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3 **ROPIVACAINE HYDROCHLORIDE**

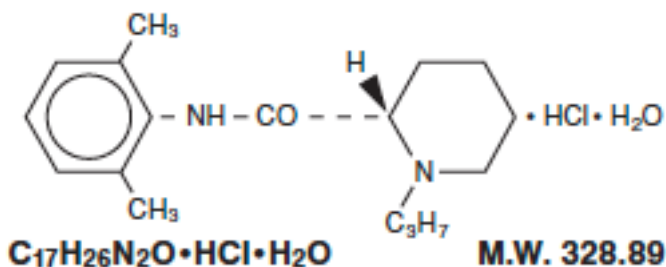
4 *INJECTION, USP*

5

6 Rx only

7 **DESCRIPTION:**

8 Ropivacaine Hydrochloride Injection, USP contains ropivacaine HCl which is a member  
9 of the amino amide class of local anesthetics. Ropivacaine Hydrochloride Injection, USP  
10 is a sterile, isotonic solution that contains the enantiomerically pure drug substance,  
11 sodium chloride for isotonicity and water for injection. Sodium hydroxide and/or  
12 hydrochloric acid may be used for pH adjustment. It is administered parenterally.  
13 Ropivacaine HCl is chemically described as S-(-)-1-propyl-2',6'-pipecoloxylidide  
14 hydrochloride monohydrate. The drug substance is a white crystalline powder, with the  
15 following structural formula:



16

17

18 At 25°C ropivacaine HCl has a solubility of 53.8 mg/mL in water, a distribution

19 ratio between n-octanol and phosphate buffer at pH 7.4 of 14:1 and a pKa of 8.07 in 0.1

20 M KCl solution. The pKa of ropivacaine is approximately the same as bupivacaine (8.1)

1 and is similar to that of mepivacaine (7.7). However, ropivacaine has an intermediate  
2 degree of lipid solubility compared to bupivacaine and mepivacaine.

3 Ropivacaine Hydrochloride Injection, USP is preservative-free and is available in  
4 single dose containers in 2 (0.2%), 5 (0.5%), 7.5 (0.75%) and 10 mg/mL (1%)  
5 concentrations. The specific gravity of Ropivacaine Hydrochloride Injection, USP  
6 solutions range from 1.002 to 1.005 at 25°C.

## 7 **CLINICAL PHARMACOLOGY:**

### 8 *Mechanism of Action*

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

## 17 **PHARMACOKINETICS:**

### 18 *Absorption*

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

22 From the epidural space, ropivacaine shows complete and biphasic absorption.

23 The half-lives of the 2 phases, (mean  $\pm$  SD) are  $14 \pm 7$  minutes and  $4.2 \pm 0.9$  h,

1 respectively. The slow absorption is the rate limiting factor in the elimination of  
2 ropivacaine that explains why the terminal half-life is longer after epidural than after  
3 intravenous administration. Ropivacaine shows dose-proportionality up to the highest  
4 intravenous dose studied,  
5 80 mg, corresponding to a mean  $\pm$  SD peak plasma concentration of  $1.9 \pm 0.3$  mcg/mL.

6 **Table 1**  
7 **Pharmacokinetic (plasma concentration-time) data from clinical trials**

Route	Epidural Infusion*		Epidural Infusion*	Epidural Block <sup>†</sup>	Epidural Block <sup>†</sup>	Plexus Block <sup>‡</sup>	IV Infusion <sup>§</sup>
Dose (mg)	1493 $\pm$ 10	2075 $\pm$ 206	1217 $\pm$ 277	150	187.5	300	40
N	12	12	11	8	8	10	12
C <sub>max</sub> (mg/L)	2.4 $\pm$ 1 <sup>¶</sup>	2.8 $\pm$ 0.5 <sup>¶</sup>	2.3 $\pm$ 1.1 <sup>¶</sup>	1.1 $\pm$ 0.2	1.6 $\pm$ 0.6	2.3 $\pm$ 0.8	1.2 $\pm$ 0.2 <sup>#</sup>
T <sub>max</sub> (min)	n/a <sup>▲</sup>	n/a	n/a	43 $\pm$ 14	34 $\pm$ 9	54 $\pm$ 22	n/a
AUC <sub>0-</sub> (mg.h/L)	135.5 $\pm$ 50	145 $\pm$ 34	161 $\pm$ 90	7.2 $\pm$ 2	11.3 $\pm$ 4	13 $\pm$ 3.3	1.8 $\pm$ 0.6
CL (L/h)	11.03	13.7	n/a	5.5 $\pm$ 2	5 $\pm$ 2.6	n/a	21.2 $\pm$ 7
t <sub>1/2</sub> (hr) <sup>♥</sup>	5 $\pm$ 2.5	5.7 $\pm$ 3	6 $\pm$ 3	5.7 $\pm$ 2	7.1 $\pm$ 3	6.8 $\pm$ 3.2	1.9 $\pm$ 0.5

8  
9 \* Continuous 72 hour epidural infusion after an epidural block with 5 or 10 mg/mL.

10 † Epidural anesthesia with 7.5 mg/mL (0.75%) for cesarean delivery.

11 ‡ Brachial plexus block with 7.5 mg/mL (0.75%) ropivacaine.

12 § 20 minute IV infusion to volunteers (40 mg).

13 ¶ C<sub>max</sub> measured at the end of infusion (ie, at 72 hr).

14 # C<sub>max</sub> measured at the end of infusion (ie, at 20 minutes).

