Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ropivacaine Readyfusor 10 mg/h solution for infusion in administration system

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for infusion contains ropivacaine as ropivacaine hydrochloride monohydrate, equivalent to 2 mg ropivacaine hydrochloride.

1 bottle of 250 ml solution for infusion contains ropivacaine as ropivacaine hydrochloride monohydrate, equivalent to 500 mg ropivacaine hydrochloride.

The administration system delivers a flow rate of approximately 5 ml/h, equivalent to 10 mg/h, over a maximum of 48 hours.

Excipient with known effect
Each ml solution for infusion contains 0.15 mmol (3.4 mg) sodium.
Each 250 ml bottle solution for infusion contains 37 mmol (850 mg) sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion

Clear, colourless solution.
Osmolality: 270 - 320 mOsmol/kg.
pH is in the range of 4.0 - 6.0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ropivacaine Readyfusor is indicated for acute, postoperative pain management in adults.

Ropivacaine Readyfusor is used to maintain a continuous peripheral nerve block via a continuous infusion.

4.2 Posology and method of administration

Ropivacaine Readyfusor should only be used by, or under the supervision of clinicians experienced in regional anaesthesia.

Equipment and medicinal products necessary for monitoring and emergency resuscitation should be immediately available. The clinician responsible should be appropriately trained and familiar with diagnosis and treatment of undesirable effects, systemic toxicity and other complications (see sections 4.8 and 4.9).

Posology
Adults
The administration system delivers a flow rate of approximately 5 ml/h, equivalent to 10 mg/h, over a maximum of 48 hours.

The fixed infusion rate of 5 ml (10 mg) per hour provides adequate analgesia with only slight and non-progressive motor block in most cases of moderate to severe postoperative pain.

To maintain a continuous peripheral nerve block via a continuous perineural infusion for postoperative pain management, the following technique can be recommended:

- First, unless perioperatively instituted, a block is induced with ropivacaine 7.5 mg/ml.
- Analgesia is then maintained with Ropivacaine Readyfusor.

Depending on the patient's clinical status, prescription of other oral analgesics (for patient-controlled analgesia), or additional bolus injections of a local anaesthetic should be considered.

Close monitoring of analgesic effect should be performed in order to discontinue the pain management as soon as the pain condition allows it.

Paediatric population
Ropivacaine Readyfusor is not indicated in children and adolescents.

Method of administration
For perineural use.

- The administration system is only intended for single use. It must not be reused.
- The administration system must not be autoclaved. The fluid path in the dispensing system has been sterilised.
- The administration system must not be connected to an IV line.
- Kinking of the tubing line must be avoided, as this could result in an improper fluid delivery rate.
- No tight wrappings should be placed around the tubing line.
- The administration system should not be used if any part has been damaged or cracked, or if the connector on the tubing line appears broken, cracked, or damaged in any way.
- The flow restrictor (clear rectangle) must remain taped to the patient's skin. Removing the tape or allowing the flow restrictor to lose contact with the skin may result in an improper fluid delivery rate.
- Do not place hot or cold packs over the flow restrictor as this could result in an improper fluid delivery rate.
- The administration system should not be reconnected if it is accidentally disconnected from the port during medication delivery, as this may cause an infection.
- Patients should not bathe or shower with the administration system, or while the port is still in place, as this could cause an infection.
- Patients should not tamper with the wound dressings or with the port as this could cause an infection.

For instructions for handling of the medicinal product, see section 6.6.

4.3 Contraindications

-Hypersensitivity to the active substance or to other local anaesthetics of the amide-type or to any of the excipients listed in section 6.1.
-Intravenous regional anaesthesia.
-Obstetric paracervical anaesthesia.
-Hypovolaemia.

4.4 Special warnings and precautions for use

Intrathecal and intracerebral administration infusion with Ropivacaine Readyfusor are not recommended, as the efficacy and safety have not been established.

Due to the constantly administered flow rate Ropivacaine Readyfusor is not recommended for epidural administration.

Cardiovascular
Patients treated with anti-arrhythmic medicinal products class III (e.g. amiodarone) should be under close surveillance and ECG monitoring should be considered, since cardiac effects may be additive.

