered according to the proposed dose recommendations. However, it should be noted that superficial lesions of the urethral mucosa and/or surface enlargement due to urethral dilatation may lead to increased absorption of lidocaine (Axelsson et al. 1983). Thus, the occurrence of those adverse drug reactions should be considered, particularly if high doses (e.g. 800 mg lidocaine hydrochloride monohydrate) are administered.

### IV.5.2 Safety of lidocaine hydrochloride monohydrate after intrarectal administration

In 1991, van Hoogdalem and co-workers provided a literature overview of the pharmacokinetics of rectal drug administration including a data review on the risk of rectal irritation. They reported that for some drugs long term rectal application has been described as possibly inducing rectal ulceration in humans, resulting in clinical features such as rectal bleeding and pain. However, the data indicated that rectal ulcers and stenoses may become evident only after long term daily suppository use. In most of the reports, mucosal damage was suggested to be associated with the presence of ergotamine or aspirin in the suppositories used, while a possible role of paracetamol was also considered. Rectal delivery of lidocaine was not associated with rectal ulcerations (van Hoogdalem et al. 1991).

In 2000, Issa et al. rated the use of intrarectal lidocaine gel as safe based on their prospective randomized study of a total of 50 men undergoing transrectal prostate biopsy. They compared the use of 2% intrarectal lidocaine gel with no anaesthesia as control. No lidocaine related adverse events were noted (Issa et al. 2000).

In a large prospective randomized study, Saad and co-workers compared the use of 2% lidocaine gel with another lubricating gel during prostate biopsy in 360 patients. Only minor biopsy-related complications occurred and no adverse reactions to lidocaine were

reported. The authors evaluate rectal administration of lidocaine gel therefore as safe (Saad et al. 2002). In a meta-analysis published in 2007, Tiong et al. evaluated 25 studies including 1685 patients. They compared the use of intrarectal lidocaine gel and lidocaine injection for prostate biopsy. No adverse events from local anaesthetic administration were reported in any of the included studies (Tiong et al. 2007).
In 2015, Caliskan and Mutlu published the results of a clinical study investigating the efficacy of intrarectal ice application as anaesthesia in TRUS-guided biopsy. Patients were equally randomised as group one and two with 60 patients each. Ice was applied as an anaesthetic method five min before procedure to the patients in group one. Patients in group two were applied 10 mL of 2% lidocaine gel ten min before procedure. There was also no difference in complications between two groups about presence and duration of macroscopic haematuria and rectal bleeding. Vasovagal syncope developed in one patient from lidocaine gel group. However, the relation to the study medication remains unclear (Caliskan et al. 2015).
Kucur et al. compared PPNB + intrarectal local anaesthesia (IRLA) with low-dose spinal anaesthesia. No significant difference in complications was observed. 4/7 (group one – intrarectal local anaesthesia with lidocaine + periprostatic nerve blockade / group two – selective spinal anaesthesia) patients had a change in blood pressure of 20% or more. Heart rate was changed by more than 10% in 13 patients in group one and 14 patients in group two. Acute prostatitis occurred in three patients of group one and in two patients of group two. Acute urinary retention occurred in one patient of group one. None of the patients experienced hypotension or bradycardia (Kucur et al. 2015).
Imani and co-workers compared lidocaine gel (n = 38), lidocaine gel + diltiazem (n = 36) and lidocaine + diltiazem + meperidine (n = 26) in patients undergoing transrectal ultrasound (TRUS). No adverse effects were reported (Imani et al. 2018).
In the study by Temiz and co-workers, IRLA was compared with PPNB in TRUS procedures regarding cancer detection rate. There was no significant difference in terms of adverse events between the two groups. Complications included vasovagal hypotension, mild haematuria, rectal bleeding, haematospermia, and lower urinary tract symptoms which may be attributed to biopsy. However, cancer detection rate was found to be decreased in the IRLA group (Temiz et al. 2015).

For some of the published studies on the intrarectal use of 2% lidocaine gels, adverse events have been reported, which are not necessarily related to the active substance, but rather to the intervention itself (e.g. rectal bleeding, haematuria, haematochezia or haematospermia). Furthermore, more detailed information regarding the adverse events, e.g. severity, is frequently lacking. Moreover, many studies did not include any control group. Thus, severity and frequency of expected adverse reactions upon intrarectal treatment with 2% lidocaine gel can hardly be determined.
TRUS-guided prostate biopsies are associated with finite complications including pain or discomfort, haematuria, haematospermia, rectal bleeding as well as infections (Siddiqui et al. 2006). Compared to placebo groups, patients receiving local anaesthesia with lidocaine showed no gross difference in the occurrence of adverse events. Interestingly, several cases of vasovagal syncope or vasovagal shock have been observed during prostate biopsy procedures. In six studies, this side effect has been observed in patients receiving lidocaine anaesthesia (Chang et al. 2001, Obek et al. 2004, Song et al. 2006, Saha et al. 2014, Caliskan

et al. 2015, Celebi et al. 2004). However, no placebo groups have been included in three of them (Song et al. 2006, Saha et al. 2014, Celebi et al. 2004). One can only speculate that the occurrence of those vasovagal events is associated with lidocaine administration. Unfortunately, the reported cases lack any additional information such as age or pre-existing organ failures in the affected patients. Furthermore, the underlying reason for the syncope events have not been discussed by the authors. In a retrospective evaluation on 422 patients published by Temiz and co-workers in 2015, vasovagal hypotension has been observed in eight patients receiving local anaesthesia compared to 17 patients in the placebo group (Temiz et al. 2015). Therefore, from the published clinical trials, the occurrence of vasovagal syncope or shock cannot necessarily considered to be associated with local lidocaine anaesthesia. However, syncope is stated in the product information of other comparable lidocaine medicinal products such as Cathejell and Xylocaine as potential systemic side effect. Usually, serious side effects of lidocaine are described in conjunction with overdosage, which is usually not deemed very likely upon topical administration of 2% lidocaine gel. Nevertheless, systemic side effects may occur, especially after topical administration to patients with wounds or ulcers or to vulnerable patient populations and therefore, the occurrence of such adverse reactions should be considered possible.

