SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Instillido 20 mg/ml gel in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml gel contains 20.1 mg lidocaine hydrochloride equivalent to 21.5 mg lidocaine hydrochloride monohydrate.

Each pre-filled syringe with 6 ml gel contains 120.6 mg lidocaine hydrochloride.

Each pre-filled syringe with 11 ml gel contains 221.1 mg lidocaine hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

Gel
Clear, nearly colourless, sterile gel.
The pH of the gel is 6.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Instillido is intended for surface anaesthesia and lubrication for:

- the male and female urethra during cystoscopy, catheterisation, sonography and other endourethral procedures;
- proctoscopy and rectoscopy;
- symptomatic treatment of pain in connection with cystitis.

Instillido is indicated in adults, adolescents and children from 2 years of age.

4.2 Posology and method of administration

When Instillido is used concomitantly with other products containing lidocaine, the total dose contributed by all formulations must be taken into consideration.

The following dosage recommendations should be regarded as a guide.

The dose must be individually adjusted by an experienced physician.

The dosage varies and depends upon the area to be anaesthetised, the vascularity of the tissues, individual tolerance and the technique of anaesthesia. The lowest dosage that results in effective anaesthesia should be used to avoid high plasma levels and serious undesirable effects.

Anaesthesia is achieved within 5 - 15 minutes, depending on the area of application. The duration of anaesthesia is approximately 20 to 30 minutes.

Posology

Adults

Urethral anaesthesia

Male patients

For adequate analgesia in males, 20 ml gel (approximately 400 mg lidocaine hydrochloride) is usually required. The gel is instilled slowly into the urethra until the patient has a feeling of tension (approximately 10 ml). A penile clamp is then applied for at least 5 minutes at the corona, after which the rest of the gel is instilled.

When anaesthesia is especially important, e.g. for sonography or cystoscopy, 10-20 ml (approximately 200-400 mg lidocaine hydrochloride) are instilled. If adequate analgesia is not achieved, re-administration of 10-20 ml (approximately 200-400 mg lidocaine hydrochloride) is possible. The maximum dose of approximately 800 mg lidocaine hydrochloride must not be exceeded.

To anaesthetise only the anterior male urethra, e.g. for catheterisation (including self-catheterisation), small volumes (5-10 ml, i.e. approximately 100-200 mg lidocaine hydrochloride) are usually adequate for lubrication.

Female patients

In women, the amount of gel instilled is adapted to the individual urethra anatomy.

Usually, 5-10 ml of gel (approximately 100-200 mg lidocaine hydrochloride) are instilled in small portions to fill the whole urethra. If desired, some gel may be applied to the urethral orifice and spread with a cotton swab. In order to obtain adequate anaesthesia, at least 5 minutes should be allowed prior to performing urological procedures.

Symptomatic treatment of pain in connection with cystitis

For adequate analgesia, 10-20 ml of gel (approximately 200-400 mg lidocaine hydrochloride) is usually required.

At the beginning of the treatment, the gel is usually administered once a day for one week. Subsequently, the physician decides on the frequency and duration of use based on the patient's symptoms and condition. The maximum dose is 20 ml (approximately 400 mg lidocaine hydrochloride) once a day.

Proctoscopy and rectoscopy

Instillation of 10-20 ml gel (approximately 200-400 mg lidocaine hydrochloride) is recommended for adequate analgesia and a small amount should be applied to lubricate the endoscope. When combined with other lidocaine products, the total dose of lidocaine hydrochloride should not exceed approximately 400 mg.

The degree of absorption is particularly high in the rectum.

Maximum dosage

Adults

The dose depends on the application site. A safe dose for use in the urethra and bladder is 40 ml gel (approximately 800 mg lidocaine hydrochloride). The maximum recommended daily dose for adults is approximately 800 mg lidocaine hydrochloride.

Paediatric population

Children < 2 years of age
Instillido is contraindicated in children < 2 years of age (see section 4.3).

