At 25°C ropivacaine HCl has a solubility of 53.8 mg/mL in water, a distribution ratio between octanol and phospholipid buffer at pH 7.4 of 14.1 and a pKa of 0.07 in 0.1 M phosphate buffer. The pKa of ropivacaine is approximately the same as bupivacaine (8.1) and is similar to that of mepivacaine (7.7). However, ropivacaine has an intermediate degree of lipid solubility compared to bupivacaine and mepivacaine.

Ropivacaine HCl is chemically described as S-(±)-1-propyl-2',6'-pipecoloxylidide hydrochloride. The drug substance is a white crystalline powder, with a molecular formula of C_{26}H_{33}N_{2}O_3.HCl, molecular weight of 310.87 and the following structural formula:

CH_{3}\[N\]CO-O-\[C_6H_{13}\]-CH_{2}\][\text{Cl}]

CL (L/h)
AUC (mg.min/L) 
T_{1/2} (hr)

### Clinical Pharmacology

#### Mechanism of Action
Ropivacaine is a member of the amino amide class of local anesthetics and is supplied as the pure S-(±)-enantiomer. Local anesthetics block the generation and/or conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

#### Pharmacokinetics

**Absorption**
The systemic concentration of ropivacaine is dependent on the total dose and concentration of drug administered, the route of administration, the patient's hemodynamic/circulatory condition, and the vascularity of the administration site.

From the epidural space, ropivacaine shows complete and biphasic absorption. The half-lives of the 2 phases, (mean ± SD) are 14 ± 7 minutes and 4.2 ± 0.9 hours, respectively. The slow absorption is the rate limiting factor in the elimination of ropivacaine that explains why the terminal half-life is longer after epidural than after intravenous administration. Ropivacaine shows dose-proportionality up to the highest intravenous dose studied, 80 mg, corresponding to a mean ± SD peak plasma concentration of 1.9 ± 0.3 mcg/mL.

**Distribution**
After intravenous infusion, ropivacaine has a steady-state volume of distribution of 41 ± 7 liters. Ropivacaine is 94% protein bound, mainly to α1-acid glycoprotein. An increase in total plasma concentrations during continuous epidural infusion has been observed, related to a postoperative increase of α1-acid glycoprotein. Variations in unbound, ie, pharmacologically active, concentrations have been less than in total plasma concentration. Ropivacaine readily crosses the placenta and equilibrates in regard to unbound concentration will be rapidly reached (see PRECAUTIONS, Labor and Delivery).

**Metabolism**
Ropivacaine is extensively metabolized in the liver, predominantly by aromatic hydroxylation mediated by cytochrome P450 1A1 to 3-hydroxy ropivacaine. After a single IV dose approximately 37% of the total dose is excreted in the urine as both free and conjugated 3-hydroxy ropivacaine. Low concentrations of 3-hydroxy ropivacaine have been found in the plasma. Urinary excretion of the 4-hydroxy ropivacaine, and both the 3-hydroxy N-de-allylated (3-OH-PPX) and 4-hydroxy N-de-allylated (4-OH-PPX) metabolites account for less than 3% of the dose. A non-allylated metabolite, 2-hydroxyethyl-ropivacaine, has been identified but not quantified in the urine. The N-de-allylated metabolite of ropivacaine (PPX) and 3-OH-ropivacaine are the major metabolites exceeded the urine during epidural infusion. Total PPX concentration in the plasma was about half as that of total ropivacaine; however, unbound concentrations of PPX were about 7 to 9 times higher than that of unbound ropivacaine following continuous epidural infusion up to 72 hours. Unbound PPX, 3-hydroxy and 4-hydroxy ropivacaine, have a pharmacological activity in animal models less than that of ropivacaine. There is no evidence of in vitro racemization in urine of ropivacaine.

**Elimination**
The kidney is the main excretory organ for most local anesthetic metabolites. In total, 86% of the ropivacaine dose is excreted in the urine after intravenous administration of which only 1% relates to unchanged drug. After intravenous administration ropivacaine has a mean ± SD total plasma clearance of 387 ± 97 mL/min, an unbound plasma clearance of 7.2 ± 1.6 mL/min, and a renal clearance of 1 mL/min. The mean ± SD terminal half-life is 1.8 ± 0.7 h after intravenous administration and 4.2 ± 1 h after epidural administration (see Absorption).

**Pharmacodynamics**
Studies in humans have demonstrated that, unlike most other local anesthetics, the presence of...
epidural anesthesia has no major effect on either the time of onset or the duration of action of ropivacaine. Likewise, addition of epidural to ropivacaine has no effect on limiting systemic absorption of ropivacaine.

Systemic absorption of local anesthetics can produce effects on the central nervous and cardiovascular systems. At blood concentrations achieved with therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance have been reported. Toxic blood concentrations depress cardiac conduction and excitability, which may lead to arrhythmias. Block of ventricular and vagal afferents to the heart occurs, sometimes resulting in tachycardia. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure.

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression or both. Apparent central stimulation is usually manifested as restlessness, tremors and shivering, progressing to convulsions, followed by depression and coma, progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited stage.

In 2 clinical pharmacology studies (total n=24) ropivacaine and bupivacaine were infused (10 mg/min) in human volunteers until the appearance of CNS symptoms, eg, visual or hearing disturbances, perioral numbness, tingling and others. Similar symptoms were seen with both drugs. In 1 study, the mean ± SD maximum tolerated intravenous dose of ropivacaine infused (12.4 ± 3.8 mg) was significantly higher than that of bupivacaine (9.9 ± 3.0 mg) while in the other study the doses were not different (15.1 ± 2.9 mg of ropivacaine and 10.3 ± 3.0 mg of bupivacaine). In the latter study, the number of subjects reporting each symptom was similar for both drugs with the exception of muscle twitching which was reported by more subjects with bupivacaine than ropivacaine at comparable intravenous doses. At the end of the infusion, ropivacaine in both studies caused significantly less depression of cardiac conductivity (less QRS widening) than bupivacaine. Ropivacaine and bupivacaine caused evidence of depression of cardiac contractility, but there were no changes in cardiac output.

