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 – nearly colorless, clear, viscous liquid.

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 otherwise prescribed, for urological use:

a) during catheterisation:
Instill 6 ml or 11 ml. After the usual cleaning of the glans and the external urethral orifice, Instillagel is instilled slowly into the urethra and the glans is compressed until the local anaesthetic and antiseptic effect has set in.

b) during cystoscopy and endoscopy:
Instill 11 ml, and if necessary an additional 6 ml or 11 ml. The entire urethra, including the external sphincter, must be covered with the lubricating film and be anaesthetised for germ-free and painless insertion of instruments. A penis clamp should be applied in the region of the coronal sulcus.

c) in urethral strictures (stricture division, bougienation):
Instill 11 ml, and if necessary an additional 6 ml or 11 ml, and apply a penis clamp. The required urethral anaesthesia will be achieved 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 onset of the full local anaesthetic and disinfectant (antiseptic) effect of Instillagel is achieved after 5-10 minutes.

Instillagel must not be used in children below the age of 2 years.
In general, the maximum dose should not exceed 2.9 mg of lidocaine hydrochloride per kg of body weight in children between 2 and 12 years of age. This is equivalent to 1.5 ml of Instillagel per 10 kg of body weight.
The systemic absorption of lidocaine may be increased in children and caution is therefore required.

4.3. Contraindications

Do not use Instillagel
- in the presence of known hypersensitivity to lidocaine and other local anaesthetics of the amide type,
- in patients with significant disorders of the conduction system,
- in patients with known hypersensitivity (allergy) to the active substances or to any of the 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 medicine contains methyl and propyl 4-hydroxybenzoate, which may cause allergic reactions (possibly delayed) (see also section 4.8).

Propylene glycol may cause skin irritation.

Instillagel must not come into contact with the eyes. Severe cases of persistent corneal injury which may require corneal transplantation have been reported after inadvertent exposure of the eyes to medicinal products containing chlorhexidine. In these cases, despite eye protection measures the solution reached outside the area intended for preparation of the surgical intervention. During use, the utmost care should be taken to ensure that Instillagel does not reach outside the intended area of application and come into contact with the eyes.
Particular caution is advised in anaesthetised patients, who are unable to immediately report any ocular exposure. If Instillagel comes into contact with the eyes, the eyes should be thoroughly rinsed with water immediately. An ophthalmologist should be consulted.

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

A dose-dependent increase in lidocaine toxicity was observed in animal studies (in mice) when administered at the same time as pethidine.

4.6. Fertility, pregnancy and lactation

<u>Pregnancy</u>
Lidocaine should not be used during the first three months of pregnancy unless absolutely necessary.

<u>Lactation</u>

It is not known whether lidocaine passes into human milk; for this reason, the woman should not breast-feed for up to around 12 hours after administration.

Fertility
There is currently no evidence to suggest an impact of lidocaine on fertility.

4.7. Effects on ability to drive and use machines

If this medicine is used during surgery or over extensive areas, the doctor will have to decide on a case-by-case basis whether the patient may drive or use machines.

4.8. Undesirable effects

The assessment of undesirable effects is based on the following frequency categories:
- 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)

Possible adverse reactions:

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

Injury, poisoning and procedural complications
Not known: Despite the proven wide safety range of Instillagel, systemic adverse effects of the local anaesthetic lidocaine, such as anaphylactic shock, a fall in blood pressure, bradycardia or seizures, are possible in the case of severe urethral damage.

Eye disorders

Not known: Corneal erosion, epithelial defect/corneal injury, significant permanent visual impairment (see section 4.4)

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

In patients with severely bleeding wounds, adverse reactions can occur due to potential lidocaine absorption.

The doctor will decide on the necessary therapeutic 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

To prevent damage of the urethras and infections of the lower urinary tract, the use of a sterile, sterile packaged, disinfecting and locally anaesthetising lubricant is required in the event of urethral probe insertions, catheterisation and cystoscopy.

Instillagel adheres well to the mucosa, has excellent lubricant qualities and leaves instruments with a clear view.

Instillagel contains the local anaesthetic lidocaine.

Lidocaine is a local anaesthetic of the amide type. To prevent secondary infections and hospitalism, Instillagel contains a disinfectant mixture comprising chlorhexidine digluconate, methyl-4-hydroxybenzoate and propyl-4-hydroxybenzoate.

Long-term investigations for a tumorigenic potential have not been carried out with Instillagel or with lidocaine.