Children (2-12 years) and adolescents (above 12 years of age)
In children (2-12 years) and adolescents (above 12 years of age), the effect of lidocaine hydrochloride gel is not well demonstrated and therefore its use should be assessed by the physician. Specific dosage recommendations cannot be given for these groups of patients, but as a general rule, the amount of gel instilled is adapted to the individual urethra anatomy.

The systemic absorption of lidocaine can be increased in children and caution is accordingly required.

In general, the maximum dose of 2.9 mg/kg lidocaine hydrochloride should not be exceeded in children aged 2 to 12 years (Table 1).

Table 1: Maximum amount of Instillido calculated according to body weight

Weight [kg body weight]	**Maximum dose [ml] Instillido**
7-13	1 ml
14-20	2 ml
21-27	3 ml
28-34	4 ml
35-41	5 ml
42-48	6 ml
49-55	7 ml
56-62	8 ml
63-69	9 ml

Special populations

Renal or hepatic impairment
Due to the extensive first-pass metabolism in the liver and its excretion via the kidney, lidocaine doses must be reduced in patients with renal or hepatic impairment to prevent potential metabolite accumulation (see section 4.4).

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 (see section 4.4).

The maximum dose of 2.9 mg/kg lidocaine hydrochloride should not be exceeded in these special populations.

Method of administration

The pre-filled graduated syringes are available with 6 ml or 11 ml gel.

Each graduation on the syringe is equivalent to approximately 1 ml of gel (20.1 mg lidocaine hydrochloride).

For urethral use

Instructions for use:

The blister package contains a sterile syringe. Do not open the blister pack until ready to use.

1. Clean and disinfect the external urethral orifice.
2. When ready to use, open the blister and drop the syringe onto a sterile field.
3. Before removing the tip cap, press it against a finger or other solid object. Press in the plunger to remove any resistance that may be present. This helps ensure that the syringe will empty easily and uniformly.
4. Remove the tip cap from the syringe. The syringe is now ready for use.
5. The gel should be instilled slowly and evenly into the urethra.
6. Wait for a few minutes after instillation of the gel for the anaesthetic to take full effect. The full anaesthetic effect will occur within 5 to 15 minutes after complete instillation.

For other treatments or procedures/examinations

(intravesical, rectal)

Instructions for use:

1. When ready to use, open the blister and drop the syringe onto a sterile field.
2. Before removing the tip cap, press it against a finger or other solid object. Press in the plunger to remove any resistance that may be present. This helps ensure that the syringe will empty easily and uniformly.
3. Remove the tip cap from the syringe. The syringe is now ready for use.
4. The full anaesthetic effect will occur within 5 to 15 minutes after complete instillation.

Any gel not been used in a single application must be discarded.

4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
- Hypersensitivity to local anaesthetics of the amide type.
- Children under 2 years.

4.4 Special warnings and precautions for use

Excessive absorption

Excessive dosage or short intervals between doses can lead to high plasma levels and serious undesirable effects. Patients should be instructed to adhere strictly to the recommended dosage and administration guidelines (the management of serious adverse reactions may require the use of resuscitative equipment, oxygen and other resuscitative drugs)

Absorption from wound surfaces and mucous membranes is relatively high. Because of the possibility of significant systemic absorption with an increased risk for toxic symptoms, such as seizures, Instillido should be used with caution in patients with traumatised mucosa and/or sepsis in the region of the proposed application.

If more than the recommended amount is instilled during urethral anaesthesia and a significant amount of the gel penetrates into the bladder, or if the urethra is inflamed and/or ulcerating, this can generally lead to increased absorption of lidocaine and consequently to overdose with

central nervous and cardiovascular undesirable effects (see also section 4.9), especially in children and elderly patients.

If the dose or administration is likely to result in high blood levels, some patients require special attention to prevent potentially dangerous side effects:

- Elderly patients, patients in poor general health and patients with sepsis (see section 4.2);
- Patients with epilepsy;
- Patients with bradycardia or impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by local anaesthetics of the amide type;
- Patients with heart failure or AV block;
- Patients with shock;
- Patients with impaired renal function and hepatic disease (see section 4.2);
- Patients with respiratory dysfunction;
- Patients suffering from myasthenia gravis, as they are particularly sensitive to local anaesthetics.