Clinical data in one published article indicate that differences in various pharmacodynamic measures were observed with increasing age. In one study, the upper level of analgesia increased with age, the maximum decrease of mean arterial pressure (MAP) declined with age during the first hour after epidural administration, and the intensity of motor block increased with age. However, no pharmacokinetic differences were observed between elderly and younger patients.

In non-clinical pharmacology studies comparing ropivacaine and bupivacaine in several animal species, the cardiac toxicity of ropivacaine was less than that of bupivacaine, although both were considerably more toxic than lidocaine. Arrhythmogenic and cardiodepressant effects were seen in animals at significantly higher doses of ropivacaine than bupivacaine. The incidence of successful resuscitation was not significantly different between the ropivacaine and bupivacaine groups.

Clinical Trials

Ropivacaine was studied as a local anesthetic both for surgical anesthesia and for acute pain management. (see DOSAGE AND ADMINISTRATION).

The onset, depth and duration of sensory block are, in general, similar to bupivacaine. However, the depth and duration of motor block, in general, are less than that with bupivacaine.

Epidural Administration In Surgery

There were 25 clinical studies performed in 100 patients to evaluate ropivacaine hydrochloride epidural injection for general surgery. Ropivacaine hydrochloride was used in doses ranging from 75 to 200 mg. In doses of 100 to 200 mg, the median (1st to 3rd quartile) onset time to achieve a T10 sensory block was 10 (5 to 13) minutes and for the median (1st to 3rd quartile) duration at the T10 level was 4 (3 to 5) hours (see DOSAGE AND ADMINISTRATION). Higher doses produced a more profound block with a greater duration of effect.

Epidural Administration In Cesarean Section

A total of 12 studies were performed with epidural administration of ropivacaine hydrochloride for cesarean section. Eight of these studies involved 218 patients using the concentration of 5 mg/mL. (0.5%) in doses up to 150 mg. Median onset measured at T6 ranged from 11 to 26 minutes. Median duration of sensory block at T6 ranged from 1.7 to 3.2 h, and duration of motor block ranged from 1.4 to 2.9 h. Ropivacaine hydrochloride provided adequate analgesic relaxation in surgery in all cases. In addition, 4 active controlled studies for cesarean section were performed in 204 patients at a concentration of 5 mg/mL. (0.5%) in doses up to 187.5 mg. Median onset measured at T6 ranged from 4 to 21 minutes. Seventy-seven to 56% of ropivacaine hydrochloride-exposed patients reported no pain at delivery. Some patients received other anesthetic, analgesic, or sedative modalities during the course of the operative procedure.

Epidural Administration In Labor And Delivery

A total of 9 double-blind clinical studies, involving 240 patients were performed to evaluate ropivacaine hydrochloride for epidural block for management of labor pain. When administered in doses up to 275 mg as intermittent injections or as a continuous infusion, ropivacaine hydrochloride produced adequate pain relief.

A prospective meta-analysis of 6 of these studies provided detailed evaluation of the delivered newborn and showed no difference in clinical outcomes compared to bupivacaine. There were significantly fewer instrumental deliveries in mothers receiving ropivacaine as compared to bupivacaine.

Table 2 LABOR AND DELIVERY META-ANALYSIS: MODE OF DELIVERY

<table>
<thead>
<tr>
<th>Delivery Mode</th>
<th>Ropivacaine n=199</th>
<th>Bupivacaine n=188</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Vertex</td>
<td>16</td>
<td>92</td>
</tr>
<tr>
<td>Vacuum Extrator</td>
<td>28</td>
<td>31</td>
</tr>
<tr>
<td>Forceps</td>
<td>28</td>
<td>42</td>
</tr>
<tr>
<td>Cesarean Section</td>
<td>29</td>
<td>15</td>
</tr>
</tbody>
</table>

* p<0.001 versus bupivacaine

Epidural Administration In Postoperative Pain Management

There were 8 clinical studies performed in 382 patients to evaluate ropivacaine hydrochloride 2 mg/mL. (0.2%) for postoperative pain management after upper and lower abdominal surgery and after orthopedic surgery. The studies utilized intravenous morphine via PCA as a rescue medication and quantified as an efficacy variable.

Epidural anesthesia with ropivacaine hydrochloride 5 mg/mL. (0.5%) was used intrathecally for each of these procedures prior to initiation of postoperative ropivacaine hydrochloride. The incidence and intensity of the motor block were dependent on the dose rate of ropivacaine hydrochloride and the site of injection. Cumulative doses of up to 700 mg of ropivacaine were administered over 24 hours. (0-1, 2, or 4 mg/min) with postoperative continuous infusion. The overall quality of pain relief, as judged by the patients, in the ropivacaine groups was rated as good or excellent (73% to 100%). The intensity of the motor block were dependent on the dose rate of ropivacaine hydrochloride and the site of injection. Cumulative doses of up to 700 mg of ropivacaine were administered over 24 hours. (0-1, 2, or 4 mg/min) with postoperative continuous infusion. The overall quality of pain relief, as judged by the patients, in the ropivacaine groups was rated as good or excellent (73% to 100%). The intensity of the motor block were dependent on the dose rate of ropivacaine hydrochloride and the site of injection. Cumulative doses of up to 700 mg of ropivacaine were administered over 24 hours. (0-1, 2, or 4 mg/min) with postoperative continuous infusion. The overall quality of pain relief, as judged by the patients, in the ropivacaine groups was rated as good or excellent (73% to 100%).
Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use.

General and ECG monitoring considered, since cardiac effects may be additive. Patients treated with class III antiarrhythmic drugs (eg, amiodarone) should be under close surveillance for adverse events when spinal anesthesia blockade was achieved.