There have been rare reports of cardiac arrest during the use of ropivacaine for epidural anaesthesia or peripheral nerve blockade, especially after unintentional accidental intravascular administration in elderly patients and in patients with concomitant heart disease. In some instances, resuscitation has been difficult. Should cardiac arrest occur, prolonged resuscitative efforts may be required to improve the possibility of a successful outcome.

Head and neck blocks

Certain local anaesthetic procedures, such as injections in the head and neck regions, may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used.

Major peripheral nerve blocks
Major peripheral nerve blocks may imply the administration of a large volume of local anaesthetic in highly vascularised areas, often close to large vessels where there is an increased risk of intravascular injection and/or rapid systemic absorption, which can lead to high plasma concentrations.

Hypersensitivity
A possible cross–hypersensitivity with other amide-type local anaesthetics should be taken into account.

Hypovolaemia
Patients with hypovolaemia due to any cause can develop sudden and severe hypotension during epidural anaesthesia, regardless of the local anaesthetic used.

Patients in poor general health
Patients in poor general condition due to ageing or other compromising factors such as partial or complete heart conduction block, advanced liver disease or severe renal dysfunction require special attention, although regional anaesthesia is frequently indicated in these patients.

Patients with hepatic and renal impairment
Ropivacaine is metabolised in the liver and should therefore be used with caution in patients with severe liver disease; repeated doses may need to be reduced due to delayed elimination. Normally there is no need to modify the dose in patients with impaired renal function when used for single dose or short-term treatment. Acidosis and reduced plasma protein concentration, frequently seen in patients with chronic renal failure, may increase the risk of systemic toxicity.

Acute porphyria
Ropivacaine Readyfusor is possibly porphyrinogenic and should only be prescribed to patients with acute porphyria when no safer alternative is available. Appropriate precautions should be taken in the case of vulnerable patients, according to standard textbooks and/or in consultation with disease area experts.

Chondrolysis
There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anaesthetics, including ropivacaine. The majority of reported cases of chondrolysis have involved the shoulder joint.

Intra-articular continuous infusion with Ropivacaine Readyfusor is not recommended, as the efficacy and safety have not been established.

Prolonged administration
Prolonged administration of ropivacaine should be avoided in patients concomitantly treated with strong CYP1A2 inhibitors, such as fluvoxamine and enoxacin (see section 4.5).

When prolonged blocks through continuous infusion are used, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. Cumulative doses up to 675 mg ropivacaine for postoperative analgesia administered over 24 hours were well tolerated in adults, as were postoperative continuous epidural infusions at rates up to 28 mg/hour for 72 hours. In a limited number of patients, higher doses of up to 800 mg/day have been administered with relatively few adverse reactions.

Paediatric population
Ropivacaine Readyfusor is not recommended in children and adolescents due to the fixed infusion rate of 5 ml (10 mg) per hour.

Excipients with recognised action/effect
This medicinal product contains 3.4 mg sodium per ml, equivalent to 0.17 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Ropivacaine Readyfusor should be used with caution in patients receiving other local anaesthetics or active substances structurally related to amide-type local anaesthetics, e.g. certain antiarrhythmics, such as lidocaine and mexiletine, since the systemic toxic effects are additive. Simultaneous use of Ropivacaine Readyfusor with general anaesthetics or opioids may potentiate each other's (adverse) effects. Specific interaction studies with ropivacaine and anti-arrhythmic medicinal products class III (e.g. amiodarone) have not been performed, but caution is advised (see also section 4.4).

Cytochrome P450 (CYP) 1A2 is involved in the formation of 3-hydroxy-ropivacaine, the major metabolite. In vivo, the plasma clearance of ropivacaine was reduced by up to 77 % during co-administration of fluvoxamine, a selective and potent CYP1A2 inhibitor. Thus, strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin given concomitantly during prolonged administration of Ropivacaine Readyfusor, can interact with Ropivacaine Readyfusor. Prolonged administration of ropivacaine should be avoided in patients concomitantly treated with strong CYP1A2 inhibitors (see also section 4.4).

In vivo, the plasma clearance of ropivacaine was reduced by 15 % during co-administration of ketoconazole, a selective and potent inhibitor of CYP3A4. However, the inhibition of this isozyme is not likely to have clinical relevance.

