# Summary of product characteristics

## 1. NAME OF THE MEDICINAL PRODUCT

Cathejell with Lidocaine

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of gel contains:
20 mg Lidocaine hydrochloride (2% w/w)
0.5 mg Chlorhexidine dihydrochloride (0.05% w/w)

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Water-soluble and clear, colourless anaesthetising gel.
Sterile single-use form.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Instillation into the urethra prior to the instillation of a catheter or other instruments (catheterization, cystoscopy) and manipulations which require the use of a local anesthetic.

### 4.2 Posology and method of administration

Cathejell with Lidocaine is instilled into the urethra prior to the insertion of instruments and/or applicated onto the instrument.

The content of one syringe is sufficient to fill the urethra.
Never instill more than one syringe.

The tubes contain 12,5 g, of which 10 g are instilled into the urethra.

Slow instillation of the gel into the urethra prior to the insertion of instruments (by a physician or trained medical qualified personnel).

Handling:

1. Clean and disinfect the external orifice of the urethra.
2. Peel off the paper from the blister back cover (possibly up to the waist of the transparent blister material).
3. Break off the applicator tip (in the blister pack if required).
Take care to remove the tip completely to prevent insertion into the urethra.
4. Release one drop of gel for easier insertion of the applicator.
5. Complete extrusion by applying slight steady pressure to the accordion

The duration of application is not limited.

### 4.3 Contraindications

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

- Hypersensitivity to other local anaesthetics of the amide type.

- Infants under 2 years of age.

- Bulbocavernosus (urethrocavernous) reflux, an injury to the thin urethral mucosa which may lead to intrusion of the lubricant into erectile tissue, where absorption might occur.

- Severe heart failure, pronounced bradycardia, AV block, cardiogenic or hypovolaemic shock.

**4.4 Special warnings and precautions for use**

Under general anesthesia, a lubricant without lidocaine should be preferred.

Cathejell with Lidocaine should be used with caution in patients with
- Severe impairment of hepatic and renal function (see also section 4.2),
- Cardiac or respiratory dysfunction.

Special care is advised in the following cases:

- high doses or short intervals between doses. These may lead to high plasma levels and severe adverse reactions. The extent of mucosal absorption varies but is particularly high in the bronchial tree. Use in the bronchial tree may therefore lead to rapidly increasing or elevated plasma levels and is associated with an increased risk of toxic symptoms such as convulsions.
- in elderly, debilitated and acutely ill patients, as well as patients prone to seizures (see also section 4.2).
- patients with wounds, traumatized mucosa, ulcerative tissue or sepsis in the region of the proposed application site. Damaged mucosa leads to increased systemic absorption.
- Patients who are treated with class III antiarrhythmic (e.g. amiodarone); they must be carefully monitored and ECG monitoring should be taken into consideration, as the effects on the heart may be additive.

Cathejell with Lidocaine is probably porphyrinogenic and should therefore not be administered to patients with acute porphyria unless strictly indicated. In patients with porphyria, appropriate precautions must be taken.

If more than the recommended amount is instilled, a large amount of gel infiltrates the urinary bladder or if the urethra is inflamed and ulcerous, the absorption of lidocaine through the mucous membranes is generally increased - particularly in children and elderly patients - resulting in possible overdoses with central nervous and cardiovascular adverse reactions (see also section 4.9).

Patients suffering from myasthenia gravis are particularly sensitive to local anaesthetics.

Cathejell with Lidocaine must not come into contact with the eyes.

**4.5 Interaction with other medicinal products and other forms of interaction**

Cathejell with Lidocaine should not be applied concomitantly with other medicinal products containing lidocaine hydrochloride or other local anaesthetics of the amide type, as this may cause unpredictable mutual potentiation of the effects.

Due to possible additive effects on the heart, lidocaine should be used with caution in patients concomitantly receiving antiarrhythmic agents such as mexiletine and tocainide, beta-blockers (e.g. propranolol) or calcium channel antagonists (e.g. diltiazem, verapamil).

Propranolol, diltiazem and verapamil lead to a significant increase of the elimination half-life due to decreased lidocaine clearance. Medicinal products that reduce lidocaine clearance may lead to potentially toxic plasma concentrations if lidocaine is repeatedly administered at high doses over a prolonged period. In short-term treatment with recommended doses of Cathejell with Lidocaine, such interactions should therefore be without clinical significance.

No specific interaction studies have been performed with lidocaine and class III antiarrhythmic agents (e.g. amiodarone); however, caution is advised (see also section 4.4).