Two hours. The results of these two clinical studies showed that a 3 mL dose did not produce any serious adverse events. Sensory levels as high as T5 and T4, respectively. Anesthesia to pinprick started in the sacral dermatomes in 2 to 3 minutes, extended to the T10 level in 10 to 13 minutes and lasted for approximately 2 hours. The quality of analgesia and muscle relaxation as judged by both the investigator and surgeon. Using the subclavian perivascular technique, no statistically significant difference was found in the quality of analgesia and muscle relaxation as judged by both the investigator and surgeon. The use of ropivacaine hydrochloride 7.5 mg/ml for block of the brachial plexus via the subclavian perivascular approach using 30 ml. (0.25%) or via the axillary approach using 45 ml. (0.3%) both provided effective and reliable anesthesia.

INDICATIONS AND USAGE

Ropivacaine hydrochloride Injection is indicated for the production of local or regional anesthesia for surgery and for acute pain management.

Surgical Anesthesia: epidural block for surgery including cesarean section major nerve block; local infiltration

Acute Pain Management: epidural continuous infusion or intermittent bolus, eg, postoperative or labor; local infiltration

CONTRAINDICATIONS

Ropivacaine hydrochloride is contraindicated in patients with a known hypersensitivity to ropivacaine or to any local anesthetic agent of the amide type.

WARNINGS

In performing ropivacaine hydrochloride blocks, unintended intravascular injection is possible and may result in cardiac arrhythmia or cardiac arrest. The potential for successful resuscitation has not been studied in humans. There have been rare reports of cardiac arrest during the use of ropivacaine hydrochloride for epidural anesthesia or peripheral nerve blockade, the majority of which occurred 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 probability of a successful outcome.

Ropivacaine hydrochloride should be administered in incremental doses. It is not recommended for emergency situations, where a fast onset of surgical anesthesia is necessary. Historically, pregnant patients were reported to have a higher risk for cardiac arrhythmias, cardiac arrest and death when 0.75% bupivacaine (another member of the amino amide class of local anesthetics) was inadvertently rapidly injected intravenously.

Prior to receiving major blocks the general condition of the patient should be optimized and the patient should have an IV line inserted. All necessary precautions should be taken to avoid intravascular injection. Local anesthetics should only be administered by clinicians who are well versed in the diagnosis and management of dose-related toxicity and who are familiar with the signs and symptoms of adverse reaction. Intra-articular injection of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of chondrolysis in patients receiving such injections. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of gleno-humeral chondrolysis have been described in pediatric and adult patients following intra-articular injection of local anesthetics with and without epinephrine for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are not associated with these findings. The time of onset of symptoms, such as joint pain, stiffness and loss of motion can be variable, but may begin as early as the 2nd month after surgery. There is no effective treatment for chondrolysis; patients who experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

It is essential that aspiration for blood or cerebrospinal fluid (where applicable) be done prior to injecting any local anesthetic, both the original dose and all subsequent doses, to avoid intravascular or subarachnoid injection. However, a negative aspiration does not ensure against an intravascular or subarachnoid injection.

A well-known risk of epidural anesthesia may be an unintentional subarachnoid injection of local anesthetic. Two clinical studies have been performed to verify the safety of ropivacaine hydrochloride at a volume of 5 ml injected into the subarachnoid space since this dose represents an incremental epidural volume that could be unintentionally injected. The 7.5 and 22.5 mg doses injected resulted in sensory levels as high as T5 and T4, respectively. Anesthesia to pinprick started in the sacral dermatomes in 2 to 3 minutes, extended to the T10 level in 10 to 13 minutes and lasted for approximately 2 hours. The results of these two clinical studies showed that a 3 ml dose did not produce any serious adverse events when spinal anesthesia blockade was achieved.

Ropivacaine hydrochloride should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects of these drugs are additive.

Patients treated with class III antiarrhythmic drugs (eg, amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be additive.

PRECAUTIONS

General

The safe and effective use of local anesthetics depends on proper dosage, correct technique, adequate precautions and readiness for emergencies.

Reuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use.
In rats, subcutaneous doses of 5.3, 11 and 26 mg/kg/day were administered during gestation days 6 to 20. Reproduction toxicity studies have been performed in pregnant New Zealand white rabbits and Sprague-Dawley rats, and Pregnancy Category B was assigned. Studies performed with ropivacaine in rats did not demonstrate an effect on fertility or general reproductive performance. The weak signs of mutagenic activity in the mouse lymphoma test were not further studied. Mutagenicity was not noted in the other assays. Cytokines of cytokine, such as interleukin-2, are detectable in the plasma of patients receiving ropivacaine, possibly indicating activation of cytokine production. In the absence of human studies of ropivacaine hemodynamics, it is recommended that test doses be administered initially and that the patient be monitored for central nervous system cardiovascular toxicity, as well as for signs of unintended intrathecal administration before proceeding. Where clinical conditions permit, consideration should be given to employing local anesthetic solutions, which contain epinephrine for the test dose because circulatory changes compatible with epinephrine may also occur as a warning sign of unintended intravascular injection. An intravenous injection is still possible even if epinephrine does not occur. Administration of higher recommended doses of ropivacaine hydrochloride to achieve greater motor blockade or increased duration of sensory blockade, may result in cardiovascular depression, particularly in the event of inadvertent intravascular injection. Tolerance to elevated blood levels varies with the physical condition of the patient, debilitated, elderly patients, and acutely ill patients should be given reduced doses commensurate with their age and physical condition. Local anesthetics should be used with caution in patients with hypertension, hypovolemia or heart block. Careful and constant monitoring of cardiovascular and respiratory vital signs (adequacy of ventilation) and the patient's state of consciousness should be performed after each local anesthetic injection. It should be kept in mind that at such times that restlessness, anxiety, incoherent speech, light-headedness, numbness and tingling of the mouth and lips, metallic taste, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity. Because amide-type local anesthetics such as ropivacaine are metabolized by the liver, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations. Local anesthetics should also be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs. Many drugs used during the conduct of anesthesia are considered potential triggering agents for malignant hyperthermia (MH). Amide-type local anesthetics are not known to trigger this reaction. However, since some of the drugs used for supplemental general anesthesia cannot be predicted in advance, it is suggested that standard protocol for MH management should be available.

