Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Instillagel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml gel contains:
Active ingredients:

Lidocaine hydrochloride 20.9 mg

Chlorhexidine digluconate 0.52 mg

Other ingredients with known action:
methyl-4-hydroxybenzoate
propyl-4-hydroxybenzoate
propylene glycol

For a complete list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Gel

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Local anesthesia prior exploration in urology (ureteroscopy, cystoscopy, urethral dilation, catheterization). For use during gynaecological investigation.

4.2 Posology and method of administration

Unless prescribed otherwise, for urological use:

a) Catheterisation:

Instill 6 ml or 11 ml. After the usual cleansing of the glans and external urethral orifice Instillagel is slowly instilled into the urethra and the glans is compressed until the local anaesthetic and disinfectant effect has occurred.

b) Cystoscopy and endoscopy:

Instill 11 ml, and an additional 6 ml or 11 ml if necessary. The entire urethra including the external sphincter must be coated with a lubricant film and anaesthetised for germ-free and painless introduction of instruments. A penis clamp is applied at the coronal sulcus.

c) Urethral strictures (stricture division, bouginage):

Instill 11 ml Instillagel, and an additional 6 ml or 11 ml if necessary, and apply a penis clamp.
The required urethral anaesthesia is obtained after 5 - 10 minutes.

For gynaecological investigations:

Slowly instill 6 ml, and where necessary another 6 ml, into the vagina. The quantity depends on the patient's anatomic conditions and/or on the procedure to be performed. Alternatively, the gel can be dispensed and distributed as evenly as possible on the instrument to be inserted.

The full local anaesthetic and disinfectant (antiseptic) effect of Instillagel occurs after 5 to 10 minutes.

Instillagel must not be used in children under 2 years.
The maximum dose in children aged between 2 and 12 years should usually not exceed 2.9 mg lidocaine hydrochloride per kg body weight. This is equivalent to 1.5 ml Instillagel per 10 kg body weight.
The systemic absorption of lidocaine can be increased in children, so caution is warranted accordingly.

4.3 Contraindications

Instillagel must not be used
- In the case of known hypersensitivity to lidocaine and other local anaesthetics of the amide type,
- In patients with significant disorders of the conduction system,
- If there is hypersensitivity (allergy) to the active substances or to one of the other excipients of Instillagel listed in section 6.1.
- In children under 2 years (see section 4.2)

4.4 Special warnings and precautions for use

See Contraindications and Undesirable effects.

This medicinal product contains methyl and propyl 4-hydroxybenzoate, which can cause allergic reactions, including late reactions (see also section 4.8.).

This medicinal product contains also 500 mg propylene glycol in 1g, which is equivalent to 522.5 mg/ml.
3.14 g propylene glycol in 6 ml gel.
5.75 g propylene glycol in 11 ml gel.

Propylene glycol can cause skin irritation.

4.5 Interaction with other medicinal products and other forms of interaction

In animal studies (mouse), a dose-dependent increase in the toxicity of lidocaine is observed when pethidine is given concomitantly.

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>
Lidocaine should be used in the first three months of pregnancy only when absolutely necessary.

<u>Lactation</u>
It is not known whether lidocaine passes into breast milk so patients should not breast-feed until 12 hours after administration.

<u>Fertility</u>
There is currently no evidence that lidocaine impairs fertility.

4.7 Effects on ability to drive and use machines

When this medicinal product is used at operation or over a large area, the physician must decide in the individual case whether the patient may drive or use machines.

4.8 Undesirable effects

The assessment of undesirable effects is based on the following frequencies:
- 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)
— Unknown (frequency cannot be assessed on the basis of the available data)

Possible undesirable effects:

Immune system disorders
Very rare: Allergic reactions (anaphylactic shock in the most severe cases) to a local anaesthetic of the amide type and/or to chlorhexidine
Very rare: hypersensitivity reactions, including late reactions, due to chlorhexidine and/or methyl or propyl 4-hydroxybenzoate

Injuries, poisoning and complications due to procedures
Unknown: Despite the proven great safety range of Instillagel, with severe urethral injuries systemic undesirable effects of the local anaesthetic lidocaine are possible, such as anaphylactic shock, fall in blood pressure, bradycardia or seizures.

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

Undesirable effects due to possible lidocaine absorption can occur with heavily bleeding wounds.

The physician decides on necessary treatment measures.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group:
Local anaesthetics – amides - lidocaine, combinations Antiseptics and disinfectants – biguanides and amidines – chlorhexidine, combinations

ATC code: N01BB52, D08AC52

For urethral probing, catheterisation and cystoscopy, use of a sterile, sterile-packed, disinfectant and local anaesthetic gel is required to avoid injuries of the urethra and infections of the lower urinary tract.

Instillagel adheres well to the mucosa, has outstanding lubricant properties and leaves the optics of the instruments clear.

Instillagel contains the local anaesthetic lidocaine.