In vitro, ropivacaine is a competitive inhibitor of CYP2D6 but does not seem to inhibit this isozyme at clinically attained plasma concentrations.

4.6 Fertility, pregnancy and lactation

Pregnancy
Apart from epidural administration for obstetrical use, there are no adequate data on the use of ropivacaine in human pregnancy. Experimental animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

As a precautionary measure**,** it is preferable to avoid the use of Ropivacaine Readyfusor during pregnancy.

Breastfeeding
There are no data available concerning the excretion of ropivacaine into human milk.

Fertility
No clinical data are available.

4.7 Effects on ability to drive and use machines

No data are available. Depending on the dose, local anaesthetics may have a minor influence on mental function and co-ordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness.

4.8 Undesirable effects

The adverse reaction profile for Ropivacaine Readyfusor is similar to those for other long acting local anaesthetics of the amide-type. Adverse drug reactions should be distinguished from the physiological effects of the nerve block itself.

The frequencies used in the following table are: 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) and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Undesirable Effect
Immune system disorders	Rare	Allergic reactions (anaphylactic reactions, anaphylactic

		shock, angioneurotic oedema and urticaria)
Psychiatric disorders	Uncommon	Anxiety
Nervous system disorders	Common	Paraesthesia, dizziness, headache
	Uncommon	Symptoms of CNS toxicity (convulsions, Grand mal convulsions, seizures, light-headedness, circumoral paraesthesia, numbness of the tongue, hyperacusis, tinnitus, visual disturbances, dysarthria, muscular twitching, tremor)*, hypoaesthesia
	Not known	Dyskinesia
Cardiac disorders	Common	Bradycardia, tachycardia
	Rare	Cardiac arrest, cardiac arrhythmias
Vascular disorders	Very common	Hypotension
	Common	Hypertension
	Uncommon	Syncope
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting
Musculoskeletal and connective tissue disorders	Common	Back pain
Renal and urinary disorders	Common	Urinary retention
General disorders and administration site conditions	Common	Temperature elevation, chills
	Uncommon	Hypothermia

* These symptoms usually occur because of inadvertent intravascular injection, overdose or rapid absorption, see section 4.9.

Class-related adverse drug reactions

Neurological complications

Neuropathy and spinal cord dysfunction (e.g. anterior spinal artery syndrome, arachnoiditis, cauda equina), which may result in rare cases of permanent sequelae, have been associated with regional anaesthesia, regardless of the local anaesthetic used.

Acute systemic toxicity

Systemic toxic reactions primarily involve the central nervous system (CNS) and the cardiovascular system (CVS). Such reactions are caused by high blood concentration of a local anaesthetic, which may appear due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularised areas (see also section 4.4). CNS reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the active substance, both quantitatively and qualitatively.

Treatment of acute systemic toxicity

See section 4.9.

Central nervous system toxicity

Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. Initially symptoms such as visual or hearing disturbances, perioral numbness, dizziness, light-headedness, tingling and paraesthesia are seen. Dysarthria, muscular rigidity and muscular twitching are more serious and may precede the onset of generalised convulsions. These signs must not be mistaken for neurotic behaviour. Unconsciousness and grand mal convulsions may follow, which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly during convulsions due to the increased muscular activity, together with the interference with respiration. In severe cases even apnoea may occur. The respiratory and metabolic acidosis increases and extends the toxic effects of local anaesthetics.

Recovery follows the redistribution of the local anaesthetic from the central nervous system and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the active substance have been injected.

Cardiovascular system toxicity

Cardiovascular toxicity indicates a more severe situation. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics. In volunteers the intravenous infusion of ropivacaine resulted in signs of depression of conductivity and contractility.

Cardiovascular toxic effects are generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anaesthetic or is heavily sedated with medicinal products such as benzodiazepines or barbiturates.

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

Symptoms
Accidental intravascular injections of local anaesthetics may cause immediate (within seconds to a few minutes) systemic toxic reactions. In the event of overdose, peak plasma concentrations may not be reached for one to two hours, depending on the site of the injection, and signs of toxicity may thus be delayed (see section 4.8).