Epidural Anesthesia

During epidural administration, ropivacaine hydrochloride should be administered in incremental doses of 3 to 5 mL, with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Syringe aspiration should also be performed before and during each supplemental injection in continuous (intermittent) catheter techniques. An intrathecal injection is still possible even if aspiration for blood is negative. During the administration of epidural anesthesia, it is recommended that a test dose be administered initially and that the effects monitored before the full dose is given. Where clinical conditions permit, the test dose should contain an appropriate dose of epinephrine to serve as a warning of unintentional intravascular injection. If injected into a blood vessel, this amount of epinephrine is likely to produce a transient "epinephrine response" within 5 seconds, consisting of an increase in heart rate and systolic blood pressure, circumoral pallor, palpitations and nervousness in the unsedated patient. The sedated patient may exhibit only a pulse rate increase of 20 or more beats per minute for 15 or more seconds. Therefore, following the test dose, the heart should be continuously monitored for a heart rate increase. Patients on beta-blockers may not manifest changes in heart rate, but blood pressure monitoring can detect a rise in systolic blood pressure. A test dose of a short-acting amide such as lidocaine is recommended to detect an unintentional intrathecal administration. This will be manifested within a few minutes by signs of spinal block (eg, decreased sensation of the buttocks, paralysis of the legs, or, in the sedated patient, absent knee jerk). An intrathecal or subarachnoid injection is still possible even if results of the test dose are negative. The test dose itself may produce a systemic toxic reaction, high spinal or epinephrine-induced cardiovascular effects.

Use in Brachial Plexus Block

Ropivacaine plasma concentrations may approach the threshold for central nervous system toxicity after the administration of 300 mg of ropivacaine for brachial plexus block. Caution should be exercised whenever using the 300 mg dose (see OVERDOSAGE). The dose for a major nerve block should be adjusted according to the site of administration and patient status. Supraventricular brachial plexus blocks may be associated with a higher frequency of serious adverse reactions, regardless of the local anesthetic used.

Use in Peripheral Nerve Block

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

Use in Head and Neck Area

Small doses of local anesthetics injected into the head and neck area may produce adverse reactions similar to systemic toxicity even with unintentional intravascular injection of larger doses. The injection procedure requires the utmost care. Confusion, convolution, respiratory depression, and respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the central circulation. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed. Resuscitation equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded (see DOSAGE AND ADMINISTRATION).

Use in Ophthalmic Surgery

The use of ropivacaine hydrochloride in retrobulbar blocks for ophthalmic surgery has not been studied. Until appropriate experience is gained, the use of ropivacaine hydrochloride for such surgery is not recommended.

Information for Patients

When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity in the anesthetized part of the body following proper administration of lumbar epidural anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions associated with the Ropivacaine Hydrochloride Injection package insert.

Drug Interactions

Specific trials studying the interaction between ropivacaine and class III antiarrhythmic drugs (eg, amiodarone) have not been performed, but caution is advised (see WARNINGS). Ropivacaine hydrochloride should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects of these drugs are additive. Cytosine (PGE1) is involved in the formation of 3-hydroxy ropivacaine, the major metabolite. In vivo, the plasma clearance of ropivacaine was reduced by 70% during coadministration of fluvastatin (25 mg bid for 2 days), a selective and potent CYP3A4 inhibitor. This strong inhibitors of cytochrome P450C1A2, such as fluvastatin, given concomitantly during administration of ropivacaine hydrochloride, can interact with ropivacaine hydrochloride leading to increased ropivacaine plasma levels. Caution should be exercised when CYP3A4 is coadministered. Possible interactions with drugs known to be metabolized by CYP3A4 via competitive inhibition, such as theophylline and imipramine may also occur. Coadministration of a selective and potent inhibitor of CYP3A4, ketoconazole (100 mg bid for 2 days with ropivacaine infusion administered 3 hour after ketoconazole) caused a 15% reduction in in vivo plasma clearance of ropivacaine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals of most local anesthetics, including ropivacaine, to evaluate the carcinogenic potential have not been conducted. Weak mutagenic activity was seen in the mouse lymphoma test. Mutagenicity was not noted in the other assays, demonstrating that the weak sign of in vitro activity in the mouse lymphoma test were not manifested in vivo under diverse in vitro conditions. Studies performed with ropivacaine in rats did not demonstrate an effect on fertility or general reproductive performance over 2 generations.

Pregnancy Category B

Reproductive toxicity studies have been performed in pregnant New Zealand white rabbits and Sprague-Dawley rats. During gestation days 6 to 18, rabbits received 1.3, 4.2, or 13 mg/kg/day subcutaneously. In rats, subcutaneous doses of 5.3, 11, and 26 mg/kg/day were administered during gestation days 6 to
15. No pharmacokinetic effects were observed in rats and rabbits at the highest doses tested. The highest doses of 13 mg/kg/day (rabbits) and 26 mg/kg/day (rats) are approximately 12.5% of the maximum recommended human dose (epidural, 770 mg/24 hours) based on mg/m² basis. In 2 preclinical and postnatal studies, the female rats were dosed daily from day 15 of gestation to day 20 postpartum. The doses were 5.3, 11, and 26 mg/kg/day subcutaneously. There were no treatment-related effects on plasma and urinary excretion of ropivacaine hydrochloride and its metabolites. In one study with rabbits, the ratio of plasma ropivacaine concentration on day 1 of gestation to day 15 of gestation was 2.5. However, no treatment-related effects on plasma ropivacaine concentration on day 1 of gestation to day 15 of gestation were observed in rats.

16. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

17. Ropivacaine hydrochloride injection is being administered to the mother. The effects of ropivacaine on the developing fetus have been observed in rats and rabbits at the maximum recommended human dose based on body surface area. In rats, the maximum recommended human dose is equivalent to 844 mg/kg (19% of the maximum recommended human dose based on body surface area). In rabbits, the maximum recommended human dose is equivalent to 1,720 mg/kg (48% of the maximum recommended human dose based on body surface area). The doses used were approximately equal to total daily dose based on body surface area.

