Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lidocaine 20 mg/ ml (2% w/v) solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection contains 20 mg of lidocaine hydrochloride (as lidocaine hydrochloride monohydrate).
Each 10 ml pre-filled syringe contains 200 mg of lidocaine hydrochloride (as lidocaine hydrochloride monohydrate).

Excipient with known effect:

Each ml of solution for injection contains 2.3 mg equivalent to 0.10 mmol of sodium.
Each 10 ml pre-filled syringe contains 23 mg equivalent to 1.0 mmol of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).
Clear and colorless solution
pH: 5.0 to 6.5
Osmolality: 270-330 mOsm/Kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lidocaine is indicated in infiltration anaesthesia and peripheral nerve block anaesthesia.
Lidocaine 20 mg/ml (2 % w/v) is indicated for adults.

4.2 Posology and method of administration

Lidocaine should only be used by or under the supervision of, doctors with experience of regional anaesthesia and resuscitative skills. Facilities for resuscitation should be available when administering local anaesthetics.

Posology

The lowest concentration and smallest dose producing the required effect should be given.

Adults

The dose should be adjusted according to the response of the patient, the site of administration, and the expected duration of the surgical procedure.
It should be considered that usual total dose of lidocaine is 3–5 mg/kg; corresponding to volumes of 2 to 20 mL (at 10 mg/ml) and 1 to 10 mL (at 20 mg/ml).

The generally maximum recommended total dose of lidocaine should not exceed 200 mg in adults for infiltration and peripheral nerve block, but depending on the procedure and patient factors, higher maximum doses may be required.

The volume of the solution used plays a role in the size of the area of spread of anaesthesia.

Special populations

Elderly
For elderly patients, the doses are calculated individually according to the patients' age and body weight. Doses may need adaptation as cardiac output and hepatic blood flow decrease with advanced age indicating a decreased clearance of lidocaine (see section 5.2).

Patients with renal impairment
Patients should be monitored as renal impairment may cause toxic effects due to the accumulation of active metabolites (see section 4.4 and 5.2). The dose may need to be adapted due to reduced clearance and increased half-life of lidocaine.

Patients with hepatic impairment
The dose may need to be reduced by up to a half in patients with cardiac or hepatic insufficiency (see section 4.4).

Patients with cardiac insufficiency
The dose may need to be reduced by up to a half in patients with cardiac or hepatic insufficiency (see section 4.4).

Other special population
Doses may need to be reduced in patients with poor general condition or in those with reduced protein binding capacity (resulting e.g. from renal insufficiency, liver insufficiency, cancer, pregnancy).

Paediatric population

Lidocaine should not be used in children younger than two years of age as there are limited data to support the safety and efficacy of this medicinal product in this patient population at this time.

Special care has to be exercised when treating children between 2 and 4 years.

Only the low strength (10 mg/ml) should be used.

The doses are calculated individually according to the patients' age, body weight and the nature of the procedure. The usual dosage for children (above 2 years of age) is 3-4 mg/kg body weight of a 10 mg/ml solution. For calculation, the average age weight is to be considered for overweight children.

For small children, the administered dose may represent a volume of less than half syringe. In small children, the required dose not exceeding 3-4 mg/kg should be calculated and the excess dose must be emptied from the syringe prior to injection in the child. For the dose remaining in the syringe, slow incremental injections are recommended.

Method of administration

Infiltration (intradermal, subcutaneous, or submucosal use) injection into the surroundings of peripheral nerves.
Lidocaine is a ready to administer pre-filled syringe which is not designed for administration with an electronic syringe pump (for continuous infusion or patient controlled repeated bolus epidural administration).

4.3 Contraindications

- Hypersensitivity to the active substance, amide-type local anaesthetics or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Lidocaine should be used with caution in patients with:

- epilepsy: patients with cerebral seizure disorders must be monitored very closely for manifestation of central nervous symptoms. Also low doses of lidocaine can cause increased convulsive readiness.
- renal or liver insufficiency;

- myasthenia gravis;
- block of the cardiac conduction system due to the fact that local anaesthetics may suppress atrioventricular conduction;
- patients with reduced cardiovascular function;
- bradycardia;
- respiratory depression;
- the elderly and generally debilitated patients.
- coagulopathy or treatment with anticoagulants (eg. Heparin), NSAIDs or plasma substitutes as accidental injury of blood vessels may lead to serious bleedings.