Class III antiarrhythmic drugs

Patients treated with class III antiarrhythmic drugs (e.g. amiodarone) should be under close surveillance and ECG monitoring should be considered since cardiac effects may be additive (see section 4.5).

Methaemoglobinaemia

Cases of methaemoglobinaemia have been reported in association with local anaesthetic use. Patients with glucose-6-phosphate dehydrogenase deficiency, hereditary or idiopathic methaemoglobinaemia are more susceptible to active substance-induced signs of methaemoglobinaemia. In patients with glucose-6-phosphate dehydrogenase deficiency, the antidote methylene blue is ineffective in reducing methaemoglobin, and is itself capable of oxidising haemoglobin, and therefore methylene blue therapy cannot be given.

Porphyric patients

Lidocaine is pssibly porphyrinogenic and should only be used in patients with acute porphyria if strongly or urgently indicated while being closely monitored. Appropriate precautions should be taken for all porphyric patients

4.5 Interaction with other medicinal products and other forms of interactions

Pharmacodynamic interactions

Local anaesthetics and agents structurally related to amide-type local anaesthetics
Instillido should not be used in patients receiving lidocaine or other local anaesthetics or agents structurally related to amide-type local anaesthetics since the toxic effects are additive.

Antiarrhythmic drugs
Class I antiarrhythmic drugs (such as mexiletine) should be used with caution since toxic effects are additive and potentially synergistic.

Specific interaction studies with lidocaine and Class III antiarrhythmic drugs (e.g. amiodarone) have not been performed, but caution is advised (see section 4.4).

Due to possible additive effects on the heart, lidocaine must be used with caution in patients receiving other antiarrhythmic drugs such as beta-blockers (e.g. propranolol, metoprolol) or calcium channel antagonists (e.g. diltiazem, verapamil).

Pharmacokinetic interactions

Beta-receptor blockers, cimetidine

Beta-receptor blockers (e.g. propranolol, metoprolol (see also above) and cimetidine (see also below)) reduce cardiac output and/or hepatic blood flow and therefore reduce the plasma clearance of lidocaine, prolonging its elimination half-life. Due account should therefore be taken of the possibility of accumulation of lidocaine.

Inhibitors of CYP 3A4 and/or CYP 1A2

Concurrent administration of lidocaine with inhibitors of CYP 3A4 and/or CYP 1A2 may lead to increased plasma concentrations of lidocaine. Increased plasma levels have been reported for e.g. erythromycin, fluvoxamine, amiodarone, cimetidine and protease inhibitors (e.g. ritonavir).

When lidocaine is used topically, plasma concentrations are of importance for safety reasons (see section 4.4). However, when Instillido is used according to the dosage recommendations, the systemic exposure is low and therefore the above-mentioned metabolic interactions are not expected to be of clinical significance.

Methaemoglobinaemia

Methaemoglobinaemia may be accentuated in patients already taking methaemoglobin-inducing medicinal products (e.g. sulphonamides, nitrofurantoin, phenytoin, phenobarbital). This list is not exhaustive. See also section 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of lidocaine in pregnant women. Lidocaine crosses the placenta. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at exposures relevant for topical application of lidocaine (see section 5.3). The use of Instillido may be considered during pregnancy if clinically needed.

Breastfeeding

Lidocaine is excreted in breast milk, but at therapeutic doses of Instillido no effects on breastfed newborns/infants are anticipated.

Fertility

There are no data on the effect of lidocaine on fertility in humans. Animal studies have shown no impairment of the fertility in male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Effects on the ability to drive and use machines are unlikely, but cannot be completely ruled out in cases of increased individual sensitivity.