Caution should be exercised if cimetidine, an $H_2$ antagonist, is co-administered. Elevated lidocaine plasma levels may occur due to reduced hepatic perfusion and inhibition of microsomal enzymes.

**4.6 Fertility, pregnancy and lactation**

***Pregnancy***

No controlled clinical studies with pregnant women are available. 50-60% of maternal lidocaine plasma concentrations pass through the placenta. In cases of high systemic exposure, foetal depression may occur. In animal studies, adverse reactions in foetuses were shown only following prenatal exposure to high lidocaine doses (see section 5.3). The potential risk for humans is unknown.

With regard to chlorhexidine in Cathejell with Lidocaine, there is virtually no risk, as only very small amounts are absorbed into the maternal circulation.

During pregnancy, Cathejell with Lidocaine should only be used after careful consideration of the benefits and risks by a doctor and after establishing the individual dose. Repeated use during pregnancy is not recommended.

***Breast-feeding***

Only small amounts of lidocaine are excreted in human milk. If Cathejell with Lidocaine is used correctly (see section 4.2), there are virtually no safety concerns for the child during lactation.

There are no data on the excretion of chlorhexidine in human milk. Based on the very low systemic absorption of chlorhexidine following intraurethral instillation, the expected amount in human milk is clinically negligible.

During lactation, Cathejell with Lidocaine should be used only if the need and the individual dose have been established, There should be an interval of 12 hours between the instillation of Cathejell with Lidocaine and subsequent breast-feeding. Repeated use during lactation cannot be recommended.

**4.7 Effects on ability to drive and use machines**

Cathejell with Lidocaine has no or negligible influence on the ability to drive or use machines. However, in case of increased individual sensitivity, such effects cannot be ruled out entirely.

**4.8 Undesirable effects**

An accurate estimation of the frequency of undesirable effects is not possible due to lacking data.

The following incidence rates are used in the evaluation of undesirable effects:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥ 1/10,000 to < 1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data)

Adverse reactions rarely occur after the use of Cathejell with Lidocaine, provided that the product is used according to the dosage recommendations/recommendations for use and the necessary precautions are taken.
In rare cases, local and/or systemic hypersensitivity reactions to lidocaine and/or chlorhexidine may occur.

***Systemic adverse reactions***

Systemic adverse reactions can be caused by high plasma levels, rapid absorption or overdose, as well as by hypersensitivity, idiosyncrasy or reduced tolerance, with possible onset of the following symptoms:

CNS: nervousness, lightheadedness, blurred vision, tremor. These signs may or may not occur. In some patients, intoxication manifests itself in the form of sleepiness, unconsciousness or respiratory arrest.
Cardiovascular: hypotension, bradycardia, asystole. For treatment of intoxication, see section 4.9.

***General disorders and administration site conditions***

Only low lidocaine blood levels are likely when used in urology; other systemic adverse reactions after instillation of Cathejell with Lidocaine into the urethra (see sections 4.4 and 4.9) are therefore normally not expected.

***Immune system disorders***

Allergic reactions to local amide-type anaesthetics (in extremely rare cases, anaphylactic shock) are rare. Bronchospasm, respiratory distress syndrome, cutaneous lesions, urticaria and oedema may occur as hypersensitivity to lidocaine or chlorhexidine and should be conventionally treated.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (https://sideeffects.health.gov.il).

**4.9 Overdose**

When Cathejell with Lidocaine is used properly (see sections 4.2 and 4.4), virtually no toxic plasma concentrations > 5µg/mL are reached. However, concomitant administration of other local anaesthetics may lead to additive effects and may result in an overdose with systemic toxicity reactions.

***Symptoms of intoxication***

Should symptoms of systemic intoxication nevertheless occur, the nature of these symptoms will be similar to those which can occur with other methods of local anaesthetic administration (e.g. infiltration anaesthesia and nerve block).

The course of lidocaine intoxication is biphasic:

- Stimulation: In low toxic concentrations, lidocaine acts as a central nervous stimulant, resulting in CNS excitation with restlessness, vertigo, tremor and cardiovascular stimulation with accelerated heart rate, increased blood pressure and reddening of the skin.

- Depression: In high toxic ranges, depression occurs in the region of the CNS and cardiovascular system (somnolence, sedation, pallor, coma).

CNS toxicity reactions usually precede those of the cardiovascular system, as the former occur at lower plasma concentrations.