### IV.5.3 Microbial safety

The prevalence of allergic diseases and hypersensitive reactions is increasing dramatically in industrialized countries. The MAH is of the opinion that medicinal products – especially those used in topical application – which are stable and sterile throughout granted shelf-life without disinfectant or preservatives, have a major advantage. The proposed medicinal product has the same qualitative and quantitative composition as the medicinal products Glydo and Jelido already authorized and marketed in the US and Canada, respectively. In the post-marketing surveillance data available, infections after use of the medicinal products Glydo and Jelido have not been reported. Moreover, other comparable medicinal products such as Cathejell, which are already authorised in the EU, are free of any desinfectants and parabens as well. This is considered acceptable.

### IV.5.4 Conclusion on clinical safety

To summarize, the following adverse reactions have been reported upon intraurethral, intravesical or intrarectal administration of 2% lidocaine gel in the course of published clinical trials and case reports:

| System Organ Class | Adverse reaction |
|---|---|
| Immune system disorders | Hypersensitivity, incl. anaphylaxis* |
| Infections and infestations | UTI†, urosepsis†, bacteriuria† |
| Nervous system disorders | Seizure, vasovagal syncope, vasovagal shock |
| Psychiatric disorders | Dizziness†, confusion and disorientation |
| Cardiac disorders | Vasovagal hypotension |
| Reproductive system and breast disorders | Haematospermia†, epididymitis† |

| | |
|---|---|
| Renal and urinary disorders | Dysuria, urinary retention, haematuria†, micturition urgency, pollakiuria |
| General disorders and administration site conditions | Administration site pain, administration site irritation, administration site haemorrhage, pyrexia† |

*Table 5. Adverse reactions after lidocaine gel administration per organ class.*

** considered related to other ingredients of the preparations used (chlorhexidine, parabens)*

*† considered related to the diagnostic procedure itself (e.g. TRUS-guided prostate biopsy)*

In general, systemic adverse reactions to lidocaine are dose-related and may result from high plasma levels caused by overdosage or rapid absorption or from hypersensitivity to lidocaine. Usually, signs and symptoms of mild toxicity become apparent at plasma levels > 5 µg/mL. At plasma levels about 10 µg/mL, seizures or loss of consciousness may occur. At levels about 15 µg/mL, the myocardium and CNS are further depressed, progressing to cardiac arrhythmias, respiratory arrest and cardiac arrest at lidocaine plasma levels about 20 µg/mL. As for other local anaesthetics of the amide-type, hypersensitivity reactions to lidocaine itself are considered rare. More frequently, hypersensitivity occurs in relation to other ingredients of the lidocaine preparations used such as chlorhexidine or parabens.

A further potential risk related to the use of local amide-type analgesia is the occurrence of methaemoglobinaemia. Actually, methaemoglobinaemia secondary to lidocaine exposure is considered a rare complication (Barash et al. 2015). Certain conditions may predispose a patient to developing methaemoglobinaemia specifically caused by lidocaine, including drug displacement and impaired clearance. In a retrospective case-control study published by Chouwdhary and co-workers, the incidence and risk factors for procedure-related methaemoglobinaemia in high-risk populations have been investigated (Chowdhary et al. 2013). The following procedures have been included in the analysis: bronchoscopy, nasogastric tube placement, oesophagogastroduodenoscopy, transoesophageal echocardiography, and endoscopic retrograde cholangiopancreatography. The following topical anesthetic combinations had been used: 17 patients (55%) received benzocaine, 20%; six patients (19%) received lidocaine, 1% to 2%; five patients (16%) received a combination of benzocaine, 14%, butamben, 2%, and tetracaine hydrochloride, 2%; two patients (6%) received a combination of benzocaine, 20%, and lidocaine, 1% to 2%; and one patient (3%) received lidocaine of unspecified potency. Among 94,694 procedures, 33 cases of methaemoglobinaemia occurred. The prevalence rates were 0.160% for bronchoscopy, 0.005% for oesophagogastroduodenoscopy, 0.250% for transesophageal echocardiogram, and 0.030% for endoscopic retrograde cholangiopancreatography. Hospitalization at the time of the procedure was a major risk factor for the development of methaemoglobinaemia (0.14 cases per 10,000 outpatient procedures vs. 13.7 cases per 10 000 inpatient procedures, $P < 0.001$). Thus, the overall prevalence of methaemoglobinaemia was low at 0.0035% (Chowdhary et al. 2013). As low systemic lidocaine levels are to be expected when lidocaine is applied via the intraurethral, intravesical or intrarectal route, the risk for the occurrence of methaemoglobinaemia is considered very low. However, reliable data from those procedures does not exist and higher systemic exposure due to impaired clearance must be considered as risk factor. Thus, the occurrence of methaemoglobinaemia cannot be fully excluded in patients receiving 2% lidocaine gel intraurethrally, intravesically or intrarectally. However, the

frequency of this potential adverse reaction after intraurethral, intravesical and intrarectal administration is unknown.

Cardiovascular adverse reactions may occur after use of lidocaine, independently of the route of administration. Of cause, the risk for the occurrence of those adverse reactions is low when lidocaine is administered via the intraurethral, intravesical or intrarectal route compared to indications where lidocaine is applied parenterally, e.g. in anti-arrhythmic use, due to the low systemic exposure. However, the occurrence of cardiac adverse events upon topical use of lidocaine has been described (Lin et al. 2008) and should therefore also be taken into consideration when 2% lidocaine gel is administered topically.

Adverse reactions related to CNS toxicity have been described after topical lidocaine use such as confusional state or vasovagal syncope, even at moderate lidocaine amounts used (e.g. 10 mL 2% lidocaine gel). Therefore, those adverse events should be taken into consideration when administering the proposed medicinal product.

