SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ropivacaine 2 mg/ml solution for infusion in administration system

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

1 dispensing device (Ropivacaine ReadyfusOR infusion pump) contains 250 ml ropivacaine hydrochloride monohydrate solution for infusion, equivalent to 500 mg ropivacaine hydrochloride.

Excipient(s) with known effect

Each ml contains 0.15 mmol (3.4 mg) sodium. Each unit contains 37 mmol (850 mg) sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion in administration system

Clear, colourless solution in a bellows bottle, contained in a dispensing device (Ropivacaine ReadyfusOR infusion pump, see section 6.6).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Ropivacaine is used:

- To maintain a continuous peripheral nerve block via a continuous infusion.
- For continuous wound infiltration.

4.2 Posology and method of administration

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

Posology

Adults

The dispensing device, the Ropivacaine ReadyfusOR infusion pump, 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.

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. The product information of the other medicinal products should also be considered in that case.

Paediatric population

Ropivacaine is not indicated in children and adolescents.

Method of administration

For perineural use and infiltration.

To maintain a continuous peripheral nerve block via a continuous perineural infusion, 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.

For continuous wound infiltration a fenestrated catheter should be placed in wound during surgery (see sections 6.5 and 6.6).

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

Precautions to be taken before handling or administering the medicinal product

For instructions on the preparation of the medicinal product before administration, 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.
- Intravascular use.
- Intrathecal use.
- Intracerebral use.
- Intra-articular use.

4.4 Special warnings and precautions for use

Regional anaesthetic procedures should always be performed in a properly equipped and staffed area. Equipment and drugs necessary for monitoring and emergency resuscitation should be immediately available. The clinician responsible should be appropriately trained and familiar with diagnosis and treatment of side effects, systemic toxicity and other complications (see sections 4.8 and 4.9).

The following data is pertaining to all routes of administration of ropivacaine 2 mg/ml solution in order to cover the full spectrum of safety data.

Cardiovascular

Patients treated with anti-arrhythmic drugs 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 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.

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 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 is not an approved indication for Ropivacaine. Intra-articular continuous infusion with Ropivacaine should be avoided, as the efficacy and safety has 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.

In clinical studies an epidural infusion of ropivacaine 2 mg/ml alone or mixed with fentanyl 1 - 4 μg/ml has been given for postoperative pain management for up to 72 hours. The combination of ropivacaine and fentanyl provided improved pain relief but caused opioid side effects. The combination of ropivacaine and fentanyl has been investigated only for ropivacaine 2 mg/ml.

Paediatric population

Ropivacaine is not indicated in children and adolescents.

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 should be used with caution in patients receiving other local anaesthetics or agents 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 with general anaesthetics or opioids may potentiate each other's (adverse) effects. Specific interaction studies with ropivacaine and anti-arrhythmic drugs 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, can interact with Ropivacaine. 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

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 during pregnancy.

Breast-feeding

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

Breast-feeding should be temporarily interrupted during treatment with Ropivacaine. The milk should be pumped and discarded for this period.

Fertility

No 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 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, 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

System Organ Class	Frequency	Undesirable Effect
	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 drug, both quantitatively and qualitatively.

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 drug from the central nervous system and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the drug 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 drugs such as benzodiazepines or barbiturates.

Treatment of acute systemic toxicity

See section 4.9.

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 the Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 drugs.

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 agents 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 drug 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 AAG 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 or hydrochloric acid for pH adjustment

Water for injections

6.2 Incompatibilities

In alkaline solutions precipitation may occur as ropivacaine shows poor solubility at pH > 6.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The Ropivacaine ReadyfusOR infusion pump is an orange cylinder with black caps on each side. It is designed to contain a transparent HDPE bellows bottle with 250 ml

ropivacaine hydrochloride monohydrate solution for infusion. A latex free tubing line with connector (Luer lock) is permanently attached to it.

Each pack contains one Ropivacaine ReadyfusOR infusion pump and a carrying pouch. Sets further including a sterile latex free fenestrated catheter for placement in the wound (length 6.5 or 15 cm) are also available.

6.6 Special precautions for disposal and other handling

Ropivacaine is preservative-free and is intended for single use only.

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.