First signs of an overdose are initially excitatory; patients become restless, complain of lightheadedness, auditory and visual disturbances, tingling of the tongue and lip region or nystagmus. Subconvulsive plasma levels of lidocaine often lead to sleepiness and sedation. Shivering and muscle twitches are precursors of an

imminent generalized seizure. As CNS intoxication progresses, increasing brain stem dysfunction occurs with symptoms of respiratory depression and even coma.

A decrease in blood pressure and bradycardia are the first signs of toxic effects of lidocaine on the cardiovascular system, ultimately followed by myocardial depression and an increase in the ventricular activation time. The cardiovascular effects normally occur only at very high plasma concentrations of lidocaine and are, clinically speaking, of relatively minor importance.

***Emergency procedures in the event of an overdose***

Treatment of intoxication in the CNS region (convulsions, CNS depression) or the cardiovascular system is symptomatic, e.g. with administration of anticonvulsants and/or emergency cardiopulmonary support:
- Immediate discontinuation of lidocaine administration
- Maintenance of airway patency
- Oxygen administration until all vital functions have normalized
- Monitoring of blood pressure, pulse and pupil width.

***Other possible interventions***

For acute life-threatening hypotension, elevation of the legs and slow IV injection of a beta-sympathomimetic (e.g. 10 to 20 drops per minute of a 1 mg isoprenaline solution in 200 ml glucose solution 5%) and additional volume replacement.

In case of increased vagal tone (bradycardia), 0.5 to 1.0 mg atropine is administered IV.

Convulsions lasting for more than 30 seconds are treated by administering an anticonvulsant (thiopental sodium 1 to 3 mg/kg IV or diazepam 0.1 mg/kg BW IV).

Persistent convulsions can be controlled by injecting a muscle relaxant (e.g. succinylcholine (suxamethonium) 1 mg/kg BW).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: local anaesthetics, amides, lidocaine, combinations
ATC code: N01BB52

***Mechansim of Action***

Cathejell with Lidocaine is a sterile and antiseptic gel with a local anaesthetic effect. Via local topical anaesthesia, Cathejell with Lidocaine produces anaesthesia of the mucous membranes, resulting in rapid symptomatic pain relief. The onset of action occurs as early as 5 to 10 minutes post administration and lasts for 20 to 30 minutes. In addition to pain relief, Cathejell with Lidocaine is thought to widely prevent urinary tract infections post catheterisation.

***Pharmacodynamic effects***
Lidocaine is a medically proven acid amide-type local anaesthetic. Lidocaine reversibly and locally inhibits conductivity of sensitive nerve fibres. Sensations are reduced sequentially in the order of cold/heat, touch and pressure. In topical anaesthesia, the onset of action generally occurs after about 3 to 5 min. The effect is reduced in inflamed tissue, due to the acidic pH value found there.
In addition to use as an anaesthetic, lidocaine also has an antiarrhythmic effect. Unlike most other local anaesthetics, lidocaine has no vasodilatory effect.

Chlorhexidine has antimicrobial activity against many gram-positive and gram-negative bacteria, as well as against a range of fungi and viruses. At the concentration in this product, it acts as a prophylactic against iatrogenic infections in the topical range of use.

**5.2 Pharmacokinetic properties**

***Absorption***

Lidocaine is rapidly absorbed into the blood circulation via the mucous membranes. The amount absorbed following local mucosal application is dependent on the concentration and total administered dose, the specific site of application and duration of use. Local anaesthetics are generally absorbed most rapidly following intratracheal and bronchial use, which may lead to rapidly increasing or very high plasma concentrations with an increased risk of toxic symptoms.

Lidocaine is rapidly absorbed from the gastrointestinal tract, although only little intact active substance enters the circulation due to metabolic degradation in the liver (“first-pass effect”).

45 to 60 minutes after intraurethral instillation of 10 to 40 ml lidocaine gel 2% (200 to 800 mg lidocaine), peak plasma concentrations of 0.06 to 0.2 µg/ml lidocaine are reached. These values are 7.5 to 27.5 times lower than the plasma concentrations of 1.5 to 5.5 µg/ml which are therapeutically relevant for the antiarrhythmic effect, and are lower than toxic plasma concentrations by a factor of 30 (5 to 8 µg/ml).

It should be remembered that severe inflammation of the urethral mucosa and surface enlargement due to urethral dilation can lead to increased absorption of lidocaine.

Chlorhexidine is absorbed in only very small amounts after topical use.

***Distribution***

Lidocaine has a volume of distribution of 1.3 to 1.6 L/kg; it is rapidly distributed to all tissues, especially highly vascularised organs, such as the lung, kidneys and skeletal muscles.