15 ▲ n/a=not applicable

16 ♥ t<sub>1/2</sub> is the true terminal elimination half-life. On the other hand, t<sub>1/2</sub> follows absorption-dependent  
17 elimination (flip-flop) after non-intravenous administration.  
18

1 In some patients after a 300 mg dose for brachial plexus block, free plasma  
2 concentrations of ropivacaine may approach the threshold for CNS toxicity (see  
3 **PRECAUTIONS**). At a dose of greater than 300 mg, for local infiltration, the terminal  
4 half-life may be longer (>30 hours).

#### 5 ***Distribution***

6 After intravascular infusion, ropivacaine has a steady-state volume of distribution of  $41 \pm$   
7 7 liters. Ropivacaine is 94% protein bound, mainly to  $\alpha_1$ -acid glycoprotein. An increase  
8 in total plasma concentrations during continuous epidural infusion has been observed,  
9 related to a postoperative increase of  $\alpha_1$ -acid glycoprotein. Variations in unbound, ie,  
10 pharmacologically active, concentrations have been less than in total plasma  
11 concentration. Ropivacaine readily crosses the placenta and equilibrium in regard to  
12 unbound concentration will be rapidly reached (see **PRECAUTIONS, Labor and**  
13 ***Delivery***).

#### 14 ***Metabolism***

15 Ropivacaine is extensively metabolized in the liver, predominantly by aromatic  
16 hydroxylation mediated by cytochrome P4501A to 3-hydroxy ropivacaine. After a single  
17 IV dose approximately 37% of the total dose is excreted in the urine as both free and  
18 conjugated 3-hydroxy ropivacaine. Low concentrations of 3-hydroxy ropivacaine have  
19 been found in the plasma. Urinary excretion of the 4-hydroxy ropivacaine, and both the  
20 3-hydroxy N-de-alkylated (3-OH-PPX) and 4-hydroxy N-de-alkylated (4-OH-PPX)  
21 metabolites account for less than 3% of the dose. An additional metabolite, 2-hydroxy-  
22 methyl-ropivacaine, has been identified but not quantified in the urine. The N-de-  
23 alkylated metabolite of ropivacaine (PPX) and 3-OH-ropivacaine are the major

1 metabolites excreted in the urine during epidural infusion. Total PPX concentration in  
2 the plasma was about half as that of total ropivacaine; however, mean unbound  
3 concentrations of PPX were about 7 to 9 times higher than that of unbound ropivacaine  
4 following continuous epidural infusion up to 72 hours. Unbound PPX, 3-hydroxy and 4-  
5 hydroxy ropivacaine, have a pharmacological activity in animal models less than that of  
6 ropivacaine. There is no evidence of *in vivo* racemization in urine of ropivacaine.

### 7 ***Elimination***

8 The kidney is the main excretory organ for most local anesthetic metabolites. In total,  
9 86% of the ropivacaine dose is excreted in the urine after intravenous administration of  
10 which only 1% relates to unchanged drug. After intravenous administration ropivacaine  
11 has a mean  $\pm$  SD total plasma clearance of  $387 \pm 107$  mL/min, an unbound plasma  
12 clearance of  $7.2 \pm 1.6$  L/min, and a renal clearance of 1 mL/min. The mean  $\pm$  SD  
13 terminal half-life is  $1.8 \pm 0.7$  h after intravascular administration and  $4.2 \pm 1$  h after  
14 epidural administration (see ***Absorption***).

### 15 ***Pharmacodynamics***

16 Studies in humans have demonstrated that, unlike most other local anesthetics, the  
17 presence of epinephrine has no major effect on either the time of onset or the duration of  
18 action of ropivacaine. Likewise, addition of epinephrine to ropivacaine has no effect on  
19 limiting systemic absorption of ropivacaine.

20 Systemic absorption of local anesthetics can produce effects on the central  
21 nervous and cardiovascular systems. At blood concentrations achieved with therapeutic  
22 doses, changes in cardiac conduction, excitability, refractoriness, contractility, and  
23 peripheral vascular resistance have been reported. Toxic blood concentrations depress

1 cardiac conduction and excitability, which may lead to atrioventricular block, ventricular  
2 arrhythmias and to cardiac arrest, sometimes resulting in fatalities. In addition,  
3 myocardial contractility is depressed and peripheral vasodilation occurs, leading to  
4 decreased cardiac output and arterial blood pressure.

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

11       In 2 clinical pharmacology studies (total n=24) ropivacaine and bupivacaine were  
12 infused (10 mg/min) in human volunteers until the appearance of CNS symptoms, eg,  
13 visual or hearing disturbances, perioral numbness, tingling and others. Similar symptoms  
14 were seen with both drugs. In 1 study, the mean  $\pm$  SD maximum tolerated intravenous  
15 dose of ropivacaine infused ( $124 \pm 38$  mg) was significantly higher than that of  
16 bupivacaine ( $99 \pm 30$  mg) while in the other study the doses were not different ( $115 \pm 29$   
17 mg of ropivacaine and  $103 \pm 30$  mg of bupivacaine). In the latter study, the number of  
18 subjects reporting each symptom was similar for both drugs with the exception of muscle  
19 twitching which was reported by more subjects with bupivacaine than ropivacaine at  
20 comparable intravenous doses. At the end of the infusion, ropivacaine in both studies  
21 caused significantly less depression of cardiac conductivity (less QRS widening) than  
22 bupivacaine. Ropivacaine and bupivacaine caused evidence of depression of cardiac  
23 contractility, but there were no changes in cardiac output.

