SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ropivacaine Altan 2 mg/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

1 bag of 100 ml contains ropivacaine hydrochloride monohydrate equivalent to 200 mg ropivacaine hydrochloride.

1 bag of 200 ml contains ropivacaine hydrochloride monohydrate equivalent to 400 mg ropivacaine hydrochloride.

Excipients:
Each bag of 100 ml contains 14.5 mmol (334 mg) sodium.
Each bag of 200 ml contains 29 mmol (669 mg) sodium.
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for infusion for epidural and perineural administration
Clear, colorless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute pain management in adults and adolescents above 12 years of age for:

Continuous epidural infusion or intermittent bolus administration during postoperative or labour pain.
Field blocks.
Peripheral nerve block via continuous infusion or intermittent bolus injections, e.g: postoperative pain management.

4.2 Posology and method of administration

For epidural and perineural use.
Ropivacaine hydrochloride should only be used by, or under the supervision of, clinicians experienced in regional anaesthesia.

ADULTS AND ADOLESCENT ABOVE 12 YEARS OF AGE

Posology

The following table is a guide to dosage for the more commonly used blocks. The smallest dose

required to produce an effective block should be used. The clinician's experience and knowledge of the patient's physical status are of importance when deciding the dose.

Dosage recommendations for Ropivacaine Altan 2 mg/ml in adults and adolescents above 12 years of age.

	Conc. mg/ml	Volume ml	Dose (§) mg	Onset minutes	Duration hours
ACUTE PAIN MANAGEMENT					
Lumbar epidural administration					
Bolus	2	10-20	20-40	10-15	0.5-1.5
Intermittent injections (top-up) (e.g. labour pain management)	2	10-15 (minimum interval 30 minutes)	20-30		
Continuous infusion e.g. labour pain	2	6-10 ml/h	12-20 mg/h	n/a	n/a
Postoperative pain management	2	6-14 ml/h	12-28 mg/h	n/a	n/a
Thoracic epidural administration					
Continuous infusion (postoperative pain management)	2	6-14 ml/h	12-28 mg/h	n/a	n/a
Field Block (e.g. minor nerve blocks and infiltration)	2	1-100	2.0-200	1-5	2-6
Peripheral nerve block (femoral or interscalene block)					
Continuous infusion or intermittent injections (e.g. postoperative pain management)	2	5-10 ml/h	10-20 mg/h	n/a	n/a

(§) The doses in the table refers to ropivacaine hydrochloride and are those considered to be necessary to produce a successful block and should be regarded as guidelines for use in adults. Individual variations in onset and duration occur. The figures in the column 'Dose' reflect the expected average dose range of ropivacaine hydrochloride needed. Standard textbooks should be consulted for both factors affecting specific block techniques and individual patient requirements.

Method of administration

Careful aspiration before and during injection is recommended to prevent intravascular injection. When a large dose is to be injected, a test dose of 3-5 ml lidocaine with adrenaline is recommended. An inadvertent intravascular injection may be recognised by a temporary increase in heart rate and an accidental intrathecal injection by signs of a spinal block.

Aspiration should be performed prior to and during administration of the main dose, which should be injected slowly or in incremental doses, at a rate of 25-50 mg/min, while closely observing the patient’s vital functions and maintaining verbal contact. If toxic symptoms occur, the injection should be stopped immediately.

When prolonged blocks are used, either through continuous infusion or through repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. Cumulative doses up to 675 mg ropivacaine 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.
Analgesia is maintained with ropivacaine hydrochloride 2 mg/ml infusion. Infusion rates of 6-14 ml (12-28 mg), per hour provide adequate analgesia with only slight and non-progressive motor block in most cases of moderate to severe postoperative pain. The maximum duration of epidural block is 3 days. However, close monitoring of analgesic effect should be performed in order to remove the catheter as soon as the pain condition allows it. With this technique a significant reduction in the need for opioids has been observed.
In clinical studies an epidural infusion of ropivacaine hydrochloride 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 hydrochloride and fentanyl provided improved pain relief but caused opioid side effects. The combination of ropivacaine hydrochloride and fentanyl has been investigated only for ropivacaine hydrochloride 2 mg/ml.
When prolonged peripheral nerve blocks are applied, either through continuous infusion or through repeated injections, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered.
Until further experience has been gained, ropivacaine hydrochloride cannot be recommended for use in children below the age of 12 years.

4.3 Contra-indications

- Hypersensitivity to the active substance or to any of the excipients or to other local anaesthetics of the amide type.
- General contra-indications related to epidural anesthesia, regardless of the local anaesthetic used, should be taken into account.
- Intravenous regional anaesthesia.
- Obstetric paracervical anaesthesia.
- Hypovolaemia.

4.4 Special warnings and precautions for use

Regional anaesthetic procedures should always be performed in a properly equipped and staffed area. Equipment and medicinal products necessary for monitoring and emergency resuscitation should be immediately available. Patients receiving major blocks should be in an optimal condition and have an intravenous line inserted before the blocking procedure. The clinician responsible should take the necessary precautions to avoid intravascular injection and be appropriately trained and familiar with diagnosis and treatment of side effects, systemic toxicity and other complications (See sections 4.8 Undesirable effects and 4.9 Overdose) such as inadvertent subarachnoid injection which may produce a high spinal block with apnoea and hypotension. Convulsions have occurred most often after brachial plexus block and epidural block. This is likely to be the result of either accidental intravascular injection or rapid absorption from the injection site.
Caution is required to prevent injections in inflamed areas.

Cardiovascular

Epidural and intrathecal anaesthesia may lead to hypotension and bradycardia. Hypotension should be treated promptly with a vasopressor intravenously , and with adequate vascular filling.