Approximately 65% of lidocaine is bound to plasma proteins and alpha-1 acid glycoproteins (AAGs). As the number of AAGs increases with age, after trauma, surgery and in cases of cancer and chronic inflammation, yet decreases in renal and hepatic disease, protein binding in such cases may accordingly be increased or reduced. Lidocaine passes the blood-brain barrier.

Following single intravenous administration, there is a biexponential decrease in the plasma concentration of lidocaine, with half-lives of approximately 8 minutes and of 1.6 hours.

***Biotransformation, elimination***

Lidocaine exhibits a marked first-pass metabolism. Approximately 90% of a lidocaine dose is rapidly dealkylated and metabolised in the liver to monoethylglycine xylidide (MEGX) or glycine xylidide (GX). As Na+ channel blockers, MEGX and GX are less active than lidocaine. Other metabolites are 2,6-xylidine and 4-hydroxy-2,6-xylidine.

The terminal elimination half-life ($t_{1/2}$) of 1.8 hours represents a primarily hepatic metabolism; it may be prolonged to up to 2.3 hours in the elderly. $T_{1/2}$ of the active metabolites is 0.9 hours.

The total plasma clearance of 0.95 L/min may be reduced in patients with heart failure or hepatic disease. Metabolite accumulation may occur in cases of renal insufficiency.

Less than 5% of lidocaine is excreted unchanged with the urine.

***Kinetics in hepatic, renal and cardiac insufficiency***

Due to the rapid biotransformation of lidocaine in the liver, the half-life may be prolonged 2-fold or longer in patients with impaired hepatic function, e.g. to 4.5 to 6 hours in chronic cases of alcohol-induced liver damage. In patients with severe heart failure, the elimination half-life may be prolonged to 4 to 10 h. Renal insufficiency can lead to the accumulation of metabolites.

**5.3 Preclinical Safety Data**

***Repeated-dose toxicity***

Central nervous system disturbances were observed after multiple doses of 15 mg/kg BW lidocaine IV and 30 mg/kg SC in rats and after 10 mg/kg IV and 30 mg/kg SC in dogs.

***Mutagenicity, carcinogenicity***

Genotoxicity tests with lidocaine were negative. However, *in vitro* tests with 2,6-xylidine indicate a genotoxic potential of this lidocaine metabolite.

In a carcinogenicity study in rats with *in utero* and postnatal life-long exposure to 2,6-xylidine, tumours were observed in the region of the nostrils, subcutis and liver.

The clinical significance of the observed tumorigenic effects is unknown with regard to intermittent use as a local anaesthetic. Nevertheless, frequent use of high-dose lidocaine is not recommended.

***Reproductive toxicology***

In teratogenicity studies on rats and rabbits, no teratogenic effect was observed after treatment during the organogenesis phase. Embryotoxic effects in rabbits occurred only at concentrations that were already toxic to the dam. Treatment of rates during late gestation and lactation with maternally toxic amounts altered the gestation period and led to a decrease in pup viability. Following prenatal exposure to lidocaine, there was no evidence of developmental disturbances in the offspring. Foetal exposure to high concentrations had a deleterious effect on uterine perfusion and induced convulsions in the foetus. In animal experimental studies, possible behavioural disturbances after prenatal exposure are only insufficiently documented.

As there are no systemic data available in rats and rabbits, no comparisons to humans can be made in this regard. The potential risk for humans is unknown.

No toxicological risk has been established for chlorhexidine in Cathejell with Lidocaine.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Hydroxyethylcellulose, glycerol, sodium lactate solution, water for injections, sodium hydroxide solution and hydrochloric acid solution for pH adjustment.

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

### 6.4 Special precaution for storage

- Store under 25°C
- Store in the original package (blister in carton) in order to protect from light.

Intended for single use. Discard any remaining gel in incompletely emptied syringes.

### 6.5 Nature and contents of container

Cathejell with Lidocaine gel is contained in polypropylene collapsible syringes with a break-off tip.
Individual syringes are packed in blisters and steam-sterilized. The blister material consists of thermoforming polypropylene sheet, and medicinal steam paper.
The blisters are packed in cartons containing 25 syringes.

### 6.6 Special precautions for disposal

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

## 7. MANUFACTURER

Pharmazeutische Fabrik Montavit GmbH
Salzberstrasse 96, A-6067 Absam, Austria

## 8. REGISTRATION HOLDER

Lapidot Pharma and Medical Ltd.,
8 Hashita Street, Industrial Park Caesaria 3088900, ISRAEL.

## 9. MARKETING AUTHORISATION NUMBER

134-65-31156-00

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