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

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

### 13 ***Clinical Trials***

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

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

### 19 **Epidural Administration In Surgery**

20 There were 25 clinical studies performed in 900 patients to evaluate ropivacaine epidural  
21 injection for general surgery. Ropivacaine was used in doses ranging from 75 to 250 mg.  
22 In doses of 100 to 200 mg, the median (1st to 3rd quartile) onset time to achieve a T10  
23 sensory block was 10 (5 to 13) minutes and the median (1st to 3rd quartile) duration at

1 the T10 level was 4 (3 to 5) hours (see **DOSAGE AND ADMINISTRATION**). Higher  
2 doses produced a more profound block with a greater duration of effect.

### 3 **Epidural Administration In Cesarean Section**

4 A total of 12 studies were performed with epidural administration of ropivacaine for  
5 cesarean section. Eight of these studies involved 218 patients using the concentration of  
6 5 mg/mL (0.5%) in doses up to 150 mg. Median onset measured at T6 ranged from 11 to  
7 26 minutes. Median duration of sensory block at T6 ranged from 1.7 to 3.2 h, and  
8 duration of motor block ranged from 1.4 to 2.9 h. Ropivacaine provided adequate muscle  
9 relaxation for surgery in all cases.

10 In addition, 4 active controlled studies for cesarean section were performed in 264  
11 patients at a concentration of 7.5 mg/mL (0.75%) in doses up to 187.5 mg. Median onset  
12 measured at T6 ranged from 4 to 15 minutes. Seventy-seven to 96% of ropivacaine-  
13 exposed patients reported no pain at delivery. Some patients received other anesthetic,  
14 analgesic, or sedative modalities during the course of the operative procedure.

### 15 **Epidural Administration In Labor And Delivery**

16 A total of 9 double-blind clinical studies, involving 240 patients were performed to  
17 evaluate ropivacaine for epidural block for management of labor pain. When  
18 administered in doses up to 278 mg as intermittent injections or as a continuous infusion,  
19 ropivacaine produced adequate pain relief.

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

1

**Table 2**

2

**LABOR AND DELIVERY META-ANALYSIS: MODE OF DELIVERY**

Delivery Mode	Ropivacaine n=199		Bupivacaine n=188	
	n	%	n	%
Spontaneous Vertex	116	58	92	49
Vacuum Extractor	26	}27*	33	}40
Forceps	28		42	
Cesarean Section	29	15	21	11

3

\*p=0.004 versus bupivacaine

4

**5 Epidural Administration In Postoperative Pain Management**

6

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

10

Epidural anesthesia with ropivacaine 5 mg/mL, (0.5%) was used intraoperatively for each of these procedures prior to initiation of postoperative ropivacaine. The incidence and intensity of the motor block were dependent on the dose rate of ropivacaine and the site of injection. Cumulative doses of up to 770 mg of ropivacaine were administered over 24 hours (intraoperative block plus 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 frequency of motor block was greatest at 4 hours and decreased during the infusion period in all groups. At least 80% of patients in the upper and lower abdominal studies and 42% in the orthopedic studies had no motor

18

1 block at the end of the 21-hour infusion period. Sensory block was also dose rate-  
2 dependent and a decrease in spread was observed during the infusion period.

3 A double-blind, randomized, clinical trial compared lumbar epidural infusion of  
4 ropivacaine (n=26) and bupivacaine (n=26) at 2 mg/mL (8 mL/h), for 24 hours after knee  
5 replacement. In this study, the pain scores were higher in the ropivacaine group, but the  
6 incidence and the intensity of motor block were lower.

7 Continuous epidural infusion of ropivacaine 2 mg/mL (0.2%) during up to 72  
8 hours for postoperative pain management after major abdominal surgery was studied in 2  
9 multi-center, double-blind studies. A total of 391 patients received a low thoracic  
10 epidural catheter, and ropivacaine 7.5 mg/L (0.75%) was given for surgery, in  
11 combination with GA. Post-operatively, ropivacaine 2 mg/mL (0.2%), 4 to 14 mL/h,  
12 alone or with fentanyl 1, 2, or 4 mcg/mL was infused through the epidural catheter and  
13 adjusted according to the patient's needs. These studies support the use of ropivacaine  
14 2 mg/mL (0.2%) for epidural infusion at 6 to 14 mL/h (12 to 28 mg) for up to 72 hours  
15 and demonstrated adequate analgesia with only slight and nonprogressive motor block in  
16 cases of moderate to severe postoperative pain.

17 Clinical studies with 2 mg/mL (0.2%) ropivacaine have demonstrated that  
18 infusion rates of 6 to 14 mL (12 to 28 mg) per hour provide adequate analgesia with  
19 nonprogressive motor block in cases of moderate to severe postoperative pain. In these  
20 studies, this technique resulted in a significant reduction in patients' morphine rescue  
21 dose requirement. Clinical experience supports the use of ropivacaine epidural infusions  
22 for up to 72 hours.

23

1 **Peripheral Nerve Block**

2 Ropivacaine, 5 mg/mL (0.5%), was evaluated for its ability to provide anesthesia for  
3 surgery using the techniques of Peripheral Nerve Block. There were 13 studies  
4 performed including a series of 4 pharmacodynamic and pharmacokinetic studies  
5 performed on minor nerve blocks. From these, 235 ropivacaine-treated patients were  
6 evaluable for efficacy. Ropivacaine was used in doses up to 275 mg. When used for  
7 brachial plexus block, onset depended on technique used. Supraclavicular blocks were  
8 consistently more successful than axillary blocks. The median onset of sensory block  
9 (anesthesia) produced by ropivacaine 0.5% via axillary block ranged from 10 minutes  
10 (medial brachial cutaneous nerve) to 45 minutes (musculocutaneous nerve). Median  
11 duration ranged from 3.7 hours (medial brachial cutaneous nerve) to 8.7 hours (ulnar  
12 nerve). The 5 mg/mL (0.5%) ropivacaine solution gave success rates from 56% to 86%  
13 for axillary blocks, compared with 92% for supraclavicular blocks.