Patients treated with anti-arrhythmic active substances class III (e.g., amiodarone) should be under close surveillance and ECG monitoring 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 vascularized 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.

Patient 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 solution for injection and infusion 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 Altan2 mg/ml. Intra-articular continuous infusion with Ropivacaine Altan 2 mg/ml should be avoided, as the efficacy and safety has not been established.

Excipients with recognised action/effect
This medicinal product contains 3.34 mg sodium per ml, equivalent to 0.17% of the WHO recommended maximum daily intake of 2 g of sodium for an adult.

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).

4.5 Interactions 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 active substances 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 coadministration of fluvoxamine, a selective, potent and competitive 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 coadministration 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 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/fœtal development, parturition or postnatal development (See section 5.3).

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

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 coordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness.

4.8 Undesirable effects

General

The adverse reaction profile for ropivacaine is similar to those for other long-acting local anaesthetics of the amide type. Adverse reactions should be distinguished from the physiological effects of the nerve block itself e.g. Hypotension (a decrease in blood pressure), bradycardia during spinal/ epidural block.

Table of adverse reactions

The following frequencies are used for the description of the occurrence of adverse reactions: 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 effects**
Immune system disorder	Rare	Allergic reactions (anaphylactic reactions , angioneurotic oedema and urticaria
Psychiatric Disorders	Uncommon	Anxiety
Nervous System Disorders	Common Uncommon Not known	Paraesthesia, dizziness, headache 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 Dyskinesia
Cardiac Disorders	Common Rare	Bradycardia, tachycardia Cardiac arrest, cardiac arrhythmias
Vascular Disorders	Very common Common Uncommon	Hypotension Hypertension Syncope
Respiratory, Thoracic and Mediastinal Disorders	Uncommon	Dyspnoea
Gastrointestinal Disorders	Very common Common	Nausea 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 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.

Total spinal block
Total spinal block may occur if an epidural dose is inadvertently administered intrathecally.

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 vascularized areas, see also section 4.4. CNS reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the drugs, 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 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 drugs such as benzodiazepines or barbiturates.

Treatment of acute systemic toxicity
(See section 4.9)

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose
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. Children should be given doses commensurate with age and weight.
Should cardiac arrest occur, a successful outcome may require prolonged resuscitative efforts.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anesthetics, local, amides

ATC code: N01B B09

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)). For details concerning the onset and duration of action of ropivacaine, see table under posology and method of administration.

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 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.

There is no evidence of in vivo recemisation of ropivacaine

The plasma concentration of ropivacaine depends on 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 whythe apparent elimination half-life is longer after epidural than after intravenous administration.

Distribution

Ropivacaine has a mean total plasma clearance of the order of 440 ml/min, a renal clearance of 1 ml/min, a volume of distribution at steady state of 47 liters 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 α1 -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 α1 -acid glycoprotein. Variations in unbound, i.e. pharmacologically active, concentration have been much less than in total plasma concentration.

Elimination
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 metabolite 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.

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 dosesof ropivacaine (e.g. CNS signs, including convulsions, and cardiotoxicity).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium chloride
Hydrochloric acid
Sodium hydroxide
Water for injection

6.2 Incompatibilities

Compatibility with other solutions has not been investigated, apart from those mentioned in section 6.6.

Studies carried out on alkaline solutions, showed that ropivacaine has poor solubility at pH> 6.0 and therefore precipitation may occur.

6.3 Shelf-life

The expiry date of the product is indicated on the packaging materials.
Shelf life after first opening:

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

For mixture, see section 6.6.

6.4 Special precautions for storage

Do not store above 30°C. Do not freeze.
Use immediately after opening. For storage conditions after opening, see section 6.3.

6.5 Nature and contents of container

5 PVC bags of 100 ml with a removable overwrap.
5 PVC bags of 200 ml with a removable overwrap.

Not all pack-sizes may be marketed.

6.6 Special precautions and other handling

Remove the overwrap immediately before administration.

Although the solution is sterile, the protocols related to the use of product should take into account that the outside of the bag is not sterile in his overwrapping. The removable overwrapping aims at photoprotection and allows a mechanical and physical protection of the sterile solution.

The solution for infusion is preservative free and is intended for single use only.

Discard any unused solution.

Ropivacaine Altan solution for infusion in plastic infusion bag is chemically and physically compatible with the following drugs:

Concentration of Ropivacaine Altan: 1-2 mg/ml	
Additive	Concentration*
Fentanyl citrate	1.0 - 10.0 microgram/ml
Sufentanil citrate	0.4 - 4.0 microgram/ml
Morphine sulfate	20.0 - 100 microgram/ml
Clonidine hydrochloride	5.0 - 50 microgram/ml

* The concentration ranges stated in the table are wider than those used in clinical practice. Epidural infusions of Ropivacaine Altan 2 mg/ml/sufentanil citrate, Ropivacaine Altan 2 mg/ml/morphine

sulphate and Ropivacaine Altan 2 mg/ml/clonidine hydrochloride have not been evaluated in clinical studies.

The mixtures are chemically and physically stable for 30 days at 20-30 ° C. From a microbiological point of view, the mixtures should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C.

The medicinal product is to be visually inspected prior to use. Only clear solutions practically free from particles should be used.
The intact container must not be re-autoclaved.
On the bag there are the administration port for the infusion device and the injection port to inject other pharmaceutical products into the solution.

7. LICENSE REGISTRATION NUMBER
179-77-37678-99

8. MANUFACTURER
Altan Pharmaceuticals S.A., Cólquide 6, Portal 2, Planta 1, Oficina F, Edificio Prisma, 28230 – Las Rozas (Madrid) – SPAIN

9. LICENSE HOLDER AND IMPORTER
Propharm LTD., POB 4046, 23 Ben-Gurion, Zichron Yaacov 30900

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