18. There was no evidence of any adverse effect on male reproductive function in male rats and rabbits at the maximum recommended human dose based on body surface area. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration.

19. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

20. Ropivacaine hydrochloride injection is being administered to the mother. The effects of ropivacaine on the developing fetus have been observed in rats and rabbits at the maximum recommended human dose based on body surface area. In rats, the maximum recommended human dose is equivalent to 844 mg/kg (19% of the maximum recommended human dose based on body surface area). In rabbits, the maximum recommended human dose is equivalent to 1,720 mg/kg (48% of the maximum recommended human dose based on body surface area). The doses used were approximately equal to total daily dose based on body surface area.

21. There was no evidence of any adverse effect on male reproductive function in male rats and rabbits at the maximum recommended human dose based on body surface area. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration.

22. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

23. Ropivacaine hydrochloride injection is being administered to the mother. The effects of ropivacaine on the developing fetus have been observed in rats and rabbits at the maximum recommended human dose based on body surface area. In rats, the maximum recommended human dose is equivalent to 844 mg/kg (19% of the maximum recommended human dose based on body surface area). In rabbits, the maximum recommended human dose is equivalent to 1,720 mg/kg (48% of the maximum recommended human dose based on body surface area). The doses used were approximately equal to total daily dose based on body surface area.

24. There was no evidence of any adverse effect on male reproductive function in male rats and rabbits at the maximum recommended human dose based on body surface area. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration.

25. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

26. Ropivacaine hydrochloride injection is being administered to the mother. The effects of ropivacaine on the developing fetus have been observed in rats and rabbits at the maximum recommended human dose based on body surface area. In rats, the maximum recommended human dose is equivalent to 844 mg/kg (19% of the maximum recommended human dose based on body surface area). In rabbits, the maximum recommended human dose is equivalent to 1,720 mg/kg (48% of the maximum recommended human dose based on body surface area). The doses used were approximately equal to total daily dose based on body surface area.

27. There was no evidence of any adverse effect on male reproductive function in male rats and rabbits at the maximum recommended human dose based on body surface area. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration.

28. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

29. Ropivacaine hydrochloride injection is being administered to the mother. The effects of ropivacaine on the developing fetus have been observed in rats and rabbits at the maximum recommended human dose based on body surface area. In rats, the maximum recommended human dose is equivalent to 844 mg/kg (19% of the maximum recommended human dose based on body surface area). In rabbits, the maximum recommended human dose is equivalent to 1,720 mg/kg (48% of the maximum recommended human dose based on body surface area). The doses used were approximately equal to total daily dose based on body surface area.

30. There was no evidence of any adverse effect on male reproductive function in male rats and rabbits at the maximum recommended human dose based on body surface area. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration.

31. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

32. Ropivacaine hydrochloride injection is being administered to the mother. The effects of ropivacaine on the developing fetus have been observed in rats and rabbits at the maximum recommended human dose based on body surface area. In rats, the maximum recommended human dose is equivalent to 844 mg/kg (19% of the maximum recommended human dose based on body surface area). In rabbits, the maximum recommended human dose is equivalent to 1,720 mg/kg (48% of the maximum recommended human dose based on body surface area). The doses used were approximately equal to total daily dose based on body surface area.

33. There was no evidence of any adverse effect on male reproductive function in male rats and rabbits at the maximum recommended human dose based on body surface area. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration.

34. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

35. Ropivacaine hydrochloride injection is being administered to the mother. The effects of ropivacaine on the developing fetus have been observed in rats and rabbits at the maximum recommended human dose based on body surface area. In rats, the maximum recommended human dose is equivalent to 844 mg/kg (19% of the maximum recommended human dose based on body surface area). In rabbits, the maximum recommended human dose is equivalent to 1,720 mg/kg (48% of the maximum recommended human dose based on body surface area). The doses used were approximately equal to total daily dose based on body surface area.

36. There was no evidence of any adverse effect on male reproductive function in male rats and rabbits at the maximum recommended human dose based on body surface area. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration.

37. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

38. Ropivacaine hydrochloride injection is being administered to the mother. The effects of ropivacaine on the developing fetus have been observed in rats and rabbits at the maximum recommended human dose based on body surface area. In rats, the maximum recommended human dose is equivalent to 844 mg/kg (19% of the maximum recommended human dose based on body surface area). In rabbits, the maximum recommended human dose is equivalent to 1,720 mg/kg (48% of the maximum recommended human dose based on body surface area). The doses used were approximately equal to total daily dose based on body surface area.

39. There was no evidence of any adverse effect on male reproductive function in male rats and rabbits at the maximum recommended human dose based on body surface area. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration.

40. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

41. Ropivacaine hydrochloride injection is being administered to the mother. The effects of ropivacaine on the developing fetus have been observed in rats and rabbits at the maximum recommended human dose based on body surface area. In rats, the maximum recommended human dose is equivalent to 844 mg/kg (19% of the maximum recommended human dose based on body surface area). In rabbits, the maximum recommended human dose is equivalent to 1,720 mg/kg (48% of the maximum recommended human dose based on body surface area). The doses used were approximately equal to total daily dose based on body surface area.