14 In addition, ropivacaine, 7.5 mg/mL (0.75%), was evaluated in 99 ropivacaine-  
15 treated patients, in 2 double-blind studies, performed to provide anesthesia for surgery  
16 using the techniques of Brachial Plexus Block. Ropivacaine 7.5 mg/mL was compared to  
17 bupivacaine 5 mg/mL. In 1 study, patients underwent axillary brachial plexus block  
18 using injections of 40 mL (300 mg) of ropivacaine, 7.5 mg/mL (0.75%) or 40 mL  
19 injections of bupivacaine, 5 mg/mL (200 mg). In a second study, patients underwent  
20 subclavian perivascular brachial plexus block using 30 mL (225 mg) of ropivacaine,  
21 7.5 mg/mL (0.75%) or 30 mL of bupivacaine 5 mg/mL (150 mg). There was no  
22 significant difference between the ropivacaine and bupivacaine groups in either study

1 with regard to onset of anesthesia, duration of sensory blockade, or duration of  
2 anesthesia.

3           The median duration of anesthesia varied between 11.4 and 14.4 hours with both  
4 techniques. In one study, using the axillary technique, the quality of analgesia and  
5 muscle relaxation in the ropivacaine group was judged to be significantly superior to  
6 bupivacaine by both investigator and surgeon. However, using the subclavian  
7 perivascular technique, no statistically significant difference was found in the quality of  
8 analgesia and muscle relaxation as judged by both the investigator and surgeon. The use  
9 of ropivacaine 7.5 mg/mL for block of the brachial plexus via either the subclavian  
10 perivascular approach using 30 mL (225 mg) or via the axillary approach using 40 mL  
11 (300 mg) both provided effective and reliable anesthesia.

## 12 **Local Infiltration**

13 A total of 7 clinical studies were performed to evaluate the local infiltration of  
14 ropivacaine to produce anesthesia for surgery and analgesia in postoperative pain  
15 management. In these studies 297 patients who received ropivacaine in doses up to  
16 200 mg (concentrations up to 5 mg/mL, 0.5%) were evaluable for efficacy. With  
17 infiltration of 100 to 200 mg ropivacaine, the time to first request for analgesic was 2 to 6  
18 hours. When compared to placebo, ropivacaine produced lower pain scores and a  
19 reduction of analgesic consumption.

## 20 **INDICATIONS AND USAGE:**

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

- 1 Surgical Anesthesia: epidural block for surgery including cesarean section; major  
2 nerve block; local infiltration
- 3 Acute Pain Management: epidural continuous infusion or intermittent bolus, eg,  
4 postoperative or labor; local infiltration

5 **CONTRAINDICATIONS:**

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

8 **WARNINGS:**

- 9 In performing ropivacaine blocks, unintended intravenous injection is possible and may  
10 result in cardiac arrhythmia or cardiac arrest. The potential for successful resuscitation  
11 has not been studied in humans. There have been rare reports of cardiac arrest during the  
12 use of ropivacaine for epidural anesthesia or peripheral nerve blockade, the majority of  
13 which occurred after unintentional accidental intravascular administration in elderly  
14 patients and in patients with concomitant heart disease. In some instances, resuscitation  
15 has been difficult. Should cardiac arrest occur, prolonged resuscitative efforts may be  
16 required to improve the probability of a successful outcome.

- 17 Ropivacaine should be administered in incremental doses. It is not recommended  
18 for emergency situations, where a fast onset of surgical anesthesia is necessary.

- 19 Historically, pregnant patients were reported to have a high risk for cardiac arrhythmias,  
20 cardiac/circulatory arrest and death when 0.75% bupivacaine (another member of the  
21 amino amide class of local anesthetics) was inadvertently rapidly injected intravenously.

- 22 Prior to receiving major blocks the general condition of the patient should be  
23 optimized and the patient should have an IV line inserted. All necessary precautions

1 should be taken to avoid intravascular injection. Local anesthetics should only be  
2 administered by clinicians who are well versed in the diagnosis and management of dose-  
3 related toxicity and other acute emergencies which might arise from the block to be  
4 employed, and then only after insuring the **immediate (without delay)** availability of  
5 oxygen, other resuscitative drugs, cardiopulmonary resuscitative equipment, and the  
6 personnel resources needed for proper management of toxic reactions and related  
7 emergencies (see also **ADVERSE REACTIONS, PRECAUTIONS** and  
8 **MANAGEMENT OF LOCAL ANESTHETIC EMERGENCIES**). Delay in proper  
9 management of dose-related toxicity, underventilation from any cause, and/or altered  
10 sensitivity may lead to the development of acidosis, cardiac arrest and, possibly, death.  
11 Solutions of ropivacaine should not be used for the production of obstetrical paracervical  
12 block anesthesia, retrobulbar block, or spinal anesthesia (subarachnoid block) due to  
13 insufficient data to support such use. Intravenous regional anesthesia (bier block) should  
14 not be performed due to a lack of clinical experience and the risk of attaining toxic blood  
15 levels of ropivacaine.