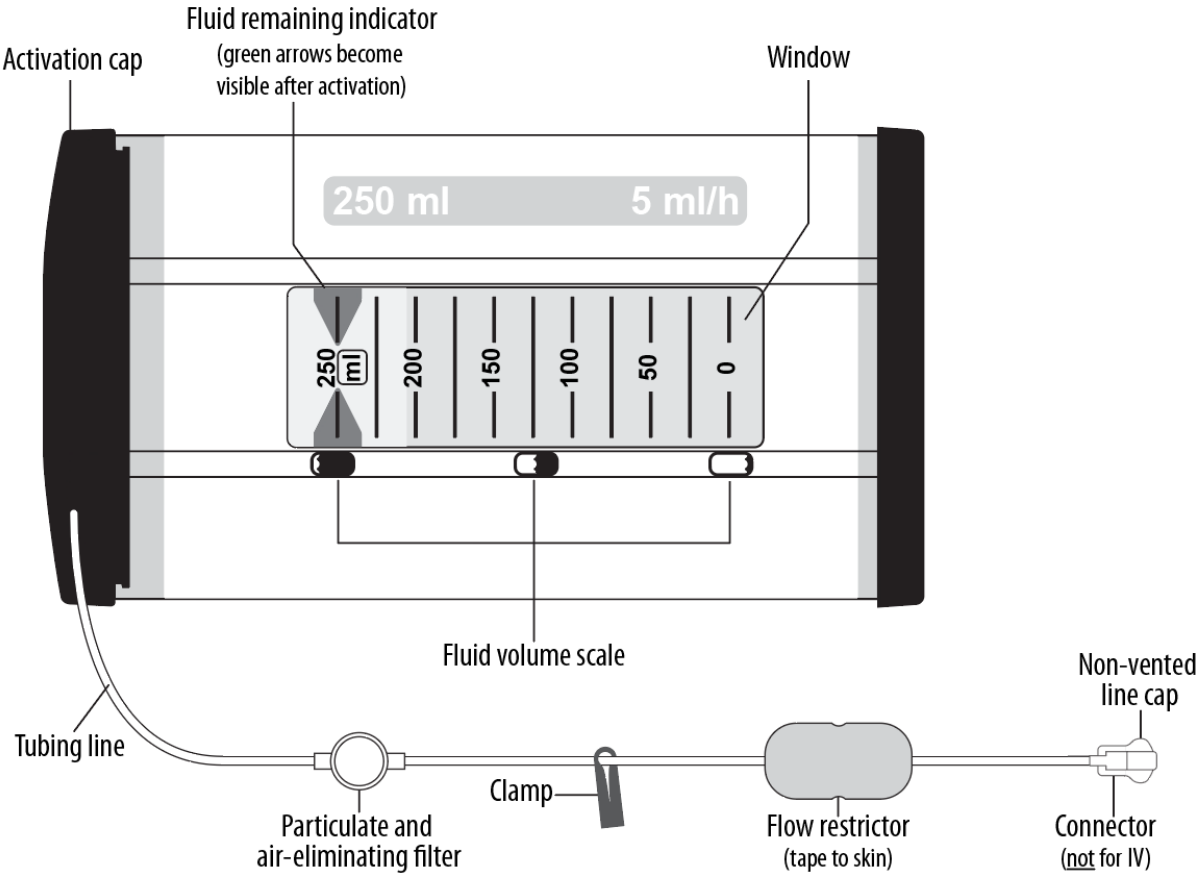
The Ropivacaine ReadyfusOR infusion pump

The Ropivacaine ReadyfusOR infusion pump (hereinafter referred to as “dispenser”) is a non-electric medication dispenser that has been designed for point of care use.

The dispenser contains a bellows bottle with 250 ml ropivacaine hydrochloride monohydrate solution for infusion. A tubing line with connector (Luer lock) is permanently attached. The tubing line, the connector, and the sterile fenestrated catheter (when enclosed in the set, see section 6.5) are latex free.

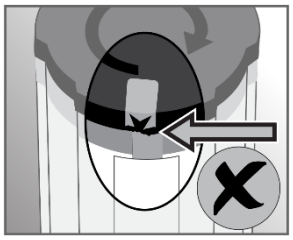
For wound infiltration, a fenestrated catheter should be placed in the wound during surgery according to clinical guidelines specific to the procedure location. The catheter (when enclosed in the set) uniformly distributes Ropivacaine along the length of the wound in a 360° radius.

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



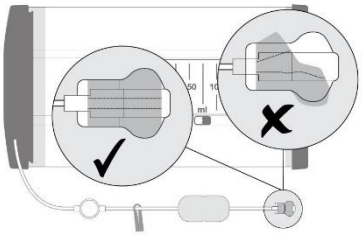
Instructions for use

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



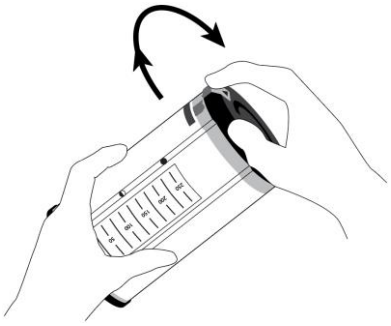
□ Verify that the orange sticker seal on the activation cap is intact.