Serious adverse reactions to lidocaine are generally systemic in nature. Actually, systemic adverse reactions, e.g. confusion and seizure, have been observed not only upon systemic administration of lidocaine, but also after topical administration as reported by several investigators of published clinical trials. Therefore, systemic adverse reactions should generally be considered, even after intraurethral, intravesical or intrarectal administration of lidocaine.

A particular issue is the determination of the frequency of reported adverse reactions. Actually, excepting hypersensitivity reactions which are described to be rare upon use of lidocaine, the exact frequency of adverse reactions is hardly to be determined from published clinical data as most of the studies are very small compared to comprehensive phase III clinical trials. The MAH provides post-marketing data of the medicinal products Glydo and Jelido, which are identical to the proposed medicinal product and are authorized and marketed in the US and Canada, respectively. In the property management system data provided by the respective marketing authorization holders, 11 serious unexpected adverse reactions have been reported. Most (n=7) of these reactions belong to the system organ class nervous system disorders. Among them, isolated cases of condition aggravated, gait disturbance, staring, hemiparesis, balance disorder as well as neurotoxicity have been reported. New safety issues have not been identified by the marketing authorization holders and therefore, no changes to the product information have been made.

Altogether, the following adverse reactions should be taken into consideration upon application of the proposed medicinal product and are also mentioned in the product information texts of comparable topical medicinal products containing 2% lidocaine hydrochloride monohydrate:

*Table 6: Adverse reactions to be considered after use of the proposed medicinal product*

| System Organ Class | Adverse reaction | Frequency |
|---|---|---|
| Blood and lymphatic system disorders | Methaemoglobinaemia | Not known |
| Immune system disorders | Hypersensitivity, incl. anaphylactic reactions (incl. bronchospasm, acute respiratory distress syndrome, skin lesions, contact dermatitis, urticaria, oedema) | rare |
| Psychiatric disorders | Psychotic disorder, nervousness, anxiety, euphoric mood | Not known |

| System Organ Class | Adverse reaction | Frequency |
|---|---|---|
| Nervous system disorders | Dizziness, somnolence, disorientation, confusional state, tremor, agitation, paraesthesia, speech disorder, seizure, loss of consciousness, coma | Not known |
| Eye disorders | Visual impairment including vision blurred or diplopia, mydriasis | Not known |
| Ear and labyrinth disorders | Tinnitus, hyperacusis | Not known |
| Cardiac disorders | Cardiac arrest, cardiovascular collapse, bradycardia, atrioventricular block, myocardial depression, hypotension, asystolia, arrhythmia, blood pressure increased, heart rate increased | Not known |
| Respiratory, thoracic and mediastinal disorders | Dyspnoea, respiratory depression, respiratory arrest | Not known |
| Gastrointestinal disorders | Nausea, vomiting | Not known |
| Musculoskeletal and connective tissue disorders | Muscle twitching | Not known |
| General disorders and administration site conditions | administration site irritation, feeling hot, feeling cold | Not known |

Taken into consideration all safety information regarding topical gel formulations containing 2% lidocaine hydrochloride monohydrate, the proposed medicinal product can be considered safe for use in the proposed indications.

## 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 Instillido.

*Table 7. 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

This decentralised procedure concerns a well-established use application for Instillido. For this authorisation, reference is made to literature. No new clinical studies were conducted. Risk management is adequately addressed. Altogether it is considered that efficacy of Instillido in the treatment of the marketed indications has been established as the majority of studies in subjects showed statistically significant and clinically relevant results. Finally, it is considered that the safety issues that are identified are adequately addressed in the SmPC.

## 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 language used for the purpose of user testing the PL was English. The test consisted of a pilot test with three participants, followed by two rounds with ten 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

Instillido 20 mg/ml gel has a proven chemical-pharmaceutical quality. Instillido has an adequate efficacy and safety profile and is considered widely established.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A biowaiver has been granted.

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 concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Instillido with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 November 2021.

## 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 |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

# LITERATURE REFERENCES

Aaronson DS, Walsh TJ, Smith JF, Davies BJ, Hsieh MH, Konety BR. Meta-analysis: does lidocaine gel before flexible cystoscopy provide pain relief? BJU international. 2009;104(4):506-9; discussion 9-10.

Abernethy DR, Greenblatt DJ. Lidocaine disposition in obesity. The American journal of cardiology. 1984;53(8):1183-6.

Anonymous, Lidocaine Lidopen. Patient information, as published at Medscape for an intravenous lidocaine preparation. Accessed online, October 22 2019, https://reference.medscape.com/drug/lidocaine-cv-lidopen-342302#0, 2019.

Antunes AA, Calado AA, Lima MC, Falcao E. Efficacy of intrarectal lidocaine hydrochloride gel for pain control in patients undergoing transrectal prostate biopsy. International braz j urol : official journal of the Brazilian Society of Urology. 2004;30(5):380-3.

Aspen. Summary of Product Characteristics: Xylocaine 20 mg/g Gel, catheterslijm. 2017.

Avelino, A., F. Cruz, and A. Coimbra, Lidocaine prevents noxious excitation of bladder afferents induced by intravesical capsaicin without interfering with the ensuing sensory desensitization: an experimental study in the rat. The Journal of urology, 1998. **159**(2): p.567-570.

Axelsson K, Jozwiak H, Lingardh G, Schonebeck J, Widman B. Blood concentration of lignocaine after application of 2% lignocaine gel in the urethra. British journal of urology. 1983;55(1):64-8.

Bastasch MD, Teh BS, Mai WY, McGary JE, Grant WH, 3rd, Butler EB. Tolerance of endorectal balloon in 396 patients treated with intensity-modulated radiation therapy (IMRT) for prostate cancer. American journal of clinical oncology. 2006;29(1):8-11.