16 Intra-articular infusions of local anesthetics following arthroscopic and other  
17 surgical procedures is an unapproved use, and there have been post-marketing reports of  
18 chondrolysis in patients receiving such infusions. The majority of reported cases of  
19 chondrolysis have involved the shoulder joint; cases of gleno-humeral chondrolysis have  
20 been described in pediatric and adult patients following intra-articular infusions of local  
21 anesthetics with and without epinephrine for periods of 48 to 72 hours. There is  
22 insufficient information to determine whether shorter infusion periods are not associated  
23 with these findings. The time of onset of symptoms, such as joint pain, stiffness and loss

1 of motion can be variable, but may begin as early as the 2nd month after surgery.  
2 Currently, there is no effective treatment for chondrolysis; patients who experienced  
3 chondrolysis have required additional diagnostic and therapeutic procedures and some  
4 required arthroplasty or shoulder replacement.

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

9 A well-known risk of epidural anesthesia may be an unintentional subarachnoid  
10 injection of local anesthetic. Two clinical studies have been performed to verify the  
11 safety of ropivacaine at a volume of 3 mL injected into the subarachnoid space since this  
12 dose represents an incremental epidural volume that could be unintentionally injected.  
13 The 15 and 22.5 mg doses injected resulted in sensory levels as high as T5 and T4,  
14 respectively. Anesthesia to pinprick started in the sacral dermatomes in 2 to 3 minutes,  
15 extended to the T10 level in 10 to 13 minutes and lasted for approximately 2 hours. The  
16 results of these two clinical studies showed that a 3 mL dose did not produce any serious  
17 adverse events when spinal anesthesia blockade was achieved.

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

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

1    **PRECAUTIONS:**

2    *General*

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

5           Resuscitative equipment, oxygen and other resuscitative drugs should be available  
6    for immediate use (see **WARNINGS** and **ADVERSE REACTIONS**). The lowest  
7    dosage that results in effective anesthesia should be used to avoid high plasma levels and  
8    serious adverse events. Injections should be made slowly and incrementally, with  
9    frequent aspirations before and during the injection to avoid intravascular injection.

10   When a continuous catheter technique is used, syringe aspirations should also be  
11   performed before and during each supplemental injection. During the administration of  
12   epidural anesthesia, it is recommended that a test dose of a local anesthetic with a fast  
13   onset be administered initially and that the patient be monitored for central nervous  
14   system and cardiovascular toxicity, as well as for signs of unintended intrathecal  
15   administration before proceeding. When clinical conditions permit, consideration should  
16   be given to employing local anesthetic solutions, which contain epinephrine for the test  
17   dose because circulatory changes compatible with epinephrine may also serve as a  
18   warning sign of unintended intravascular injection. An intravascular injection is still  
19   possible even if aspirations for blood are negative. Administration of higher than  
20   recommended doses of ropivacaine to achieve greater motor blockade or increased  
21   duration of sensory blockade may result in cardiovascular depression, particularly in the  
22   event of inadvertent intravascular injection. Tolerance to elevated blood levels varies  
23   with the physical condition of the patient. Debilitated, elderly patients and acutely ill

1 patients should be given reduced doses commensurate with their age and physical  
2 condition. Local anesthetics should also be used with caution in patients with  
3 hypotension, hypovolemia or heart block.

4 Careful and constant monitoring of cardiovascular and respiratory vital signs  
5 (adequacy of ventilation) and the patient's state of consciousness should be performed  
6 after each local anesthetic injection. It should be kept in mind at such times that  
7 restlessness, anxiety, incoherent speech, light-headedness, numbness and tingling of the  
8 mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching,  
9 depression, or drowsiness may be early warning signs of central nervous system toxicity.  
10 Because amide-type local anesthetics such as ropivacaine are metabolized by the liver,  
11 these drugs, especially repeat doses, should be used cautiously in patients with hepatic  
12 disease. Patients with severe hepatic disease, because of their inability to metabolize  
13 local anesthetics normally, are at a greater risk of developing toxic plasma  
14 concentrations. Local anesthetics should also be used with caution in patients with  
15 impaired cardiovascular function because they may be less able to compensate for  
16 functional changes associated with the prolongation of A-V conduction produced by  
17 these drugs.

18 Many drugs used during the conduct of anesthesia are considered potential  
19 triggering agents for malignant hyperthermia (MH). Amide-type local anesthetics are not  
20 known to trigger this reaction. However, since the need for supplemental general  
21 anesthesia cannot be predicted in advance, it is suggested that a standard protocol for MH  
22 management should be available.

23

1 ***Epidural Anesthesia***

2 During epidural administration, ropivacaine should be administered in incremental doses  
3 of 3 to 5 mL with sufficient time between doses to detect toxic manifestations of  
4 unintentional intravascular or intrathecal injection. Syringe aspirations should also be  
5 performed before and during each supplemental injection in continuous (intermittent)  
6 catheter techniques. An intravascular injection is still possible even if aspirations for  
7 blood are negative. During the administration of epidural anesthesia, it is recommended  
8 that a test dose be administered initially and the effects monitored before the full dose is  
9 given. When clinical conditions permit, the test dose should contain an appropriate dose  
10 of epinephrine to serve as a warning of unintentional intravascular injection. If injected  
11 into a blood vessel, this amount of epinephrine is likely to produce a transient  
12 “epinephrine response” within 45 seconds, consisting of an increase in heart rate and  
13 systolic blood pressure, circumoral pallor, palpitations and nervousness in the unsedated  
14 patient. The sedated patient may exhibit only a pulse rate increase of 20 or more beats  
15 per minute for 15 or more seconds. Therefore, following the test dose, the heart should  
16 be continuously monitored for a heart rate increase. Patients on beta-blockers may not  
17 manifest changes in heart rate, but blood pressure monitoring can detect a rise in systolic  
18 blood pressure. A test dose of a short-acting amide anesthetic such as lidocaine is  
19 recommended to detect an unintentional intrathecal administration. This will be  
20 manifested within a few minutes by signs of spinal block (eg, decreased sensation of the  
21 buttocks, paresis of the legs, or, in the sedated patient, absent knee jerk). An  
22 intravascular or subarachnoid injection is still possible even if results of the test dose are

1 negative. The test dose itself may produce a systemic toxic reaction, high spinal or  
2 epinephrine-induced cardiovascular effects.