Inadvertent intravascular administration or overdoses may cause high lidocaine blood concentrations responsible for acute central nervous and cardiovascular toxic symptoms.

Accidental intravascular injections in the head and neck areas may cause cerebral symptoms even at low doses.

Caution should also be exercised if the local anaesthetic is to be injected into inflamed (infected) tissue because of increased systemic absorption due to higher blood flow and decreased effect due to the lower pH of infected tissue.

There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anaesthetics. The majority of reported cases of chondrolysis have involved the shoulder joint. Due to multiple contributing factors and inconsistency in the scientific literature regarding mechanism of action, causality has not been established.

Paracervical block can sometimes cause foetal bradycardia or tachycardia and careful monitoring of the foetal heart rate is necessary (see section 4.6).

This medicinal product contains sodium
This medicine contains 1.0 mmol (23 mg) sodium per syringe , equivalent to 1.2 % of the WHO recommended maximum daily intake of 2g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Class I antiarrhythmics
Simultaneous administration of lidocaine and other class I antiarrhythmics should be avoided because of the risk that serious cardiac adverse effects occur.

Other anti-arrhythmics
If lidocaine is combined with other anti-arrhythmic medicinal products such as beta receptor blockers or calcium channel blockers, the inhibitory effect on atrioventricular and intraventricular conduction and on contractility may be enhanced.

Combination with other local anaesthetics
Combination of different local anaesthetics may lead to additive effects on the cardiovascular and the central nervous system.

Muscle relaxants
The effect of muscle relaxants (e.g. Suxamethonium) is prolonged by lidocaine.

Sedatives, hypnotics
Lidocaine should be administered with due caution to patients receiving medication with sedatives that also affect the function of the CNS and therefore may alter the toxicity of lidocaine. There may be an additive effect between the local anaesthetic effect and sedatives or hypnotics.

Volatile anaesthetics
If lidocaine and volatile anaesthetics are given simultaneously, the depressive effects of both may be intensified.

Medicinal products that can lower the seizure threshold

As lidocaine itself may reduce the seizure threshold co-administration with other medicinal products lowering the seizure threshold (e.g. tramadol or bupropion) may increase the risk of seizures.

Medicinal products that can raise the seizure threshold
Simultaneously administered diazepam raises the threshold for Lidocaine to produce convulsions. This must be kept in mind when monitoring patients for signs of toxicity of Lidocaine.

Vasoconstrictors:
The local anaesthetic effect is prolonged by combination with a vasoconstrictor, e.g. epinephrine. If lidocaine is given as antiarrhythmic agent, additional medication with epinephrine or norepinephrine may lead to potentiation of the cardiac undesirable effects.

Pharmacokinetic interactions

Lidocaine is mainly metabolized via the cytochrome P 450 isoenzymes CYP 3A4 and CYP 1A2 (see section 5.2). Concomitant administration with active substances that are substrates, inhibitors or inducers of hepatic enzymes, isoenzyme CYP3A4 and CYP1A2, may have an influence on the pharmacokinetics of lidocaine and thus also on its effect.

Inhibitors of CYP 3A4 and/or CYP 1A2

Concurrent administration of lidocaine with inhibitors of CYP3A4 and/or CYP1A2 may lead to accelerated plasma concentrations of lidocaine. Increased plasma levels have been reported for e.g:

- Amiodarone (CYP3A4 inhibitor): Amiodarone decreases hepatic metabolism of lidocaine, thus leading to the risk of increase of lidocaine levels, with subsequent increase of neurological and cardiovascular toxicity. Clinical monitoring, ECG and eventually control of plasma concentration of lidocaine should be performed. If needed dosage of lidocaine should be monitored during and after amiodarone therapy.
- Cimétidine (CYP3A4 and CYP1A2 inhibitor): Cimetidine used at doses equal or higher than 800 mg/day: increase of plasma concentration of lidocaine with subsequent increase of neurological and cardiovascular toxicity. Clinical survey, ECG and eventually control of plasma concentration of lidocaine should be performed. If needed dosage of lidocaine should be monitored during and after cimetidine therapy.
- Fluvoxamine (CYP3A4 and CYP1A2 inhibitor): Increase of lidocaine levels, thus enhancing risk of neurological and cardiovascular toxicity. Clinical monitoring, ECG and eventually control of plasma concentration of lidocaine should be performed. If needed dosage of lidocaine should be monitored during and after the association.
- Betablockers (except esmolol): Lidocaine intravenous: increase of lidocaine levels, with subsequent increase of neurological and cardiovascular toxicity. Clinical monitoring, ECG and eventually control of plasma concentration of lidocaine should be performed. If needed dosage of lidocaine should be monitored during and after betablockers therapy.
- Other known inhibitors of CYP3A4: protease inhibitors (e.g. ritonavir), macrolides antibiotics (e.g. erythromycine), antifungals (e.g. ketoconazole, itraconazole).
- Other known inhibitors of CYP1A2: ciprofloxacin.