Barash M, Reich KA, Rademaker D. Lidocaine-induced methemoglobinemia: a clinical reminder. The Journal of the American Osteopathic Association. 2015;115(2):94-8.

Bergey, J.L., K. Nocella, and J.D. McCallum, Acute coronary artery occlusion reperfusion-induced arrhythmias in rats, dogs and pigs: antiarrhythmic evaluation of quinidine, procainamide and lidocaine. European journal of pharmacology, 1982. **81**(2): p. 205-216.

Berggren, S., et al., Characterization of jejunal absorption and apical efflux of ropivacaine, lidocaine and bupivacaine in the rat using in situ and in vitro absorption models. European journal of pharmaceutical sciences, 2004. **21**(4): p. 553-560.

Berton, P., et al., Transdermal bioavailability in rats of lidocaine in the forms of ionic liquids, salts, and deep eutectic. ACS medicinal chemistry letters, 2017. **8**(5): p. 498-503.

Bill, T.J., et al., Lidocaine metabolism pathophysiology, drug interactions, and surgical implications. Aesthetic surgery journal, 2004. **24**(4): p. 307-311.

Birch, B.R. and R.A. Miller, Absorption characteristics of lignocaine following intravesical instillation. Scandinavian journal of urology and nephrology, 1994. **28**(4): p. 359-364.

Blumer, J., J.M. Strong, and A.J. Atkinson, The convulsant potency of lidocaine and its N-dealkylated metabolites. Journal of Pharmacology and Experimental Therapeutics, 1973. **186**(1): p. 31-36.

Borch M, Scosyrev E, Baron B, Encarnacion J, Smith EM, Messing E. A randomized trial of 2% lidocaine gel versus plain lubricating gel for minimizing pain in men undergoing flexible cystoscopy. Urologic nursing. 2013;33(4):187-93.

Brown, R.S. and N.L. Rhodus, Epinephrine and local anesthesia revisited. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology, 2005. **100**(4): p. 401-408.

Byrne, K. and C. Engelbrecht, Toxicity of local anaesthetic agents. Trends in Anaesthesia and Critical Care, 2013. **3**(1): p. 25-30.

Caliskan B, Mutlu N. Intrarectal ice application prior to transrectal prostate biopsy: a prospective randomised trial accessing pain and collateral effects. International braz j urol : official journal of the Brazilian Society of Urology. 2015;41(1):101-8 discussion 9.

Caracas HC, Maciel JV, Martins PM, de Souza MM, Maia LC. The use of lidocaine as an anti-inflammatory substance: a systematic review. Journal of dentistry. 2009;37(2):93-7.

Carr TW. Severe allergic reaction to an intraurethral lignocaine preparation containing parabens preservatives. British journal of urology. 1990;66(1):98.

Carson, B., Local anesthetics that metabolize to 2, 6-xylidine or o-toluidine. Final review of toxicological literature, 2000.

Celebi I, Irer B, Kefi A, Kurtulan E, Goktay Y, Ergin T. Relationship between complications due to prostate biopsy and the scores of pain and discomfort. Urologia internationalis. 2004;72(4):303-7.

Chadwick, H., Toxicity and resuscitation in lidocaine-or bupivacaine-infused cats. Anesthesiology, 1985. **63**(4): p. 385-390.

Chang SS, Alberts G, Wells N, Smith JA, Jr., Cookson MS. Intrarectal lidocaine during transrectal prostate biopsy: results of a prospective double-blind randomized trial. The Journal of urology. 2001;166(6):2178-80.

Chen YT, Hsiao PJ, Wong WY, Wang CC, Yang SS, Hsieh CH. Randomized doubleblind comparison of lidocaine gel and plain lubricating gel in relieving pain during flexible cystoscopy. Journal of endourology. 2005;19(2):163-6.

Chen, Y.-W., et al., Dextromethorphan or dextrorphan have a local anesthetic effect on infiltrative cutaneous analgesia in rats. Anesthesia & Analgesia, 2007. **104**(5): p. 1251-1255.

Chen, Y.-W., et al., Propranolol elicits cutaneous analgesia against skin nociceptive stimuli in rats. Neuroscience letters, 2012. **524**(2): p. 129-132.1

Chen, Y.W., et al., Naloxone prolongs cutaneous nociceptive block by lidocaine in rats. Fundamental & clinical pharmacology, 2017. **31**(6): p. 636-642.4

Chitale S, Hirani M, Swift L, Ho E. Prospective randomized crossover trial of lubricant gel against an anaesthetic gel for outpatient cystoscopy. Scandinavian journal of urology and nephrology. 2008;42(2):164-7.

Choong S, Whitfield HN, Meganathan V, Nathan MS, Razack A, Gleeson M. A prospective, randomized, double-blind study comparing lignocaine gel and plain lubricating gel in relieving pain during flexible cystoscopy. British journal of urology. 1997;80(1):69-71.

Chowdhary S, Bukoye B, Bhansali AM, Carbo AR, Adra M, Barnett S, et al. Risk of topical anesthetic-induced methemoglobinemia: a 10-year retrospective case-control study. JAMA internal medicine. 2013;173(9):771-6.

Chua ME, Firaza PNB, Ming JM, Silangcruz JMA, Braga LH, Lorenzo AJ. Lidocaine Gel for Urethral Catheterization in Children: A Meta-Analysis. The Journal of pediatrics. 2017;190:207-14.e1.

Colatsky, T.J., Mechanisms of action of lidocaine and quinidine on action potential duration in rabbit cardiac Purkinje fibers. An effect on steady state sodium currents? Circulation Research, 1982. **50**(1): p. 17-27.

Collinsworth KA, Strong JM, Atkinson AJ, Jr., Winkle RA, Perlroth F, Harrison DC. Pharmacokinetics and metabolism of lidocaine in patients with renal failure. Clinical pharmacology and therapeutics. 1975;18(1):59-64.