### 3 *Use in Brachial Plexus Block*

4 Ropivacaine plasma concentrations may approach the threshold for central nervous  
5 system toxicity after the administration of 300 mg of ropivacaine for brachial plexus  
6 block. Caution should be exercised when using the 300 mg dose (see **OVERDOSAGE**).

7       The dose for a major nerve block must be adjusted according to the site of  
8 administration and patient status. Supraclavicular brachial plexus blocks may be  
9 associated with a higher frequency of serious adverse reactions, regardless of the local  
10 anesthetic used.

### 11 *Use in Peripheral Nerve Block*

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

### 16 *Use in Head and Neck Area*

17 Small doses of local anesthetics injected into the head and neck area may produce  
18 adverse reactions similar to systemic toxicity seen with unintentional intravascular  
19 injections of larger doses. The injection procedures require the utmost care. Confusion,  
20 convulsions, respiratory depression, and/or respiratory arrest, and cardiovascular  
21 stimulation or depression have been reported. These reactions may be due to intra-  
22 arterial injection of the local anesthetic with retrograde flow to the cerebral circulation.  
23 Patients receiving these blocks should have their circulation and respiration monitored

1 and be constantly observed. Resuscitative equipment and personnel for treating adverse  
2 reactions should be immediately available. Dosage recommendations should not be  
3 exceeded (see **DOSAGE AND ADMINISTRATION**).

#### 4 ***Use in Ophthalmic Surgery***

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

#### 8 ***Information for Patients***

9 When appropriate, patients should be informed in advance that they may experience  
10 temporary loss of sensation and motor activity in the anesthetized part of the body  
11 following proper administration of lumbar epidural anesthesia. Also, when appropriate,  
12 the physician should discuss other information including adverse reactions in the  
13 ropivacaine package insert.

#### 14 ***Drug Interactions***

15 Specific trials studying the interaction between ropivacaine and class III antiarrhythmic  
16 drugs (eg, amiodarone) have not been performed, but caution is advised (see  
17 **WARNINGS**).

18 Ropivacaine should be used with caution in patients receiving other local  
19 anesthetics or agents structurally related to amide-type local anesthetics, since the toxic  
20 effects of these drugs are additive. Cytochrome P4501A2 is involved in the formation of  
21 3-hydroxy ropivacaine, the major metabolite. *In vivo*, the plasma clearance of  
22 ropivacaine was reduced by 70% during coadministration of fluvoxamine (25 mg bid for  
23 2 days), a selective and potent CYP1A2 inhibitor. Thus strong inhibitors of cytochrome

1 P4501A2, such as fluvoxamine, given concomitantly during administration of  
2 ropivacaine, can interact with ropivacaine leading to increased ropivacaine plasma levels.  
3 Caution should be exercised when CYP1A2 inhibitors are coadministered. Possible  
4 interactions with drugs known to be metabolized by CYP1A2 via competitive inhibition  
5 such as theophylline and imipramine may also occur. Coadministration of a selective and  
6 potent inhibitor of CYP3A4, ketoconazole (100 mg bid for 2 days with ropivacaine  
7 infusion administered 1 hour after ketoconazole) caused a 15% reduction in *in vivo*  
8 plasma clearance of ropivacaine.

### 9 ***Carcinogenesis, Mutagenesis, Impairment of Fertility***

10 Long-term studies in animals of most local anesthetics, including ropivacaine, to evaluate  
11 the carcinogenic potential have not been conducted.

12 Weak mutagenic activity was seen in the mouse lymphoma test. Mutagenicity  
13 was not noted in the other assays, demonstrating that the weak signs of *in vitro* activity in  
14 the mouse lymphoma test were not manifest under diverse *in vivo* conditions.

15 Studies performed with ropivacaine in rats did not demonstrate an effect on  
16 fertility or general reproductive performance over 2 generations.

### 17 ***Pregnancy Category B***

18 Reproduction toxicity studies have been performed in pregnant New Zealand white  
19 rabbits and Sprague-Dawley rats. During gestation days 6 to 18, rabbits received 1.3, 4.2,  
20 or 13 mg/kg/day subcutaneously. In rats, subcutaneous doses of 5.3, 11 and  
21 26 mg/kg/day were administered during gestation days 6 to 15. No teratogenic effects  
22 were observed in rats and rabbits at the highest doses tested. The highest doses of

1 13 mg/kg/day (rabbits) and 26 mg/kg/day (rats) are approximately 1/3 of the maximum  
2 recommended human dose (epidural, 770 mg/24 hours) based on a mg/m<sup>2</sup> basis. In 2  
3 prenatal and postnatal studies, the female rats were dosed daily from day 15 of gestation  
4 to day 20 postpartum. The doses were 5.3, 11 and 26 mg/kg/day subcutaneously. There  
5 were no treatment-related effects on late fetal development, parturition, lactation,  
6 neonatal viability, or growth of the offspring.

7 In another study with rats, the males were dosed daily for 9 weeks before mating  
8 and during mating. The females were dosed daily for 2 weeks before mating and then  
9 during the mating, pregnancy, and lactation, up to day 42 post coitus. At 23 mg/kg/day,  
10 an increased loss of pups was observed during the first 3 days postpartum. The effect  
11 was considered secondary to impaired maternal care due to maternal toxicity.