Inducers of CYP 3A4 and/or CYP 1A2

Active substances inducing CYP3A4 and/or CYP 1A2 such as barbiturates (mainly phenobarbital), carbamazepine, phenytoin or primidone, accelerate the plasmatic clearance of lidocaine and thus reduce the efficacy of lidocaine.

Other pharmacokinetic interactions

Medicinal products that alter the metabolism, hepatic blood flow, cardiac output or peripheral distribution of lidocaine may influence plasma levels of lidocaine.

Medicinal products that cause hypokalaemia
The electrophysiological effects of lidocaine are highly dependent on the extracellular potassium concentration and can be almost completely blocked by hypokalemia. Concomitant use of medicinal products that can cause severe hypokalemia (e.g. acetazolamide, loop diuretics and thiazides) should therefore be avoided or used under careful monitoring of serum potassium concentration.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of lidocaine in pregnant women.
Lidocaine passes the placenta (see section 5.2). It is reasonable to assume that a large number of pregnant women and women of child-bearing age have been given lidocaine. No specific disturbances to the reproductive process have so far been reported, e.g., no increased incidence of malformations, or direct or indirect effect on the foetus. However, the risks for humans are not completely investigated.

Animalstudies have shown reproductivetoxicity (seesection 5.3).

In short term use during pregnancy and at delivery the benefits should be weighed against the risks. Paracervical blockade or pudendal blockade with lidocaine increases the risk of reactions such as bradycardia/tachycardia in the foetus. The heart rate of the foetus must therefore be carefully monitored.

Lactation

Lidocaine is excreted into human breastmilk in small amounts. The use of lidocaine at recommended doses is unlikely to affect the breast-fed child. Breast-feeding can therefore be continued during treatment with lidocaine.

Fertility

No human data on the effect of lidocaine on fertility are available.

4.7 Effects on ability to drive and use machines

Lidocaine may have influence on the ability to drive and use machines. After injection of local anaesthetics a transient sensory loss and/or motor blockade, may occur. Until the effects subside patients should not drive vehicles or use machines.

4.8 Undesirable effects

Summary of the safety profile

The frequency and severity of the undesirable effects of lidocaine depend upon the dose, the method of administration and the patient's individual sensitivity.

The undesirable effects related to local anaesthetics are rare in the absence of an overdose, abnormal rapid systemic absorption or accidental intravascular injection; in such cases, they can be very serious, in particular in terms of cardiac and neurologic function.

Adverse reactions caused by lidocaine may be difficult to distinguish from the physiological effects of the nerve block (e.g. hypotension, bradycardia), events caused directly (e.g. neurological lesions) or indirectly by needle puncture.

Symptoms of local toxicity may occur after the administration of lidocaine. Systemic adverse effects may be expected at plasma concentrations of lidocaine exceeding 5-10 mg/l. They become manifest in the form of both CNS symptoms and cardiovascular symptoms.

The possible undesirable effects after administration of lidocaine as local anaesthetic are largely the same as those produced by other amide-type local anaesthetics

Tabulated list of adverse reactions

The adverse reactions listed in this section fall in to 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).

The following table lists adverse reactions associated with the use of lidocaine as anaesthetic.