42. There was no evidence of any adverse effect on male reproductive function in male rats and rabbits at the maximum recommended human dose based on body surface area. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration.
Incidence < 1%
The following adverse events were reported during the ropivacaine hydrochloride clinical program in more than one patient (N=3018), occurred at an overall incidence of < 1%, and were considered relevant:

**Application Site Reactions** - injection site pain

**Cardiovascular System** - vasovagal reaction, syncope, postural hypotension, non-specific ECG abnormalities

**Female Reproductive** - poor progression of labor, uterine atony

**Gastrointestinal System** - fecal incontinence, tenesmus, neonatal vomiting

**General and Other Disorders** - hypothermia, malaise, asthma, accident and/or injury

**Hearing and Vestibular** - tinnitus, hearing abnormalities

**Hematologic System** - extravasation, non-specific anaphylactoid, allergic reaction

**Musculoskeletal System** - myalgia

**Musculoskeletal/Pernurtrition** - ST segment changes, myocardial infarction

**Nervous System** - tremor, Horner’s syndrome, paresis, dyskinesia, neuropathy, vertigo, coma, confusion, hallucinosis, hypotension, coma, syncope, amnesia, hallucination, emotional lability, insomnia, nightmares

**Respiratory System** - bronchospasm, coughing

**Skin Disorders** - rash, urticaria

**Urogenital System** - urinary incontinence, micrurination disorder

**Vascular** - deep vein thrombosis, phlebitis, pulmonary embolism

**Vision** - vision abnormalities

For the indication epidural anesthesia for surgery, the 15 most common adverse events were compared between different concentrations of ropivacaine hydrochloride and bupivacaine. Table 4 is based on data from trials in the U.S. and other countries where ropivacaine hydrochloride was administered as an epidural anesthetic for surgery.

### Table 4: Common Events (Epidural Administration)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Ropivacaine 5mg/mL</th>
<th>7.5mg/mL</th>
<th>10mg/mL</th>
<th>5mg/mL</th>
<th>7.5mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypotension</strong></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>34 (13.3)</td>
<td>68 (22.9)</td>
<td>41 (17.4)</td>
<td>36 (20.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Bradycardia</strong></td>
<td>29 (11.3)</td>
<td>58 (19.5)</td>
<td>40 (15.3)</td>
<td>32 (15.6)</td>
<td>25 (14.4)</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>18 (7)</td>
<td>33 (11.1)</td>
<td>23 (11.1)</td>
<td>19 (9.3)</td>
<td>14 (8.0)</td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td>12 (4.7)</td>
<td>20 (6.7)</td>
<td>16 (7.7)</td>
<td>13 (5.5)</td>
<td>9 (5.2)</td>
</tr>
<tr>
<td><strong>Chills</strong></td>
<td>8 (3.1)</td>
<td>5 (1.7)</td>
<td>8 (3.7)</td>
<td>11 (4.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>2 (0.8)</td>
<td>7 (2.4)</td>
<td>4 (1.7)</td>
<td>3 (1.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Paresthesia</strong></td>
<td>2 (0.8)</td>
<td>10 (3.4)</td>
<td>7 (3.4)</td>
<td>7 (4.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Pruritus</strong></td>
<td>14 (5.7)</td>
<td>3 (1.4)</td>
<td>7 (4.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Using data from the same studies, the number (%) of patients experiencing hypotension is displayed by patient age, drug and concentration in Table 5. In Table 6, the adverse events for ropivacaine hydrochloride are broken down by gender.

### Table 5: Effects of Age on Hypotension (Epidural Administration)

<table>
<thead>
<tr>
<th>AGE</th>
<th>Ropivacaine 5mg/mL</th>
<th>7.5mg/mL</th>
<th>10mg/mL</th>
<th>5mg/mL</th>
<th>7.5mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>220 (54.3)</td>
<td>138 (38.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>119 (29.4)</td>
<td>23 (6.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>65 (16.5)</td>
<td>56 (15.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>59 (14.5)</td>
<td>8 (2.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>41 (10.5)</td>
<td>23 (6.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>33 (8.7)</td>
<td>17 (4.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>18 (4.4)</td>
<td>5 (1.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>16 (4.0)</td>
<td>3 (0.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>16 (4.0)</td>
<td>1 (0.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>12 (3.1)</td>
<td>4 (1.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary retention</td>
<td>11 (2.7)</td>
<td>7 (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (2.3)</td>
<td>4 (1.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>8 (2.0)</td>
<td>0 (0.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paresthesia</td>
<td>8 (2.0)</td>
<td>10 (2.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 6: Most Common Adverse Events by Gender (Epidural Administration)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypotension</strong></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>119 (29.4)</td>
<td>23 (6.3)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>65 (16.5)</td>
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</tr>
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<td>59 (14.5)</td>
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<td>41 (10.5)</td>
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<td>33 (8.7)</td>
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<td>Chills</td>
<td>18 (4.4)</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td>Fever</td>
<td>16 (4.0)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>16 (4.0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Pain</td>
<td>12 (3.1)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>11 (2.7)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (2.3)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>8 (2.0)</td>
<td>0 (0.2)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>8 (2.0)</td>
<td>10 (2.8)</td>
</tr>
</tbody>
</table>