12 There are no adequate or well-controlled studies in pregnant women of the effects  
13 of ropivacaine on the developing fetus. Ropivacaine should only be used during  
14 pregnancy if the benefits outweigh the risk.

15 Teratogenicity studies in rats and rabbits did not show evidence of any adverse  
16 effects on organogenesis or early fetal development in rats (26 mg/kg sc) or rabbits  
17 (13 mg/kg). The doses used were approximately equal to total daily dose based on body  
18 surface area. There were no treatment-related effects on late fetal development,  
19 parturition, lactation, neonatal viability, or growth of the offspring in 2 perinatal and  
20 postnatal studies in rats, at dose levels equivalent to the maximum recommended human  
21 dose based on body surface area. In another study at 23 mg/kg, an increased pup loss  
22 was seen during the first 3 days postpartum, which was considered secondary to impaired  
23 maternal care due to maternal toxicity.

1 ***Labor and Delivery***

2 Local anesthetics, including ropivacaine, rapidly cross the placenta, and when used for  
3 epidural block can cause varying degrees of maternal, fetal and neonatal toxicity (see  
4 **CLINICAL PHARMACOLOGY** and **PHARMACOKINETICS**). The incidence and  
5 degree of toxicity depend upon the procedure performed, the type and amount of drug  
6 used, and the technique of drug administration. Adverse reactions in the parturient, fetus  
7 and neonate involve alterations of the central nervous system, peripheral vascular tone  
8 and cardiac function.

9 Maternal hypotension has resulted from regional anesthesia with ropivacaine for  
10 obstetrical pain relief. Local anesthetics produce vasodilation by blocking sympathetic  
11 nerves. Elevating the patient's legs and positioning her on her left side will help prevent  
12 decreases in blood pressure. The fetal heart rate also should be monitored continuously,  
13 and electronic fetal monitoring is highly advisable. Epidural anesthesia has been reported  
14 to prolong the second stage of labor by removing the patient's reflex urge to bear down or  
15 by interfering with motor function. Spontaneous vertex delivery occurred more  
16 frequently in patients receiving ropivacaine than in those receiving bupivacaine.

17 ***Nursing Mothers***

18 Some local anesthetic drugs are excreted in human milk and caution should be exercised  
19 when they are administered to a nursing woman. The excretion of ropivacaine or its  
20 metabolites in human milk has not been studied. Based on the milk/plasma concentration  
21 ratio in rats, the estimated daily dose to a pup will be about 4% of the dose given to the  
22 mother. Assuming that the milk/plasma concentration in humans is of the same order, the

1 total ropivacaine dose to which the baby is exposed by breast-feeding is far lower than by  
2 exposure *in utero* in pregnant women at term (see **PRECAUTIONS**).

3 ***Pediatric Use***

4 The safety and efficacy of ropivacaine in pediatric patients have not been established.

5 ***Geriatric Use***

6 Of the 2,978 subjects that were administered Ropivacaine Hydrochloride Injection, USP  
7 in 71 controlled and uncontrolled clinical studies, 803 patients (27%) were 65 years of  
8 age or older which includes 127 patients (4%) 75 years of age and over. Ropivacaine  
9 Hydrochloride Injection, USP was found to be safe and effective in the patients in these  
10 studies. Clinical data in one published article indicate that differences in various  
11 pharmacodynamic measures were observed with increasing age. In one study, the upper  
12 level of analgesia increased with age, the maximum decrease of mean arterial pressure  
13 (MAP) declined with age during the first hour after epidural administration, and the  
14 intensity of motor blockade increased with age.

15 This drug and its metabolites are known to be excreted by the kidney, and the risk  
16 of toxic reactions to this drug may be greater in patients with impaired renal function.  
17 Elderly patients are more likely to have decreased hepatic, renal, or cardiac function, as  
18 well as concomitant disease. Therefore, care should be taken in dose selection, starting at  
19 the low end of the dosage range, and it may be useful to monitor renal function (see  
20 **PHARMACOKINETICS, *Elimination***).

21 **ADVERSE REACTIONS:**

22 Reactions to ropivacaine are characteristic of those associated with other amide-type  
23 local anesthetics. A major cause of adverse reactions to this group of drugs may be

1 associated with excessive plasma levels, which may be due to overdosage, unintentional  
2 intravascular injection or slow metabolic degradation.

3 The reported adverse events are derived from clinical studies conducted in the  
4 U.S. and other countries. The reference drug was usually bupivacaine. The studies used  
5 a variety of premedications, sedatives, and surgical procedures of varying length. A total  
6 of 3,988 patients have been exposed to ropivacaine at concentrations up to 1% in clinical  
7 trials. Each patient was counted once for each type of adverse event.

#### 8 ***Incidence $\geq$ 5%***

9 For the indications of epidural administration in surgery, cesarean section, postoperative  
10 pain management, peripheral nerve block, and local infiltration, the following treatment-  
11 emergent adverse events were reported with an incidence of  $\geq$  5% in all clinical studies  
12 (N=3988): hypotension (37%), nausea (24.8%), vomiting (11.6%), bradycardia (9.3%),  
13 fever (9.2%), pain (8%), postoperative complications (7.1%), anemia (6.1%), paresthesia  
14 (5.6%), headache (5.1%), pruritus (5.1%), and back pain (5%).

#### 15 ***Incidence 1 to 5%***

16 Urinary retention, dizziness, rigors, hypertension, tachycardia, anxiety, oliguria,  
17 hypoesthesia, chest pain, hypokalemia, dyspnea, cramps, and urinary tract infection.