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

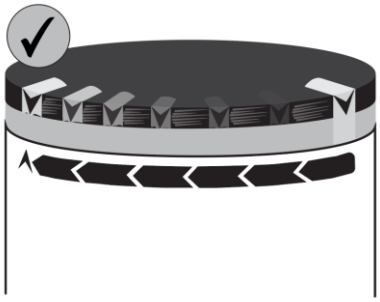


If damage is observed, or either seal has been removed or compromised, do not use this dispenser.

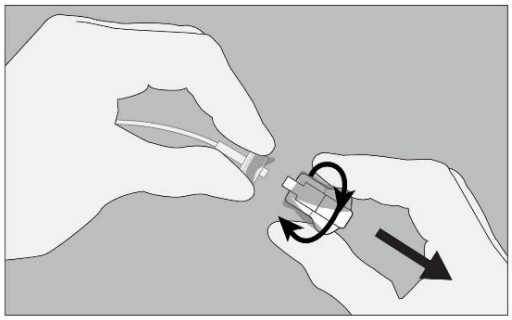
2. Initiate fluid delivery by turning the activation cap clockwise until the arrow on the orange sticker seal roughly lines up with the arrow on the label. High force is required. This is normal and prevents accidental activation. Parts inside the dispenser will move during activation.



The dispenser 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.

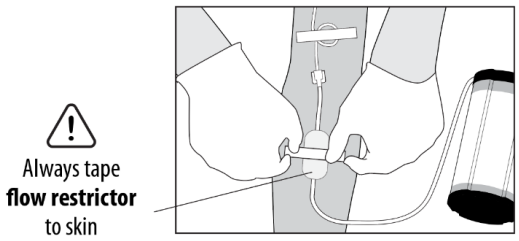


Check that the clamp is not engaged and ensure that fluid delivery has started by observing fluid flowing through the tubing line and the flow restrictor.

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

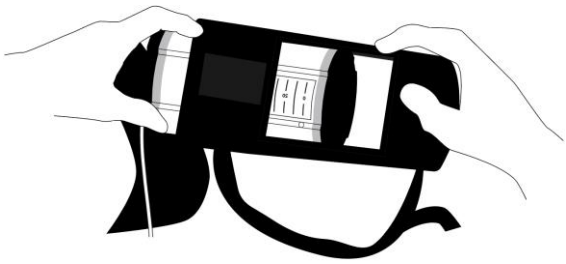
4. Connect the tubing line of the dispenser to the patient's port/catheter. **Do not connect to an IV line**.

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 catheter/port placement. Finally, secure tubing line and connections with tape.



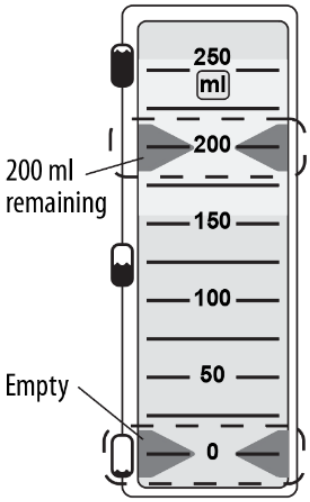
Warning: The flow restrictor must remain taped in contact with the patient's skin. If it loses contact, an improper fluid delivery rate may result.

6. Place the dispenser 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 catheter/port from being pulled out, it is recommended to keep the pouch attached to the patient with the dispenser inside at all times.

7. Fluid delivery can be observed through the window of the dispenser. The dispenser 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 dispenser.

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 dispenser from the patient after delivery is complete.

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

<u>Warnings</u>

- The dispenser is only intended for single use. Do not reuse or reconnect the dispenser.

- The dispenser must not be autoclaved. The fluid path in the dispensing system has been sterilised.
- The dispenser 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 dispenser 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 dispenser should not be reconnected if it is accidentally disconnected from the catheter/port during medication delivery, as this may cause an infection.
- The patient should not bathe or shower with the dispenser, or while the catheter/port is still in place, as this could cause an infection.
- The patient should not tamper with the wound dressings or with the catheter/port as this could cause an infection.

7 MARKETING AUTHORISATION HOLDER

BioQ Pharma Ltd

Garden Cottage, Hascombe Road

Godalming, Surrey GU8 4AE

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 45205/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/11/2017

10 DATE OF REVISION OF THE TEXT

10/2022