4.8 Undesirable effects

Summary of the safety profile
Undesirable effects are unlikely to occur after the use of Instillido as long as the medicinal product is used as recommended and the necessary precautions are taken (see sections 4.2 and 4.4).

Tabulated list of adverse reactions

Frequency categories are defined according to the following convention:
Very common (≥1/10)
Common (≥1/100, <1/10)
Uncommon (≥1/1.000, <1/100)
Rare (≥1/10.000, <1/1.000)
Very rare (<1/10.000)
Not known (cannot be estimated based on available data)

System organ class	**Adverse reaction**	**Frequency**
Immune system disorders	Hypersensitivity, anaphylactic reaction, contact dermatitis	Rare
General disorders and administration site conditions	administration site irritation	Very rare

Lidocaine may cause symptoms of systemic undesirable effects or acute toxicity if high plasma levels occur as a result of rapid absorption or overdose (see sections 4.9 Overdose and 5.1 Pharmacodynamic properties).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Healthcare professionals are asked to report any suspected adverse reactions to the Federal Institute for Drugs and Medical Devices, Pharmacovigilance Department, Kurt-Georg-Kiesinger-Allee 3, D-53175 Bonn, website: www.bfarm.de.

4.9 Overdose

Symptoms

If symptoms of systemic toxicity occur, these are of the same nature as those that occur after administration of local anaesthetics by other routes of administration.

Overdose may manifest as a transient stimulation of the central nervous system with the following early symptoms: yawning, restlessness, dizziness, nausea, vomiting, dysarthria, ataxia, hearing and vision disorders. Moderate toxicity can also cause muscle twitching and seizures. This can be followed by loss of consciousness, respiratory depression and coma. With very severe toxicity, due to reduced contractility of the myocardium and delayed stimulation conduction, hypotension and cardiovascular collapse can be expected, followed by complete heart block and cardiac arrest.

Treatment of acute toxicity

If signs of acute toxicity occur during administration of the local anaesthetic, administration of the anaesthetic should be stopped immediately.

CNS symptoms (seizures, CNS depression) must be treated promptly with appropriate airway and respiratory support and the administration of anticonvulsant drugs.

In case of circulatory arrest, immediate cardiopulmonary resuscitation should be initiated.

Optimal oxygenation, ventilation and circulatory support as well as treatment of acidosis are of vital importance.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous system, anaesthetics, local, amides
ATC code: N01BB02

Instillido is a sterile gel for topical mucosal anaesthesia.

Mechanism of action/pharmacodynamic effects

Lidocaine is a local anaesthetic of the amide type.

Instillido causes immediate and deep anaesthesia of the mucous membranes. In endoscopy and catheterisation, it also increases the lubricity of the materials to be inserted.

Instillido is particularly indicated for urethra anaesthesia. The anaesthetic effect usually occurs rapidly (within 5 minutes, depending on the area of application).

The local anaesthetic effect of lidocaine is based on inhibition of Na^+ influx into nerve fibres by blocking the voltage-dependent Na^+ channels. As the effect depends on the pH of the surrounding milieu (presence of the active substance as an uncharged base or as a cation), the efficacy of lidocaine is reduced in an inflamed area.

Local anaesthetics can have similar effects on excitable membranes in the brain and myocardium. If large amounts reach the systemic circulation rapidly, central nervous and cardiovascular toxicity symptoms and signs will occur.

5.2 Pharmacokinetic properties

Absorption

Lidocaine may be absorbed following topical application to mucous membranes, with the rate of absorption and amount of the dose absorbed dependent upon the concentration and total dose administered, the specific site of application and the duration of exposure. In general, the rate of absorption of local anaesthetic agents following topical application to wound surfaces and mucous membranes is high.

Blood concentrations of lidocaine after instillation of the gel in the intact urethra and bladder in doses of up to approx. 800 mg are fairly low and below the levels at which systemic effects or toxicity are likely to occur.

Lesions of the urethral mucosa and/or surface enlargement due to urethral dilation can lead to increased absorption of lidocaine.