Treatment
If signs of acute systemic toxicity appear, injection of the local anaesthetic should be stopped immediately and CNS symptoms (convulsions, CNS depression) must promptly be treated with appropriate airway/respiratory support and the administration of anticonvulsant medicinal products.

If circulatory arrest should occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and 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, and/or inotropic medicinal products should be considered.

Should cardiac arrest occur, a successful outcome may require prolonged resuscitative efforts.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, local, Amides, ATC code: N01BB09

Ropivacaine is a long-acting, amide-type local anaesthetic with both anaesthetic and analgesic effects. At high doses ropivacaine produces surgical anaesthesia, while at lower doses it produces sensory block with limited and non-progressive motor block.

The mechanism is a reversible reduction of the membrane permeability of the nerve fibre to sodium ions. Consequently, the depolarisation velocity is decreased and the excitable threshold increased, resulting in a local blockade of nerve impulses.

The most characteristic property of ropivacaine is the long duration of action. Onset and duration of the local anaesthetic efficacy are dependent upon the administration site and dose, but are not influenced by the presence of a vasoconstrictor (e.g. adrenaline (epinephrine)).

Healthy volunteers exposed to intravenous infusions tolerated ropivacaine well at low doses and with expected CNS symptoms at the maximum tolerated dose. The clinical experience with this active substance indicates a good margin of safety when adequately used in recommended doses.

5.2 Pharmacokinetic properties

Ropivacaine has a chiral centre and is available as the pure S-(-)-enantiomer. It is highly lipid-soluble. All metabolites have a local anaesthetic effect but of considerably lower potency and shorter duration than that of ropivacaine.

The plasma concentration of ropivacaine depends upon the dose, the route of administration and the vascularity of the injection site. Ropivacaine follows linear pharmacokinetics and the $C_{max}$is proportional to the dose.

Ropivacaine shows complete and biphasic absorption from the epidural space with half-lives of the two phases of the order of 14 min and 4 h in adults. The slow absorption is the rate-limiting factor in the elimination of ropivacaine, which explains why the apparent elimination half-life is longer after epidural than after intravenous administration. Ropivacaine shows a biphasic absorption from the caudal epidural space also in children.

Ropivacaine has a mean total plasma clearance in the order of 440 ml/min, a renal clearance of 1 ml/min, a volume of distribution at steady state of 47 litres and a terminal half-life of 1.8 h after i.v. administration. Ropivacaine has an intermediate hepatic extraction ratio of about 0.4. It is mainly bound to α^1-acid glycoprotein in plasma with an unbound fraction of about 6 %.

An increase in total plasma concentrations during continuous epidural and interscalene infusion has been observed, related to a postoperative increase of α^1-acid glycoprotein.

Variations in unbound, i.e. pharmacologically active, concentration have been much less than in total plasma concentration.

Since ropivacaine has an intermediate to low hepatic extraction ratio, its rate of elimination should depend on the unbound plasma concentration. A postoperative increase in alpha1-acid-glycoprotein will decrease the unbound fraction due to increased protein binding, which will decrease the total clearance and result in an increase in total plasma concentrations, as seen in the paediatric and adult studies. The unbound clearance of ropivacaine remains unchanged as illustrated by the stable unbound concentrations during postoperative infusion. It is the unbound plasma concentration that is related to systemic pharmacodynamic effects and toxicity.

Ropivacaine readily crosses the placenta and equilibrium in regard to unbound concentration will be rapidly reached. The degree of plasma protein binding in the foetus is less than in the mother, which results in lower total plasma concentrations in the foetus than in the mother.

Ropivacaine is extensively metabolised, predominantly by aromatic hydroxylation. In total, 86 % of the dose is excreted in the urine after intravenous administration, of which only about 1 % relates to unchanged drug. The major metabolite is 3-hydroxy-ropivacaine, about 37 % of which is excreted in the urine, mainly conjugated. Urinary excretion of 4-hydroxy-ropivacaine, the N-dealkylated metabolite (PPX) and the 4-hydroxy-dealkylated accounts for 1–3 %. Conjugated and unconjugated 3-hydroxy-ropivacaine shows only detectable concentrations in plasma.