System Organ Class	Very Common	Common	Uncommon	Rare	Very rare	Frequency Not known
Blood and lymphatic system disorders						Methaemo-globinaemia
Immune system disorders				allergic reaction*, anaphylactoid reactions, bronchospasm, and in severe cases anaphylactic shock		
Nervous system disorders		Paresthesia, loss of consciousness. Transient neurological symptoms.		Neuropathy, convulsions (overdose) persistent anaesthesia, paresis, headache accompanied by tinnitus and photophobia. Cranial nerve lesions, neurosensory deafness. Regional applications in the thoracic or head/neck region may induce sympathetic blockade resulting in transient symptoms such as Horner's syndrome, Harlequin syndrome.		
Cardiac disorders		bradycardia		Arrhythmia, myocardial depression or possibly cardiac arrest (overdose or inadvertent intravascular injection)		
Eye disorders				Double vision		
Respiratory, thoracic and mediastinal disorders				Respiratory depression		
Vascular disorders		hypotension, hypertension				
Gastrointestinal disorders	nausea	vomiting				
Skin and subcutaneous tissue disorders				rash , urticaria, oedema		

* Skin testing for allergy to lidocaine is not considered to be reliable

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Other special populations

In elderly patients the incidence of undesirable effects may be increased.

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 via
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Depending on the individual sensitivity, toxic reactions occur from a concentration of approximately 5 - 10 mg lidocaine per litre upward in venous blood.

The lethal plasma concentration for humans is in the range 6 to 33 mg lidocaine per litre.

An overdose, or an accidental intravascular injection can produce excessive plasma concentrations of lidocaine; this results in signs of acute toxicity, which can lead to very serious undesirable effects. The toxic effects of lidocaine depend on the level of the plasma concentration; the higher the plasma concentration and the more rapid its rise, the more frequent and more serious are the toxic reactions. Such toxic reactions concern the central nervous system and the cardiovascular system.

Symptoms

Low toxic overdoses of lidocaine result in stimulation of the CNS. Gross overdose, producing high toxic plasma concentrations, causes depression of the central functions.

Central nervous system toxicity is a graded response with symptoms and sign of escalating severity.

Initially, symptoms are observed such as: dizziness, vertigo, agitation, hallucination, euphoria, apprehension, yawning, logorrhoea, headaches, nausea, vomiting, labial paraesthesia, numbness of the tongue, tinnitus and dysarthria, impaired hearing and vision.

Other subjective central nervous system symptoms include: disorientation, occasional feeling of drowsiness. Tachycardia, hypertension and flushing have also been reported.

These signs of alarm necessitate attentive surveillance : muscular twitching, tremors, shivering, and generalised seizures. Simultaneously administered diazepam raises the threshold for lidocaine to produce convulsions. This must be kept in mind when monitoring patients for signs of toxicity of lidocaine.

In cases of very high dose administered: generalised depression of central nervous system, respiratory depression, coma and respiratory arrest.

Cardiovascular toxicity may be seen in severe cases : cardiac rhythm disorders such as ventricular extrasystole, ventricular fibrillation, unpalpable pulse, pallor, major bradycardia, disorders of atrioventricular conduction, decrease in cardiac contractility, hypotension and cardiac arrest.

Treatment

If signs of acute toxicity occur during administration of the local anaesthetic, administration of the anaesthetic should be stopped immediately. Intravenous fluid should be given in order to prevent hypoxia and acidosis, which potentiate local anaesthetic systemic toxicity (LAST) and exacerbate progression to cardiovascular collapse and seizure.

If convulsions occur, oxygenation should be maintained and circulation should be supported. If required, an anticonvulsant should be administered. Use of intravenous lipid emulsion should be considered.

If cardiovascular depression is evident (hypotension, bradycardia) treatment with intravascular fluid substitution, vasopressoric, chronotropic and/or inotropic drugs should be taken in consideration.

In case of circulatory arrest, immediate cardiopulmonary resuscitation should be initiated. For a successful outcome prolonged resuscitative efforts may be required.

Patients having manifested signs of LAST should be monitored for at least 12 hours, because cardiovascular depression can persist or recur after treatment.

Centrally acting analeptics are contra-indicated.

There is no specific antidote.

Lidocaine cannot be eliminated by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group Anaesthetics, local, amides: ATC code: N01B B02

Lidocaine is a local anaesthetic agent of the amide type.

Lidocaine reduces the permeability of cell membranes for cations, in particular sodium ions, at higher concentrations also for potassium ions. This leads, depending on the concentration of lidocaine, to reduced excitability of the nerve fibres because the increase of sodium permeability producing the action potential is slowed down. From inside the cell the lidocaine molecule enters the open sodium channel and blocks it by binding to a specific receptor. A direct effect of incorporation of lidocaine in the cell membrane is much less relevant.