Cox A, Golda N, Nadeau G, Curtis Nickel J, Carr L, Corcos J, et al. CUA guideline: Diagnosis and treatment of interstitial cystitis/bladder pain syndrome. Can Urol Assoc J. 2016;10(5-6):E136-E55.

Davis NF, Brady CM, Creagh T. Interstitial cystitis/painful bladder syndrome: epidemiology, pathophysiology and evidence-based treatment options. European journal of obstetrics, gynecology, and reproductive biology. 2014;175:30-7.

De Boer, A., et al., Rectal bioavailability of lidocaine in rats: Absence of significant firstpass elimination. Journal of pharmaceutical sciences, 1980. **69**(7): p. 804-807.

Dekkers BGJ, Bierman WFW, Touw DJ, Alffenaar J-WC. Relevance of the drug-drug interactions between lidocaine and the pharmacokinetic enhancers ritonavir and cobicistat. AIDS. 2019;33(6):1100-2.

Del Valle, L.J. and P.A. Orihuela, Prolonged exposure to lidocaine disturbs preimplantation mouse embryo development. Reproductive Toxicology, 1996. **10**(2): p.113-118.

De Martin S, Orlando R, Bertoli M, Pegoraro P, Palatini P. Differential effect of chronic renal failure on the pharmacokinetics of lidocaine in patients receiving and not receiving hemodialysis. Clinical pharmacology and therapeutics. 2006;80(6):597-606.

Derlet, R.W., T.E. Albertson, and R.S. Tharratt, Lidocaine potentiation of cocaine toxicity. Annals of emergency medicine, 1991. 20(2): p. 135-138.

Duque S, Fernández L. Delayed-type hypersensitivity to amide local anesthetics. Allergologia et immunopathologia. 2004;32(4):233-4.

Dyer JE, Nafie S, Mellon JK, Khan MA. Anaphylactic reaction to intraurethral chlorhexidine: sensitisation following previous repeated uneventful administration. Annals of the Royal College of Surgeons of England. 2013;95(6):e105-6.

European Association of Urology - Guidelines: EAU Guidelines on Chronic Pelvic Pain. 2016.

European Medicines Agency CVMP, CVMP assessment report regarding the request for an opinion under Article 30(3) of Regulation (EC) No 726/2004. EMA/CVMP/118717/2015 Committee for Medicinal Products for Veterinary Use (CVMP), 2015.

Farco. Summary of Product Characteristics: Instillagel (UK).

Feldman, H.S., G.R. Arthur, and B.G. Covino, Comparative systemic toxicity of convulsant and supraconvulsant doses of intravenous ropivacaine, bupivacaine, and lidocaine in the conscious dog. Anesthesia and Analgesia, 1989. **69**(6): p. 794-801.

Finholt DA, Stirt JA, DiFazio CA, Moscicki JC. Lidocaine pharmacokinetics in children during general anesthesia. Anesthesia and analgesia. 1986;65(3):279-82.

Fujinaga, M. and R.I. Mazze, Reproductive and teratogenic effects of lidocaine in Sprague-Dawley rats. Anesthesiology, 1986. **65**(6): p. 626-632.

Fujinaga, M., Assessment of teratogenic effects of lidocaine in rat embryos cultured in vitro. Anesthesiology: The Journal of the American Society of Anesthesiologists, 1998. **89**(6): p. 1553-1558.

Glowacka K, Orzechowska-Juzwenko K, Bieniek A, Wiela-Hojenska A, Hurkacz M. Optimization of lidocaine application in tumescent local anesthesia. Pharmacological reports : PR. 2009;61(4):641-53.

Goldberg MJ, Spector R, Johnson GF. Racial background and lidocaine pharmacokinetics. Journal of clinical pharmacology. 1982;22(8-9):391-4.

Goldfischer ER, Cromie WJ, Karrison TG, Naszkiewicz L, Gerber GS. Randomized, prospective, double-blind study of the effects on pain perception of lidocaine jelly versus plain lubricant during outpatient rigid cystoscopy. The Journal of urology. 1997;157(1):90-4.

Guerios, S.D., et al., Lidocaine prevents referred hyperalgesia associated with cystitis. Neurourology and Urodynamics: Official Journal of the International Continence Society, 2009. **28**(5): p. 455-460.

HENRY, R., et al., Absorption of alkalized intravesical lidocaine in normal and inflamed bladders: a simple method for improving bladder anesthesia. The Journal of urology, 2001. **165**(6): p. 1900-1903.

Heavner, J.E., Cardiac toxicity of local anesthetics in the intact isolated heart model: a review. Regional anesthesia and pain medicine, 2002. **27**(6): p. 545-555.

Hille, B., Local anesthetics: hydrophilic and hydrophobic pathways for the drug-receptor reaction. The Journal of general physiology, 1977. **69**(4): p. 497-515.

Hohenfellner R. Statement: Instillagel in der Kinderurologie. 1994.

Holmes M, Stewart J, Rice M. Flexible cystoscopy: is the volume and content of the urethral gel critical? Journal of endourology. 2001;15(8):855-8.

Holson, R.R., et al., Prenatal lidocaine (L) exposure: effect upon selected behavioral measures in rat offspring. Teratology, 1988. **37**: p. 521.1

Hoogenboom, R.L., et al., Concentrations of dimethylaniline and other metabolites in milk and tissues of dairy cows treated with lidocaine. Food Additives & Contaminants: Part A, 2015. **32**(8): p. 1256-1264.

Hung, C.-H., et al., Synergistic effects of serotonin or dopamine combined with lidocaine at producing nociceptive block in rats. Reg Anesth Pain Med, 2017. **42**(3): p. 351-356.

Hung, N.-K., et al., Effect on postoperative sore throat of spraying the endotracheal tube cuff with benzydamine hydrochloride, 10% lidocaine, and 2% lidocaine. Anesthesia & Analgesia, 2010. **111**(4): p. 882-886.