5.2. Pharmacokinetic properties

Lidocaine hydrochloride is rapidly absorbed by the mucosa and quickly distributed in the body. Only minor quantities of lidocaine are absorbed from preparations for urethral use. In contrast to ester-type local anaesthetics, lidocaine is metabolised in the liver, the metabolites are excreted predominantly in the urine, lidocaine is broken down to monoethylglycinxylidide (MEGX) and acetaldehyde through microsomal oxidative N-dealkylation, MEGX is converted into 2,6-xylidine and N-ethylglycine through microsomal hydrolysis; 2,6-xylidine is metabolised either to 2-amino-3-methylbenzoic acid or through microsomal oxidation to 4-hydroxy-2,6-xylidine. The latter is the main metabolite, up to 73 % of lidocaine is excreted in this form;

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

The half-life of lidocaine is approximately 3 hours; lidocaine crosses the placental barrier, the half-life in the foetus is approximately 4 hours.

The substances chlorhexidine gluconate and the 4-hydroxybenzoates contained in very small quantities in Instillagel can also be absorbed to a minimal extent via the mucosa or can be transported directly into the bloodstream in small quantities via small lesions.

Chlorhexidine, which is barely absorbed even when administered at high oral doses, is eliminated practically unchanged. Following hydrolysis, the 4-hydroxybenzoates are excreted in the form of 4-hydroxybenzoic acid or its derivatives.

5.3. Preclinical safety data

Acute toxicity – systemic toxicity
Acute toxicity tests of lidocaine in the animal model revealed an LD50 between 22 mg/kg BW and 48 mg/kg BW in mice. In rats, the values range between 21 and 25 mg/kg BW.

The toxic plasma concentrations or seizure threshold dose established in humans has been indicated as 5 µg/ml to > 10 µg/ml blood plasma.

Acute toxicity – local toxicity
Animal experiments on local toxicity have not been conducted. The local tolerability of the finished medicinal product Instillagel in humans is very good.

Chronic toxicity
Subchronic toxicity studies of lidocaine following local administration to animals (rats, dogs) revealed fattening of the liver with peripheral and perilobular distribution at a dose of 30 mg/kg BW in dogs (374), which is attributed to the effect of lidocaine.

Chronic toxicity studies of lidocaine in rats for a period of 6 months at doses of 6 mg/kg BW revealed no evidence of pathological changes attributable to lidocaine.

Mutagenic and carcinogenic potential
There is evidence to suggest that a metabolic breakdown product of lidocaine/etidocaine, 2,6-xylidine, that is formed in rats, but possibly also in humans, might have mutagenic effects. This evidence was established in in-vitro tests in which this metabolite was used in very high, nearly toxic concentrations. There is currently no evidence that the parent substances lidocaine and etidocaine themselves are also mutagenic.

In a carcinogenicity study with transplacental exposure and postnatal treatment of the animals for 2 years with 2,6-xylidine in rats, malignant and benign tumours, especially in the nasal cavity (ethmoturbinals), were observed in a highly sensitive test system (transplacental exposure and postnatal treatment of the animals for 2 years with very high doses). It is not altogether unlikely that these findings are relevant for humans. For this reason Instillagel should not be administered at high doses for a prolonged period.

Reproductive toxicity
Lidocaine crosses the placental barrier. The values measured in the foetus are 0.4-1.3-fold higher than the maternal serum concentration.
Previous experience in humans with the use of lidocaine as a local anaesthetic in the first three months of pregnancy (approx. 290 mother-child pairs) revealed no evidence of an increase in the rate of malformations. However, neurological behavioural changes in the neonate have been reported. The use of lidocaine for paracervical nerve blocks or as epidural anaesthesia can lead to bradycardia in the foetus.

Reproductive toxicology studies in rats showed no evidence for a teratogenic potential at doses of up to 56 mg/kg BW per day.
Behavioural changes have been described in prenatally exposed offspring.

6. PHARMACEUTICAL PARTICULARS

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

6.2. Incompatibilities
None 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 25˚C.
Store this medicinal product in a safe place. Keep away from children!

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

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

6.6. Special precautions for disposal

Once open, use the single-use syringe immediately and discard residual gel.

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

8. REGISTRATION HOLDER
Propharm Ltd.
P.O.Box 4046
Zichron Yaacov 30900
Israel

9. REGISTRATION NUMBER
160-11-35080-00

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