Because lidocaine, before reaching its site of action, must pass into the cell, its effect depends on its pKa and on the environmental pH, i.e. on the proportion of the free base which is the moiety predominantly migrating through the lipophilic membranes of nerve fibres.
In inflamed tissue the local anaesthetic effect is reduced due to the lower pH in such regions.

5.2 Pharmacokinetic properties

Absorption

Plasma levels depend on the site and method of administration. However, there is a poor relationship between the amount of local anaesthetic injected and peak plasma levels.

Maximum concentrations are achieved within latest 30 minutes, in the majority of patients maximum concentrations are met within 10-20 minutes.

After intramuscular injectionof 400 mg of lidocaine hydrochloride monohydrate for intercostal block the maximum plasma concentration (C^{max}) has been determined to be 6.48 mg/l, attained after 5 – 15 min (t^{max}).

After subcutaneous administration, C_{max}values reached 4.91 mg/l (vaginal injection) or 1.95 mg/l (abdominal injection), respectively. In a study involving 5 healthy volunteers, after maxillar-buccal infiltration anaesthesia with 36 mg of lidocaine, using a 2 % solution, the C_{max}value reached 0.31 mg/l.

Distribution

Lidocaine follows a biphasic elimination kinetic. After intravenous administration the active substance is first rapidly distributed from the central compartment into intensively perfused tissues and organs (alpha-distribution phase). This phase is followed by redistribution into skeletal muscles and adipose tissue. The half-life time during the alpha-distribution phase is approximately 4-8 minutes. Distribution into peripheral tissues is predicted to occur within 15 min.

The plasma protein binding rate is approximately 60 – 80 per cent in adults. It is dependent on the active substance concentration and additionally on the concentration of the alpha-1-acid glycoprotein (AAG). The AAG is an acute phase protein that is binding free lidocaine and may be increased e.g. after trauma, surgery or burns depending on the pathophysiological condition of the patient. To the contrary it had been shown that AAG concentrations are low in new-born infants and patients suffering from liver impairment leading to a marked reduction of lidocaine plasma protein binding.

The volume of distribution at steady state is 91 litres. The volume of distribution may be altered in patients suffering from further diseases, e.g. heart insufficiency, liver insufficiency or renal insufficiency.

Biotransformation

Lidocaine is rapidly metabolised in the liver by mono-oxygenases mainly via oxidative N-dealkylation, hydroxylation at the aromatic ring and hydrolysis of the amide bond. Hydroxylated derivatives undergo conjugation.

In total, approx. 90 % of lidocaine is metabolised to 4-hydroxy-2,6-xylidine, to 4-hydroxy-2,6-xylidine glucuronide and to a lower degree to the active metabolites monoethyl glycine xylidide (MEGX) and glycine xylidide (GX).

The latter may accumulate during longer lasting infusions or in the presence of severe renal insufficiency due to their longer half life time as compared to lidocaine itself. In the presence of liver diseases the metabolic rate may be reduced to 10 – 50 per cent of normal.

Results with human liver microsomes and recombinant human CYP isoforms demonstrated that CYP1A2 and CYP3A4 enzymes are the major CYP isoforms involved in lidocaine N-deethylation.

Elimination

Less than 10 per cent of lidocaine is excreted unchanged in urine, the remaining proportion in the form of the metabolites.

The elimination half-life time is 1.5 – 2 hours in adults and approx. 3 hours in newborns. The elimination half-life maybe increased in case of severe heart failure (up to 4 – 12 hours), or chronic liver disease (up to 4.5 – 6 hours).

The half-life times of the active metabolites monoethyl glycine xylidide (MEGX) and glycine xylidide (GX) are 2-6 hours and 10 hours, respectively. Since their plasmatic half-lives are longer than that of lidocaine, accumulation of metabolites, particularly GX, may occur during prolonged infusion.

Additionally, the elimination rate depends on the pH; it can be increased by acidification of the urine. The plasmatic clearance is about 0.95 ml/min.

The hepatic blood flow appears to limit the rate of lidocaine metabolism.

Special populations

Patients with renal impairment
The plasmatic half-life time of lidocaine seemed to be unaltered except for some accumulation of GX during infusion of 12 hours or more. This accumulation seemed to be associated with long-term administration of the drug. However in patients with severe renal insufficiency clearance of lidocaine was approximately halved and half-life time of lidocaine was about twice the amount than in healthy patients.