### Systemic Reactions

The most commonly encountered acute adverse experiences that demand immediate countermeasures are related to the central nervous system and the cardiovascular system. These adverse experiences are generally dose-related and due to high plasma levels that may result from overdose, rapid absorption from the injection site, diminished tolerance or from unintentional intravascular injection of the local...
The dose of any local anesthetic administered varies with the anesthetic procedure, the area to be
anesthetized, and during continuous infusion. At the first sign of change in mental status, oxygen should be
administered. The first step in the management of systemic toxic reactions, as well as underestimation or
overestimation, consists of immediate attention to the establishment and maintenance of a patent airway and
effective assisted or controlled ventilation with 100% oxygen. A delivery system capable of delivering immediate
positive airway pressure by mask. Circulation should be assisted as necessary. This may prevent convulsions if they have not
already occurred. If necessary, use drugs to control convulsions. Intravenous barbiturates, anticonvulsant agents, or
muscle relaxants should only be administered by those familiar with their use. Immediately after the institution of these
measures, the adequacy of the circulation should be evaluated. Supportive treatment of circulatory depression may
require administration of intravenous fluids, and, when appropriate, a vasopressor dictated by the clinical situation (such as
ephrine or epinephrine to enhance myocardial contractility). Should cardiac arrest occur, prolonged resuscitative efforts may be required to improve the probability of a successful outcome.
The mean dosages of ropivacaine producing seizures, after intravenous infusions in dogs, nonpregnant
and pregnant sheep were 4.9, 6.1 and 5.9 mg/kg, respectively. These doses were associated with peak
cerebrospinal fluid concentrations of 1.4, 4.3, and 1.2 mg/mL, respectively. In humans volunteers given intravenous ropivacaine hydrochloride, the mean (min-max) maximum
tolerated total and free plasma concentrations were 4.3 (3.4 to 5.3) and 0.6 (0.2 to 0.9) mg/mL
respectively, at which time moderate CNS symptoms (muscle twitching) were noted.
Clinical data from patients experiencing local anesthetic induced convulsions demonstrated rapid
development of hypoxia, hypercarbia and acidosis within a minute of the onset of convulsions. These
observations suggest that oxygen consumption and carbon dioxide production are greatly increased
during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation
with oxygen, which may abort cardiac arrest.
If difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support
(isoventilation or assisted) is indicated, endotracheal intubation, employing drugs and techniques familiar to the
clinician, may be indicated after initial administration of oxygen by mask.
The spine position is dangerous in pregnant women at term because of aortic compression by the
gynec area. Therefore, during treatment of systemic toxicity, maternal hypoxia and fetal
bradycardia following regional block, the patient may be maintained in the left lateral decubitus position if possible, or
manual displacement of the uterus off the great vessels should be accomplished. Reassurance of obstetrical patients may take longer than usual because of non-pregnant
patients and closed-chest cardiac compressions may be ineffective. Rapid delivery of the fetus may
improve the response to resuscitative efforts.

MANAGEMENT OF LOCAL ANESTHETIC EMERGENCIES
Therapy with ropivacaine hydrochloride should be discontinued at the first sign of toxicity. No
specific information is available for the treatment of toxicity with ropivacaine hydrochloride. Therefore,
treatment should be symptomatic and supportive. The first consideration is prevention, best
accomplished by incremental injection of ropivacaine hydrochloride, careful and constant monitoring of
cardiovascular and respiratory vital signs and the patient's state of consciousness after each local
anesthetic and during continuous infusion. At the first sign of change in mental status, oxygen should be
administered.

Management of Local Anesthetic Emergencies

Cardiovascular System Reactions
High doses or unintentional intravascular injection may lead to high plasma levels and related
depression of the myocardium, decreased cardiac output, heart block, hypotension, bradycardia, and
ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and possibly
cardiac arrest (see WARNINGS, PRECAUTIONS, and OVERDOSAGE).

Allergic Reactions
Allergic type reactions are rare and may occur as a result of sensitivity to the local anesthetic (see
WARNINGS). These reactions are characterized by signs such as urticaria, pruritus, erythema,
angioedema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness,
syncope, excessive sweating, elevated temperature, and possibly, anaphylactic symptomatology
(including severe hypotension). Cross-sensitivity among members of the amide--type local anesthetic
family has not been definitively established.

OVERDOSAGE
Acute emergencies from local anesthetics are generally related to high plasma levels encountered, or
large doses administered, during therapeutic use of local anesthetics or to unintended subarachnoid or
intravascular injection of local anesthetic solution (see ADVERSE REACTIONS, WARNINGS,
and PRECAUTIONS).

DOSAGE AND ADMINISTRATION
The rapid injection of a large volume of local anesthetic solution should be avoided and fractional
(incremental) doses should always be used. The smallest dose and concentration required to produce
the desired result should be administered.

There have been adverse event reports of chondrodysplasia in patients receiving intra-articular infusions of
local anesthetics following arthroscopic and other surgical procedures. Ropivacaine hydrochloride
injection is not approved for this use (see WARNINGS AND DOSAGE AND ADMINISTRATION).

The dose of any local anesthetic administered varies with the anesthetic procedure, the area to be
Use an adequate test dose (3 to 5 mL of a short-acting local anesthetic solution containing epinephrine) prior to induction of complete block. This test dose should be repeated if the patient is moved in a fashion to have displaced the epidural catheter. Allow adequate time for onset of anesthesia following administration of each test dose.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Solutions which are discolored or which contain particulate matter should not be administered.

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### Table 7 Dosage Recommendations

<table>
<thead>
<tr>
<th>Conc.</th>
<th>Volume</th>
<th>Dose</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/mL</td>
<td>mL</td>
<td>mg</td>
<td>min</td>
<td>hours</td>
</tr>
</tbody>
</table>

#### SURGICAL ANESTHESIA

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Conc.</th>
<th>Volume</th>
<th>Dose</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>7.5 (0.75%)</td>
<td>15 to 20</td>
<td>113 to 188</td>
<td>6 to 10</td>
<td>3 to 5</td>
</tr>
</tbody>
</table>

#### POSTOPERATIVE PAIN MANAGEMENT

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Conc.</th>
<th>Volume</th>
<th>Dose</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>7.5 (0.75%)</td>
<td>15 to 20</td>
<td>113 to 188</td>
<td>6 to 10</td>
<td>3 to 5</td>
</tr>
</tbody>
</table>

#### LABOR AND DELIVERY

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Conc.</th>
<th>Volume</th>
<th>Dose</th>
<th>Onset</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
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<td>15 to 20</td>
<td>113 to 188</td>
<td>6 to 10</td>
<td>3 to 5</td>
</tr>
</tbody>
</table>

* = Not applicable

### PRECAUTIONS

- Use only aseptic technique when preparing ropivacaine hydrochloride for administration.
- Do not use solutions that have been exposed to direct sunlight or to high temperatures.
- Do not mix ropivacaine hydrochloride with other medicaments or solutions except as specifically indicated in this package insert.
- Do not freeze.
- The solubility of ropivacaine is limited at pH above 6. Thus, care must be taken as precipitation may occur if Ropivacaine Hydrochloride Injection is mixed with alkaline solutions.