Impaired renal function has little or no influence on ropivacaine pharmacokinetics. The renal clearance of PPX is significantly correlated with creatinine clearance. A lack of correlation between total exposure, expressed as AUC, with creatinine clearance indicates that the total clearance of PPX includes a non-renal elimination in addition to renal excretion. Some patients with impaired renal function may show an increased exposure to PPX resulting from a low non-renal clearance. Due to the reduced CNS toxicity of PPX as compared to ropivacaine the clinical consequences are considered negligible in short-term treatment. Patients with end-stage renal disease undergoing dialysis have not been studied.

There is no evidence of *in vivo* racemisation of ropivacaine.

5.3 Preclinical safety data

Based on conventional studies of safety pharmacology, single and repeated dose toxicity, reproduction toxicity, mutagenic potential and local toxicity, no hazards for humans were identified other than those which can be expected on the basis of the pharmacodynamic action of high doses of ropivacaine (e.g. CNS signs, including convulsions, and cardiotoxicity).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide solution 4 % (for pH adjustment)
Hydrochloric acid 3.6 % (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

6.4 Special precautions for storage

Do not refrigerate.

6.5 Nature and contents of container

The administration system (ReadyfusOR) contains a translucent HDPE bottle with 250 ml solution for infusion.
The administration system is an orange cylinder with black caps on each side. A tubing line with connector (Luer or NRFit lock) is permanently attached to it.

Each pack contains one ReadyfusOR and a carrying pouch.

6.6 Special precautions for disposal and other handling

Ropivacaine Readyfusor is intended for single use only.

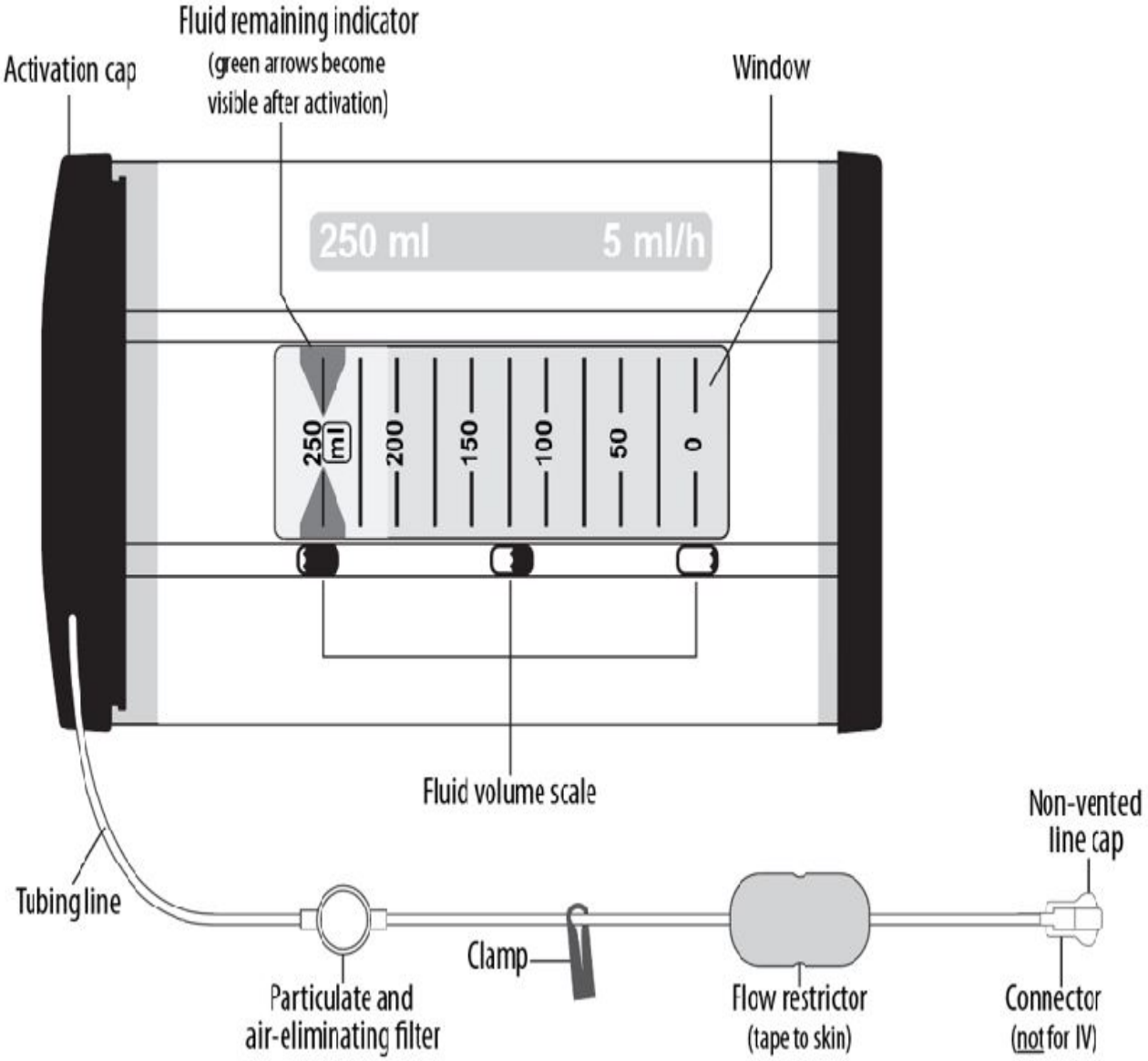
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The solution should be visually inspected prior to use. The solution should only be used if it is clear, practically free from particles and if the container is undamaged.