Imani F, Khajavi M, Gavili T, Pourfakhr P, Shariat Moharari R, Etezadi F, et al. Comparison of the Effect of Intra-Rectal Administration of Lidocaine Gel and Lidocaine Plus Fentanyl on Pain Reduction in Prostate Biopsy: A Randomized Clinical Trial. Anesthesiology and pain medicine. 2018;8(6):e82778.

Inomata, S., et al., Propofol inhibits lidocaine metabolism in human and rat liver microsomes. Journal of anesthesia, 2003. **17**(4): p. 246-250.

Issa MM, Bux S, Chun T, Petros JA, Labadia AJ, Anastasia K, et al. A randomized prospective trial of intrarectal lidocaine for pain control during transrectal prostate biopsy: the Emory University experience. The Journal of urology. 2000;164(2):397-9.

Johnson, S.M., B.E. Saint John, and A.P. Dine, Local anesthetics as antimicrobial agents: a review. Surgical infections, 2008. **9**(2): p. 205-213.

Joudrey, S., et al., Plasma concentrations of lidocaine in dogs following lidocaine patch application over an incision compared to intact skin. Journal of veterinary pharmacology and therapeutics, 2015. **38**(6): p. 575-580.

Juszczak, K., et al., Urodynamic effects of the bladder C-fiber afferent activity modulation in chronic model of overactive bladder in rats. J Physiol Pharmacol, 2009. **60**(4): p. 85-91.

Karzel K. Lokalanästhetika und Lokalanästhesie. Deutsche Apotheker Zeitung. 1981;121(4).

Keenaghan, J. and R. Boyes, The tissue distribution, metabolism and excretion of lidocaine in rats, guinea pigs, dogs and man. Journal of Pharmacology and Experimental Therapeutics, 1972. **180**(2): p. 454-463.

Kolesnikov, Y.A., I. Chereshnev, and G.W. Pasternak, Analgesic synergy between topical lidocaine and topical opioids. Journal of Pharmacology and ExperimentalTherapeutics, 2000. **295**(2): p. 546-551.

Kucur M, Goktas S, Kaynar M, Apiliogullari S, Kilic O, Akand M, et al. Selective Low-Dose Spinal Anesthesia for Transrectal Prostate Biopsy: A Prospective and Randomized Study. Journal of endourology. 2015;29(12):1412-7.

Kumar CM. Lignocaine gel 2% per rectal as an adjunct to general anaesthesia for anal stretch. Anaesthesia. 1988;43(7):614.

Lawrence, V.S., et al., Lidocaine, 2-chlorprocaine and hepatic necrosis. Anesthesia & Analgesia, 1966. **45**(1): p. 55-58.

Lin F, Chang W-H, Su Y-J, Tsai C-H. Cardiovascular Complications Resulting from Topical Lidocaine Application. International Journal of Gerontology. 2008;2(4):229-32.

Linčir, I. and K. Rošin-Grget, Pharmacotherapy of the dental patient during pregnancy and lactation. Acta stomatologica Croatica, 2001. **35**(1): p. 103-108.

Liu, P., et al., Acute cardiovascular toxicity of intravenous amide local anesthetics in anesthetized ventilated dogs. Anesthesia and analgesia, 1982. **61**(4): p. 317-322.4

London S, Hoilat GJ, Tichauer MB. Anoscopy. StatPearls. Treasure Island (FL): StatPearls Publishing, Copyright © 2020, StatPearls Publishing LLC.; 2020.

Lukawska J, Caballero M, Tsabouri S, Dugue P. Hypersensitivity to local anaesthetics- 6 Facts and 7 myths. Current Allergy and Clinical Immunology. 2009;22:117-20.

Maccagnano C, Scattoni V, Roscigno M, Raber M, Angiolilli D, Montorsi F, et al. Anaesthesia in transrectal prostate biopsy: which is the most effective technique? Urologia internationalis. 2011;87(1):1-13.

Mallick S, Humbert M, Braud F, Fofana M, Blanchet P. Local anesthesia before transrectal ultrasound guided prostate biopsy: comparison of 2 methods in a prospective, randomized clinical trial. The Journal of urology. 2004;171(2 Pt 1):730-3.

Margaria, E., G. Marchiaro, and L. Nadali, Changes in the antibody response with reference to prolonged treatment with local anaesthetics. Acta Anaesthesiologica Scandinavica, 1966. **10**: p. 610-613.

McFarlane N, Denstedt J, Ganapathy S, Razvi H. Randomized trial of 10 mL and 20 mL of 2% intraurethral lidocaine gel and placebo in men undergoing flexible cystoscopy. Journal of endourology. 2001;15(5):541-4.

Mehra P, Caiazzo A, Maloney P. Lidocaine toxicity. Anesthesia progress. 1998;45(1):38-41.

Monographie Lidocain, Bundesfachverband der Arzneimittel-Hersteller e.V., Bundesanzeiger No. 22, 03.02.1993. 1993.

Morishima, H.O., et al., Bradycardia in the fetal baboon following paracervical block anesthesia. American journal of obstetrics and gynecology, 1981. **140**(7): p. 775-780.

Morishima, H.O., et al., Adverse effects of maternally administered lidocaine on the asphyxiated preterm fetal lamb. Anesthesiology, 1989. **71**(1): p. 110-115.

Mularoni PP, Cohen LL, DeGuzman M, Mennuti-Washburn J, Greenwald M, Simon HK. A randomized clinical trial of lidocaine gel for reducing infant distress during urethral catheterization. Pediatric emergency care. 2009;25(7):439-43.

Nagashima, A., et al., A study of the in vitro interaction between lidocaine and premedications using human liver microsomes. Journal of clinical pharmacy and therapeutics, 2005. **30**(2): p. 185-188.

Nam SH, Kim KH, Choi C, Nam SH, Song T, Lee KW. Lidocaine gel versus plain lubricating gel for pain reduction during transrectal sonography (LIPS): A randomized controlled trial. European journal of obstetrics, gynecology, and reproductive biology. 2017;212:60-4.