Patients with liver impairment
The plasmatic half-lifeof lidocaine and its metabolites may be prolonged, and significant effects on pharmacokinetics and dosage requirements of lidocaine are to be expected, in patients with impaired liver perfusion, e.g. after acute myocardial infarction, in the presence of cardiac insufficiency, liver disease or congestive heart failure.

Elderly
Elimination half-life and volume of distribution may appear to be prolonged respectively increased in the elderly due to reduced cardiac output and/or hepatic blood flow.

Pregnant or breast-feeding woman
Lidocaine passes across the placental barrier by simple diffusion and reaches the foetus within a few minutes of administration. After paracervical block, markedly higher concentrations of lidocaine have been found in umbilical blood.
The foetus is able to metabolise lidocaine. The levels in foetal blood are approximately 60% of the concentrations in the maternal blood. Due to a lower plasma protein binding in foetal blood, the concentration of the pharmacologically active free lidocaine is 1.4 fold the maternal concentration.
Lidocaine is secreted into breast milk only in small amounts.

Paediatric population

In new-born infants, the α1-acid glycoprotein levels are low and protein binding may be reduced. As the free fraction may be higher, the use of lidocaine in new-born infants is not recommended.

5.3 Preclinical safety data

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

Lidocaine showed no genotoxic potential in *in vitro* and *in vivo* genotoxicity tests. However, 2,6-xylidine, a metabolite of lidocaine, showed evidence of genotoxic activity.

Cancer studies have not been performed with lidocaine. 2,6- xylidine has been shown to have carcinogenic potential in preclinical toxicological studies evaluating chronic exposure. The clinical relevance of these findings is unknown.

In studies on reproduction toxicity, embryotoxic or foetotoxic effects of lidocaine were detected at doses of 25 mg/kg s.c. in the rabbit, At doses below the maternal toxic range in the rat, lidocaine has no effect on the postnatal development of the offspring. An impairment of the fertility of male or female rats by lidocaine was not observed.
Lidocaine crosses the placental barrier by means of simple diffusion (see Section 5.2).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid, concentrated (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.
After opening, the medicinal product must be used immediately.

6.4 Special precautions for storage

Keep the pre-filled syringe in its unopened blister until use. Do not freeze.

6.5 Nature and contents of container

10 ml polypropylene pre-filled syringe, individually packaged in a blister.
Cardboard box of 1 and 10 pre-filled syringes.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use:

Please prepare the pre-filled syringe carefully as follows

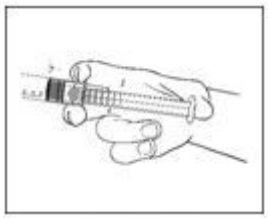
The pre-filled syringe is for single patient use only. Discard the pre-filled syringe after use. DO NOT REUSE.

The content of un-opened and un-damaged blister is sterile, and must not be opened until use.
The medicinal product should be inspected visually for particles and discolouration prior to administration. Only clear colourless solution free from particles or precipitates should be used.
The medicinal product should not be used if the tamper evident seal on the syringe is broken.

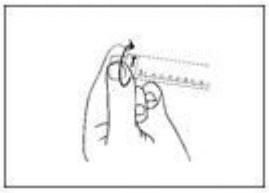
The external surface of the pre-filled syringe is sterile until blister is opened.

When handled using an aseptic method, this medicinal product can be placed on a sterile field.

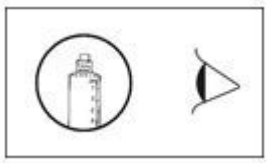
1) Withdraw the pre-filled syringe from the sterile blister.



2) Push on the plunger to free the bung. The sterilisation process may have caused adhesion of the bung to the body of the pre-filled syringe.



3) Twist off the end cap to break the seal. Do not touch the exposed luer connection in order to avoid contamination.



4) Check the pre-filled syringe seal tip has been completely removed. If not, replace the cap and twist again

5) Expel the air by gently pushing the plunger.

6) Connect the pre-filled syringe to access device or the needle. Push the plunger slowly to inject the required volume.

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

7 MARKETING AUTHORISATION HOLDER

Laboratoire AGUETTANT
1 Rue Alexander Fleming
69007 LYON
France

8 MARKETING AUTHORISATION NUMBER

PA1968/009/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20th July 2018
Date of last renewal: 22nd June 2023

10 DATE OF REVISION OF THE TEXT

October 2023