The administration system (ReadyfusOR)
The ReadyfusOR is a non-electric medicinal product administration system that has been designed for point of care use. All materials needed for the administration of the medicinal product are included.

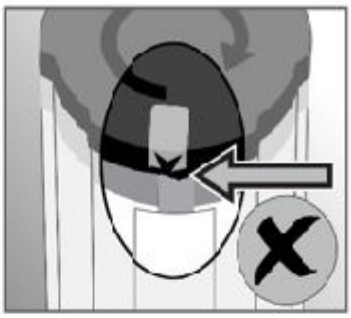
The fluid remaining indicator is a set of green arrows that indicates the amount of fluid which remains to be delivered.

As the flow rate of 5 ml/h is sensitive to temperature deviations, the administration system should be used under ambient temperature conditions, and the flow restrictor should remain taped in contact with the patient's skin at all times.


Fluid remaining indicator
(green arrows become
visible after activation)
Activation cap
Window
250 ml
5 ml/h
250
ml
200
150
100
50
0
Fluid volume scale
Non-vented
line cap
Tubing line
Clamp
Particulate and
air-eliminating filter
Flow restrictor
(tape to skin)
Connector
(not for IV)

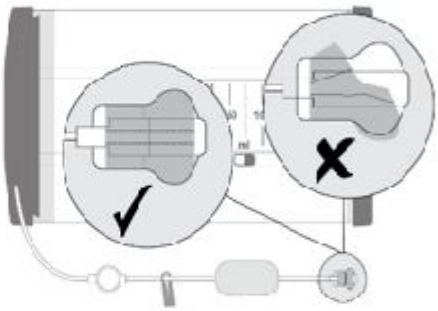
Instructions for use

1. Inspect the administration system, flow restrictor, and tubing line for damage or tampering.



☐ Verify that the orange sticker seal on the activation cap is intact.

☐ Verify that the orange tamper seal over the line cap is intact.

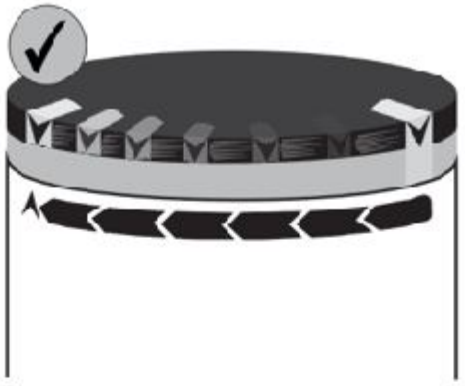


If damage is observed, or either seal has been removed or compromised, do not use this administration system.

2. Initiate fluid delivery by turning the activation cap clockwise until the arrow on the orange sticker seal roughly lines up with the arrow on the label. High force is required. This is normal and prevents accidental activation. Parts inside the administration system will move during activation.