Nazir B. Pain during transrectal ultrasound-guided prostate biopsy and the role of periprostatic nerve block: what radiologists should know. Korean journal of radiology. 2014;15(5):543-53.

Nickel JC, Moldwin R, Lee S, Davis EL, Henry RA, Wyllie MG. Intravesical alkalinized lidocaine (PSD597) offers sustained relief from symptoms of interstitial cystitis and painful bladder syndrome. BJU international. 2009;103(7):910-8.

NTP, Toxicology and carcinogenesis studies of 2,6-xylidine (2,6-dimethylaniline) (CAS No. 87-62-7) in Charles River CD rats (feed studies). Technical Report No. 278. NTIS No. PB90-256363. National Toxicology Program, Research Triangle Park, NC. 2 pp. Accessed online October 26, 2019: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr278.pdf, 1990.

Obek C, Ozkan B, Tunc B, Can G, Yalcin V, Solok V. Comparison of 3 different methods of anesthesia before transrectal prostate biopsy: a prospective randomized trial. The Journal of urology. 2004;172(2):502-5.

Otunctemur A, Dursun M, Besiroglu H, Can Polat E, Cakir SS, Ozbek E, et al. The effectivity of periprostatic nerve blockade for the pain control during transrectal ultrasound guided prostate biopsy. Archivio italiano di urologia, andrologia : organo ufficiale [di] Societa italiana di ecografia urologica e nefrologica. 2013;85(2):69-72.

Panacek E, Beninger P, Albertson T. Lidocaine toxicity from intraurethral administration. Annals of emergency medicine. 1984;13(6):483-4.

Parkes AW, Harper N, Herwadkar A, Pumphrey R. Anaphylaxis to the chlorhexidine component of Instillagel: a case series. British journal of anaesthesia. 2009;102(1):65-8.

Patel, M. and M. Jindal, Local anaesthetic activity of some lignocaine analogues. Archives internationales de pharmacodynamie et de therapie, 1965. **156**(1): p. 118-129.

Pendopharm. Product monograph: JELIDO(TM), Lidocaine hydrochloride jelly, USP, 20 mg/mL, Topical anaesthetic. 2017.

Philip J, McCabe JE, Roy SD, Samsudin A, Campbell IM, Javle P. Site of local anaesthesia in transrectal ultrasonography-guided 12-core prostate biopsy: does it make a difference? BJU international. 2006;97(2):263-5.

Poonai N, Li J, Langford C, Lepore N, Taddio A, Gerges S, et al. Intraurethral Lidocaine for Urethral Catheterization in Children: A Randomized Controlled Trial. Pediatrics. 2015;136(4):e879-86.

Procopio, M.A., et al., The in vivo effects of general and epidural anesthesia on human immune function. Anesthesia & Analgesia, 2001. **93**(2): p. 460-465.

Ramazzotto, L., et al., Toxicological assessment of lidocaine in the pregnant rat. Journal of dental research, 1985. **64**(10): p. 1214-1217.

Riedl CR, Knoll M, Plas E, Pfluger H. Electromotive drug administration and hydrodistention for the treatment of interstitial cystitis. Journal of endourology. 1998;12(3):269-72.

Rodriguez-Rubio F, Sanz G, Garrido S, Sanchez C, Estudillo F. Patient tolerance during outpatient flexible cystoscopy--a prospective, randomized, double-blind study comparing plain lubrication and lidocaine gel. Scandinavian journal of urology and nephrology. 2004;38(6):477-80.

Saad F, Sabbagh R, McCormack M, Peloquin F. A prospective randomized trial comparing lidocaine and lubricating gel on pain level in patients undergoing transrectal ultrasound prostate biopsy. The Canadian journal of urology. 2002;9(4):1592-4.

Saha PK, Alam SM, Khatun US, Rahman MH, Gupta SD. Use of local anesthesia in transrectal ultrasound guided prostatic biopsy. Mymensingh medical journal : MMJ. 2014;23(2):299-304.

Sánchez-Chapula, J., Electrophysiological interactions between quinidine-lidocaine and quinidine-phenytoin in guinea-pig papillary muscle. Naunyn-Schmiedeberg's archives of pharmacology, 1985. **331**(4): p. 369-375.

Schede J, Thuroff JW. Effects of intraurethral injection of anaesthetic gel for transurethral instrumentation. BJU international. 2006;97(6):1165-7.

Seo, N., et al., The tetraphasic action of lidocaine on CNS electrical activity and behavior in cats. Anesthesiology, 1982. **57**(6): p. 451-457.

Siddiqui EJ, Ali S, Koneru S. The rectal administration of lignocaine gel and periprostatic lignocaine infiltration during transrectal ultrasound-guided prostate biopsy provides effective analgesia. Annals of the Royal College of Surgeons of England. 2006;88(2):218-21.

Skriapas K, Konstandinidis C, Samarinas M, Kartsaklis P, Gekas A. Pain level and anal discomfort during transrectal ultrasound for guided prostate biopsy. Does intrarectal administration of local anesthetic before periprostatic anesthesia makes any difference? Minerva urologica e nefrologica = The Italian journal of urology and nephrology. 2009;61(2):137-42.

Smith, R.F., et al., Behavioral effects of prenatal exposure to lidocaine in the rat: Effects of dosage and of gestational age at administration. Neurotoxicology and teratology, 1989. **11**(4): p. 395-403.

Snyder, R.D. and J.W. Green, A review of the genotoxicity of marketed pharmaceuticals. Mutation Research/Reviews in Mutation Research, 2001. **488**(2): p. 151-169.

Sökeland J, Wolters A. Technische Verbesserungen bei perkutanen Nierenoperationen. Urologe. 1985;25:79

Song SH, Kim JK, Song K, Ahn H, Kim CS. Effectiveness of local anaesthesia techniques in patients undergoing transrectal ultrasound-guided prostate biopsy: a prospective randomized study. International journal of urology : official journal of the Japanese Urological Association. 2006;13(6):707-10.