Distribution

When lidocaine is given intravenously to normal subjects, the volume of distribution is 0.6 to 4.5 1/kg. The volume of distribution may be altered in patients suffering from further diseases such as cardiac, hepatic or renal insufficiency.

The plasma protein binding of lidocaine is dependent on the drug concentration and the bound fraction decreases with increasing concentration. At concentrations of 1 to 4 micrograms of free base per ml, 60-80% of lidocaine is protein-bound. Binding is also dependent on the plasma concentration of acid alpha-1-glycoprotein (AAG), an acute phase protein that binds free lidocaine. After trauma, surgery or burns, depending on the pathophysiological condition of the patient, the AAG concentration may be increased, resulting in an increase in lidocaine plasma protein binding, while in neonates and patients with impaired hepatic function, AAG concentrations are low, leading to a marked reduction in lidocaine plasma protein binding.

Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion.

Biotransformation

Lidocaine undergoes pronounced first-pass metabolism. In total, about 90 % of lidocaine is metabolised to 4-hydroxy-2,6-xylidine, to 4-hydroxy-2,6-xylidine glucuronide and to a lesser degree, to the active metabolites monoethyl glycine xylidide (MEGX) and glycine xylidide (GX). The pharmacological/toxicological effects of MEGX and GX are similar to, but less potent than, those of lidocaine. Lidocaine and its metabolites are predominantly excreted via the kidney.

Elimination

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 perfusion and the activity of metabolising enzymes. Approximately 90 % of lidocaine administered intravenously is excreted in the form of various metabolites, and less than 10 % is excreted unchanged in the urine. The main metabolite in urine is a conjugate of 4-hydroxy-2,6-dimethylaniline, accounting for about 70-80% of the dose excreted in urine.

Special populations

The half-life may be prolonged two-fold or more in patients with liver dysfunction. In patients with severe heart failure, the elimination half-life may be prolonged. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites.

5.3 Preclinical safety data

Safety pharmacology

In animal studies, the toxicity reported after administration of high doses of lidocaine caused effects on the central nervous system and the cardiovascular system.

Genotoxicity and carcinogenic potential

Genotoxicity tests with lidocaine showed no evidence of mutagenic potential. However, 2,6-xylidine, a minor metabolite of lidocaine, has shown genotoxic potential *in vitro* and *in vivo.*

Carcinogenicity studies have not been performed with lidocaine. 2,6-Xylidine has been shown to have carcinogenic potential (nasal and subcutaneous tumours as well as an increased rate of liver tumours) in preclinical toxicological studies evaluating chronic exposure in rats. High doses of 2,6-xylidine were needed to induce tumours in animal studies. The clinical relevance of the tumour-inducing effect of this lidocaine metabolite after intermittent use as a local anaesthetic is unknown.

Toxicity to reproduction and development

Lidocaine had no effect on embryo-foetal development/teratogenicity in reproduction studies performed in rats at doses of up to 500 mg/kg/day lidocaine. In studies of reproductive toxicity, eembryotoxic or foetotoxic effects of lidocaine were detected at doses of 25 mg/kg s.c. in the rabbit. Impairment of the fertility of male or female rats by lidocaine was not observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Sodium hydroxide (for pH adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Keep the blisters in the outer carton in order to protect from light.

6.5 Nature and contents of container

Instillido is available as a sterile pre-filled syringes containing 6 ml or 11 ml gel.

The syringes are composed of a syringe barrel 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.

Each graduation on the syringe is equivalent to approximately 1 ml of gel (20.1 mg lidocaine hydrochloride).

Pack sizes
10 pre-filled syringes with 6 ml gel each
10 pre-filled syringes with 11 ml gel each

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The product is for single use only.
The syringe and any unused gel should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

FARCO-PHARMA GmbH
Gereonsmühlengasse 1-11
50670 Cologne

8. MARKETING AUTHORISATION NUMBER(S)

2205650.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 March 2022

10. DATE OF REVISION OF THE TEXT

05/2023