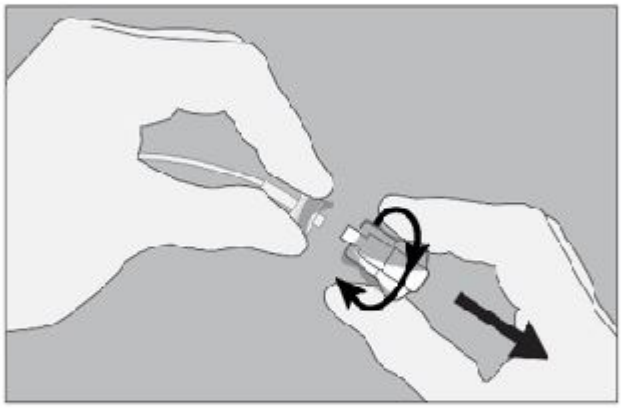
The administration system is activated when the green fluid remaining indicator arrows

become visible in the window. Fluid flow can be seen upstream of the filter within seconds, but flow will stop until the non-vented cap is removed.



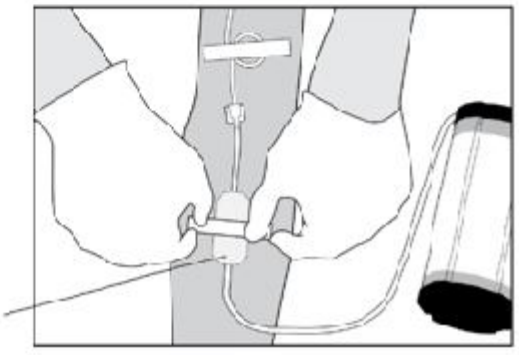
3. Twist off the tubing line cap to break the tamper seal.
Check that the clamp is not engaged and ensure that fluid delivery has started by observing fluid flowing through the tubing line and the flow restrictor.

After 1 – 2 minutes, fluid will start to drip very slowly from the end of the tubing line.



4. Connect the tubing line of the administration system to the patient's port. **Do not connect to an IV line.**

5. Tape the flow restrictor (clear rectangle) to the patient's skin. Apply tape directly over the flow restrictor as shown, away from the wound site, and make sure you do not pull at the tubing line or disturb the port placement. Finally, secure tubing line and connections with tape.



Warning: The flow restrictor must remain taped in contact with the patient's skin. If it loses contact, an improper fluid delivery rate may result.

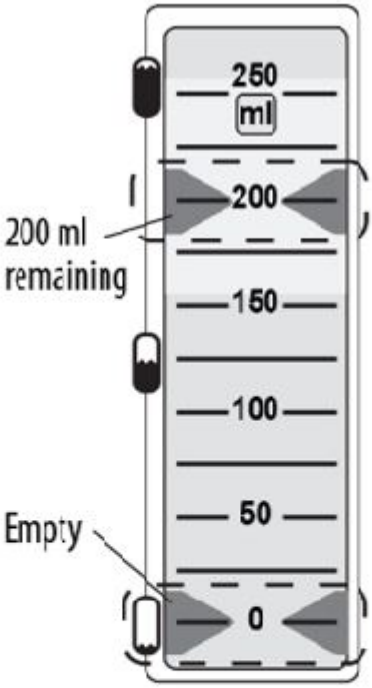
6. Place the administration system in the carrying pouch provided. The carrying pouch may either be attached to the patient as a sling around the shoulder or around the waist as a belt.

To prevent the port from being pulled out, it is recommended to keep the pouch attached to the patient with the administration system inside at all times.

7. Fluid delivery can be observed through the window of the administration system. The administration system will deliver approximately 5 ml of fluid per hour.

   The green arrows in the window indicate the amount of fluid remaining (in ml) in the administration system.

   Monitor the position of the fluid indicator arrows periodically for excessive flow rate. For symptoms of an overdose see section 4.9.



8. Delivery is complete when the unit is empty, as shown by the green fluid remaining indicator arrows reaching zero in the window.

9. Remove the administration system from the patient after delivery is complete.

10. After use, discard the empty administration system, including any unused solution, in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

BioQ Pharma B.V.
Prins Bernhardplein 200
1097 JB Amsterdam
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA2284/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th May 2018
Date of last renewal: 21st February 2023

10 DATE OF REVISION OF THE TEXT

April 2025