Stein M, Lubetkin D, Taub HC, Skinner WK, Haberman J, Kreutzer ER. The effects of intraurethral lidocaine anesthetic and patient anxiety on pain perception during cystoscopy. The Journal of urology. 1994;151(6):1518-21.

Stirling BN, Shockley KF, Carothers GG, Maatman TJ. Comparison of local anesthesia techniques during transrectal ultrasound-guided biopsies. Urology. 2002;60(1):89-92.

Sundaram MB. Seizures after intraurethral instillation of lidocaine. CMAJ. 1987;137(3):219-20.

Sweetman SC. Martindale - The Complete Drug Reference: Lidocaine, 36th Edition.2009.-81.

Tanelian, D.L. and M.B. MacIver, Analgesic concentrations of lidocaine suppress tonic A-delta and C fiber discharges produced by acute injury. Anesthesiology, 1991. **74**(5): p.b 934-936.

Tanabe P, Steinmann R, Anderson J, Johnson D, Metcalf S, Ring-Hurn E. Factors affecting pain scores during female urethral catheterization. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 2004;11(6):699-702.

Takagi, S., et al., Effect of local anaesthetics on human natural killer cell activity. Clinical and experimental immunology, 1983. **53**(2): p. 477.

Teiling, A., et al., Lack of effects of prenatal exposure to lidocaine on development of behavior in rats. Anesthesia and analgesia, 1987. **66**(6): p. 533-541.

Teiling, A., et al., Lack of Effect of Prenatal Exposure to Lidocaine on Development of Behavior in Rats. Obstetric Anesthesia Digest, 1988. **8**(3): p. 113.

Temiz MZ, Kandirali E, Colakerol A, Tuken M, Semercioz A. Local anesthesia type affects cancer detection rate in transrectal ultrasound guided prostate biopsy. International braz j urol : official journal of the Brazilian Society of Urology. 2015;41(5):859-63.

Tiong HY, Liew LC, Samuel M, Consigliere D, Esuvaranathan K. A meta-analysis of local anesthesia for transrectal ultrasound-guided biopsy of the prostate. Prostate cancer and prostatic diseases. 2007;10(2):127-36.

Tzortzis V, Gravas S, Melekos MM, de la Rosette JJ. Intraurethral lubricants: a critical literature review and recommendations. Journal of endourology. 2009;23(5):821-6.

U.S. Food and Drug Administration (FDA): FDA recommends not using lidocaine totreat teething pain and requires new Boxed Warning. 2014.

Uspal NG, Strelitz B, Gritton J, Follmer K, Bradford MC, Colton TL, et al. Randomized Clinical Trial of Lidocaine Analgesia for Transurethral Bladder Catheterization Delivered via Blunt Tipped Applicator in Young Children. Pediatric emergency care. 2018;34(4):273-9.

Van Der Burght, M., et al., Onset and duration of hypoalgesia following application of lidocaine spray on genital mucosa. Acta obstetricia et gynecologica Scandinavica, 1994. **73**(10): p. 809-811.

van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. European urology. 2008;53(1):60-7.

van Hoogdalem E, de Boer AG, Breimer DD. Pharmacokinetics of rectal drug administration, Part I. General considerations and clinical applications of centrally acting drugs. Clinical pharmacokinetics. 1991;21(1):11-26.

Vaughan, M., et al., Does lidocaine gel alleviate the pain of bladder catheterization in young children? A randomized, controlled trial. Pediatrics, 2005. **116**(4): p. 917-920.

Wang, J.-S., et al., Involvement of CYP1A2 and CYP3A4 in LidocaineN-Deethylationand 3-Hydroxylation in Humans. Drug Metabolism and Disposition, 2000. **28**(8): p. 959-965.

Weiland, L., et al., Pharmacokinetics of a lidocaine patch 5% in dogs. Journal of Veterinary Medicine Series A, 2006. **53**(1): p. 34-39.

Wenger, S., et al., Evaluation of the analgesic effect of lidocaine and bupivacaine used to provide a brachial plexus block for forelimb surgery in 10 dogs. Veterinary record, 2005. **156**(20): p. 639-642.

Weinberg L, Peake B, Tan C, Nikfarjam M. Pharmacokinetics and pharmacodynamics of lignocaine: A review. World Journal of Anesthesiology. 2015;4:17-29.

Whittet HB, Hayward AW, Battersby E. Plasma lignocaine levels during paediatric endoscopy of the upper respiratory tract. Relationship with mucosal moistness. Anaesthesia. 1988;43(6):439-42.

Wiedling, S., Contributions to the Pharmacology and Toxicology of Xylocaine 1. Acta pharmacologica et toxicologica, 1952. **8**(2): p. 117-133.

Wiedling, S. and C. Tegner, 7 Local Anaesthetics, in Progress in medicinal chemistry. 1963, Elsevier. p. 332-398.

Wiedling, S., Reproduction study of Citanest and Xylocaine. Acta anaesthesiologica Scandinavica. Supplementum, 1965. **16**: p. 45.

Wikland, M., et al., The concentration of lidocaine in follicular fluid when used for paracervical block in a human IVF-ET programme. Human Reproduction, 1990. **5**(8): p.920-923.

Wójcicki J, Kozłowski K, Droździk M, Wójcicki M. Lidocaine elimination in patients with liver cirrhosis. Acta poloniae pharmaceutica. 2002;59(4):321-4.

Wright, J.L., M.E. Durieux, and D.S. Groves, A brief review of innovative uses for local anesthetics. Current Opinion in Anesthesiology, 2008. **21**(5): p. 651-656.

Zou, Y.-X., et al., Preclinical safety assessment of antipyrine combined with lidocaine hydrochloride as ear drops. Regulatory Toxicology and Pharmacology, 2019. **103**: p. 34-40.