Lidocaine is a local anaesthetic of the amide type. To avoid secondary infection and hospitalisation, Instillagel contains a disinfectant mix of chlorhexidine digluconate, methyl 4-hydroxybenzoate and propyl 4-hydroxybenzoate.

Long-term tests for carcinogenic potential were not conducted with Instillagel or with lidocaine.

5.2. Pharmacokinetic properties
Lidocaine hydrochloride can be absorbed through the mucosa and distributed rapidly in the body. Lidocaine is absorbed only in very low amounts from preparations for urethral use. Unlike local anaesthetics of the ester type, lidocaine is metabolized in the liver and the metabolites are excreted mainly in the urine. Lidocaine is degraded by microsomal oxidative Ndealkylation to monoethylglycinexylidide (MEGX) and acetaldehyde, and 2,6-xylidine and N-ethylglycine are produced from MEGX by microsomal hydrolysis; 2,6-xylidine is metabolized either to 2-amino-3-methyl-benzoic acid or, by microsomal oxidation, to 4-hydroxy-2,6-xylidine. The latter is the main metabolite and 73 % of lidocaine is excreted in this form;

4-hydroxy-2,6-xylidine can also be produced directly from lidocaine.

The half-life of lidocaine is about 3 hours; lidocaine crosses the placenta and the half-life in the foetus is about 4 hours.

The substances chlorhexidine digluconate and t h e 4-hydroxybenzoates contained in very small amounts in Instillagel can also be absorbed through the mucosa to a very small degree and a small amount can reach the blood stream directly through minor lesions.

Chlorhexidine, which is hardly absorbed even with oral use in high doses, is eliminated practically unchanged. The 4-hydroxybenzoates are excreted after hydrolysis in the form of 4-hydroxybenzoic acid and its derivatives.

5.3 Preclinical safety data
Acute toxicity – systemic toxicity
Animal studies of the acute toxicity of lidocaine found an LD50 between 22 mg/kg BW and 48 mg/kg BW in mice. In rats the levels are between 21 and 25 mg/kg BW.

The toxic plasma concentration and seizure threshold in humans are reported as 5µg/ml to > 10µg/ml blood plasma.

Acute toxicity – local toxicity
There are no animal studies of local toxicity. The local tolerability of the finished medicinal product Instillagel in humans is very good.

Chronic toxicity
Animal studies of the subchronic toxicity of lidocaine with local application (rat, dog) showed fatty change of the liver in (374) at a dosage of 30 mg/kg BW with peripheral and perilobular distribution, which is attributed to the effect of lidocaine.

Tests of the chronic toxicity of lidocaine in rats over a period of 6 months at doses of 6 mg/kg BW yielded no evidence of pathological changes attributable to lidocaine.

Mutagenic and carcinogenic potential
There is evidence that 2,6-xylidine, a metabolic product derived from lidocaine/etidocaine in rats and possibly also in humans, could have mutagenic effects. This evidence is obtained from in-vitro tests in which this metabolite was used in very high and almost toxic concentrations. There is currently no evidence that the parent substances lidocaine and etidocaine are themselves mutagenic.

In a carcinogenicity study in rats with transplacental exposure and postnatal treatment of the animals for 2 years with 2,6-xylidine, malignant and benign tumours were observed, especially in the nasal sinus (ethmoturbinals), in a highly sensitive test system (transplacental exposure and postnatal treatment of the animals for 2 years with very high doses). The relevance of these findings for humans does not appear completely unlikely. Instillagel should therefore not be administered in high doses over a long period.

Reproductive toxicity
Lidocaine crosses the placenta. The levels measured in the foetus are 0.4-1.3 times the maternal serum concentration.
Previous experience in humans with the use of lidocaine as a local anaesthetic in the first three months of pregnancy (c. 290 mother-child pairs) did not yield any evidence of an increase in the rate of malformation. However, neurological behavioural changes in neonates have been reported. The use of lidocaine for paracervical block or epidural anaesthesia can lead to foetal bradycardia.

Reproductive toxicology studies in rats did not find any evidence for a teratogenic potential up to a dose of 56 mg/kg BW and day.
Behavioural changes were described in young animals exposed prenatally.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Propylene glycol, hydroxyethylcellulose, sodium hydroxide, methyl-4-hydroxybenzoate, propyl-4-hydroxybenzoate, purified water.

6.2 Incompatibilities
Not known.

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

6.4 Special precautions for storage
Store below 25ºC.
Keep safe from children.

6.5 Nature and contents of container
Instillagel in the single-use syringe is sterile, in sterile packaging and ready to use.

Pack sizes:
10 x 6 ml/11 ml
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

After opening, use the single-use syringe immediately and dispose of leftover gel.

7. MANUFACTURER
Klosterfrau Berlin GmbH
Motzener Strabe 41
12277 Berlin
Germany

8. REGISTRATION HOLDER
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9. REGISTRATION NUMBER

160-11-35080-00

Revised in January 2021 according to MOH guidelines.