### ADMINISTRATION

- For infiltration, continuous infusion, and epidural administration, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. Clinical experience in current textbooks should be consulted.
- The doses in the table are those considered to be necessary to produce a successful block and should be regarded as guidelines for use in adults. Individual variation in onset and duration occur. The figures reflect the expected average dose range needed. For other local anesthetic techniques standard current textbooks should be consulted.
- 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.
- Experience to date indicates that a cumulative dose of up to 770 mg of ropivacaine hydrochloride administered over 24 hours is well tolerated in adults when used for postoperative pain management (e.g., 2016 mg). Caution should be exercised when administering ropivacaine hydrochloride for prolonged periods of time, e.g., >70 hours in debilitated patients.
- For treatment of postoperative pain, the following technique can be recommended: If regional anesthesia was not used intravenously, then an initial epidural block with 5 mL of ropivacaine hydrochloride is induced via an epidural catheter. Analgesia is maintained with a titration of ropivacaine hydrochloride, 2 mg/mL (0.2%). Clinical studies have demonstrated that infusion rates of 6 to 14 mL (12 to 28 mg) per hour provide adequate analgesia with nonprogressive motor block.
- With experience and the expected average dose range needed, ropivacaine has been associated with significant reductions in the need for opioids.

### INCOMPATIBILITIES

**Cardiovascular:** Calcium gluconate, calcium chloride, calcium lactate, magnesium sulfate, amphotericin B (commercially available) (1% w/v), Foscarnet sodium, and vancomycin hydrochloride should not be mixed in the same syringe or container since the physical state of the solutions may be altered.

**Hematologic:** Sodium bicarbonate is not recommended as an antacid or buffer solution when used with ropivacaine hydrochloride.

**Ophthalmic:** Ropivacaine hydrochloride is formulated for intrathecal administration and is not recommended for subcutaneous, intramuscular, intravenous, or intranasal use.

**Respiratory:** Ropivacaine hydrochloride should not be mixed with any bronchodilator or sympathomimetic drug unless specifically indicated in this package insert.

**Urinary:** Ropivacaine hydrochloride is not recommended for intravesical instillation.

- **Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Solutions which are discolored or which contain particulate matter should not be administered.**

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The combination of ropivacaine hydrochloride with epinephrine in concentrations greater than 1:250,000 is not recommended.

- **Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Solutions which are discolored or which contain particulate matter should not be administered.**

### STABILITY

- When chemical disinfection of the container surface is desired, either isopropyl alcohol (91%) or ethyl alcohol (70%) is recommended. It is recommended that chemical disinfection be accomplished by wiping the ampule or vial stopper thoroughly with cotton or gauze that has been moistened with the recommended alcohol just prior to use. Glass containers may, as an alternative, be autoclaved once.
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### CONCLUSION

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ROPIVACAINE HYDROCHLORIDE
ropivacaine hydrochloride injection, solution

Product Information
Product Type: HUMAN PRESCRIPTION DRUG
Item Code (Source): NDC:0781-3140
Route of Administration: PARENTERAL

Active Ingredient/Active Moiety
Ingredient Name | Basis of Strength | Strength
---|---|---
ROPIVACAINE HYDROCHLORIDE (UNII: V910P86109) | ROPIVACAINE (UNII:7IO5LYA57N) | 5 mg in 1 mL

Inactive Ingredients
Ingredient Name | Strength
---|---
SODIUM CHLORIDE (UNII: 451W47IQ8X) |
SODIUM HYDROXIDE (UNII: 55X04QC32I) |
HYDROCHLORIC ACID (UNII: QTT17582CB) |
WATER (UNII: 059QF0KO0R) |
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<th>Package Description</th>
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<th>Marketing End Date</th>
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<td>5 mL in 1 BOX</td>
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<tr>
<td>NDC:0781-3140-08</td>
<td>150 mL in 1 CARTON</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 mL in 1 VIAL, SINGLE-DOSAGE</td>
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### Marketing Information

<table>
<thead>
<tr>
<th>Marketing Category</th>
<th>Application Number or Monograph Citation</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANDA</td>
<td>ANDA078601</td>
<td>07/24/2014</td>
<td></td>
</tr>
</tbody>
</table>

## ROPIVACAINE HYDROCHLORIDE

ropivacaine hydrochloride injection, solution

### Product Information

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Active Substance</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>HUMAN PRESCRIPTION DRUG</td>
<td>ropivacaine hydrochloride</td>
<td>NDC:0781-3142</td>
</tr>
</tbody>
</table>

### Route of Administration

PARENTERAL

### Active Ingredient/Active Moiety

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROPIVACAINE HYDROCHLORIDE</td>
<td>UNII: V910P86109</td>
<td>10 mg</td>
</tr>
<tr>
<td>UNII: 7IO5LYA57N</td>
<td>ROPIVACAINE</td>
<td>1 mL</td>
</tr>
</tbody>
</table>

### Inactive Ingredients

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>SODIUM CHLORIDE</td>
<td>(UNII: 451W47IQ8X)</td>
</tr>
<tr>
<td>SODIUM HYDROXIDE</td>
<td>(UNII: 55X04QC32I)</td>
</tr>
<tr>
<td>HYDROCHLORIC ACID</td>
<td>(UNII: QTT17582CB)</td>
</tr>
<tr>
<td>WATER</td>
<td>(UNII: 059QF0KO0R)</td>
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</tbody>
</table>

### Packaging

<table>
<thead>
<tr>
<th>Item Code</th>
<th>Package Description</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDC:0781-3142-14</td>
<td>5 mL in 1 BOX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDC:0781-3142-08</td>
<td>150 mL in 1 CARTON</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 mL in 1 VIAL, SINGLE-DOSAGE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<td>ANDA078601</td>
<td>07/24/2014</td>
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</tr>
</tbody>
</table>

### Labeler

- Sandoz Inc (110342024)

### Registrant

- Navinta LLC (130443810)

### Establishment

Emcure Pharmaceuticals Ltd.

### Revised by

Sandoz Inc

Revised: 9/2014

NDC:0781-3140-14

NDC:0781-3140-08

NDC:0781-3142-14

NDC:0781-3142-08