#### 18 ***Incidence in Controlled Clinical Trials***

19 The reported adverse events are derived from controlled clinical studies with ropivacaine  
20 (concentrations ranged from 0.125% to 1% for ropivacaine and 0.25% to 0.75% for  
21 bupivacaine) in the U.S. and other countries involving 3,094 patients. Table 3A and 3B  
22 list adverse events (number and percentage) that occurred in at least 1% of ropivacaine-

1 treated patients in these studies. The majority of patients receiving concentrations higher  
 2 than 5 mg/mL (0.5%) were treated with ropivacaine.

3 **Table 3A**  
 4 **Adverse Events Reported in  $\geq 1\%$  of Adult Patients Receiving Regional or Local**  
 5 **Anesthesia (Surgery, Labor, Cesarean Section, Post-Operative Pain Management,**  
 6 **Peripheral Nerve Block and Local Infiltration)**

Adverse Reaction	Ropivacaine total N=1661		Bupivacaine total N=1433	
	N	(%)	N	(%)
Hypotension	536	(32.3)	408	(28.5)
Nausea	283	(17)	207	(14.4)
Vomiting	117	(7)	88	(6.1)
Bradycardia	96	(5.8)	73	(5.1)
Headache	84	(5.1)	68	(4.7)
Paresthesia	82	(4.9)	57	(4)
Back pain	73	(4.4)	75	(5.2)
Pain	71	(4.3)	71	(5)
Pruritus	63	(3.8)	40	(2.8)
Fever	61	(3.7)	37	(2.6)
Dizziness	42	(2.5)	23	(1.6)
Rigors (Chills)	42	(2.5)	24	(1.7)
Postoperative complications	41	(2.5)	44	(3.1)
Hypoesthesia	27	(1.6)	24	(1.7)
Urinary retention	23	(1.4)	20	(1.4)
Progression of labor poor/failed	23	(1.4)	22	(1.5)
Anxiety	21	(1.3)	11	(0.8)
Breast disorder, breast-feeding	21	(1.3)	12	(0.8)
Rhinitis	18	(1.1)	13	(0.9)

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1 **Table 3B**  
 2 **Adverse Events Reported in  $\geq 1\%$  of Fetuses or Neonates of Mothers Who Received**  
 3 **Regional Anesthesia (Cesarean Section and Labor Studies)**

Adverse Reaction	Ropivacaine		Bupivacaine	
	total N=639		total N=573	
	N	(%)	N	(%)
Fetal bradycardia	77	(12.1)	68	(11.9)
Neonatal jaundice	49	(7.7)	47	(8.2)
Neonatal complication-NOS	42	(6.6)	38	(6.6)
Apgar score low	18	(2.8)	14	(2.4)
Neonatal respiratory disorder	17	(2.7)	18	(3.1)
Neonatal tachypnea	14	(2.2)	15	(2.6)
Neonatal fever	13	(2)	14	(2.4)
Fetal tachycardia	13	(2)	12	(2.1)
Fetal distress	11	(1.7)	10	(1.7)
Neonatal infection	10	(1.6)	8	(1.4)
Neonatal hypoglycemia	8	(1.3)	16	(2.8)

4

5 ***Incidence <1%***

6 The following adverse events were reported during the ropivacaine clinical program in  
 7 more than one patient (N=3988), occurred at an overall incidence of <1%, and were con-  
 8 sidered relevant:

9 *Application Site Reactions* – injection site pain

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

12 *Female Reproductive* – poor progression of labor, uterine atony

13 *Gastrointestinal System* – fecal incontinence, tenesmus, neonatal vomiting

- 1 *General and Other Disorders* – hypothermia, malaise, asthenia, accident and/or injury
- 2 *Hearing and Vestibular* – tinnitus, hearing abnormalities
- 3 *Heart Rate and Rhythm* – extrasystoles, non-specific arrhythmias, atrial fibrillation
- 4 *Liver and Biliary System* – jaundice
- 5 *Metabolic Disorders* – hypomagnesemia
- 6 *Musculoskeletal System* – myalgia
- 7 *Myo/Endo/Pericardium* – ST segment changes, myocardial infarction
- 8 *Nervous System* – tremor, Horner’s syndrome, paresis, dyskinesia, neuropathy, vertigo,
- 9 coma, convulsion, hypokinesia, hypotonia, ptosis, stupor
- 10 *Psychiatric Disorders* – agitation, confusion, somnolence, nervousness, amnesia,
- 11 hallucination, emotional lability, insomnia, nightmares
- 12 *Respiratory System* – bronchospasm, coughing
- 13 *Skin Disorders* – rash, urticaria
- 14 *Urinary System Disorders* – urinary incontinence, micturition disorder
- 15 *Vascular* – deep vein thrombosis, phlebitis, pulmonary embolism
- 16 *Vision* – vision abnormalities

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

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**Table 4**  
**Common Events (Epidural Administration)**

Adverse Reaction	Ropivacaine						Bupivacaine			
	5 mg/mL		7.5 mg/mL		10 mg/mL		5 mg/mL		7.5 mg/mL	
	total N=256		total N=297		total N=207		total N=236		total N=174	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
hypotension	99	(38.7)	146	(49.2)	113	(54.6)	91	(38.6)	89	(51.1)
nausea	34	(13.3)	68	(22.9)			41	(17.4)	36	(20.7)
bradycardia	29	(11.3)	58	(19.5)	40	(19.3)	32	(13.6)	25	(14.4)
back pain	18	(7)	23	(7.7)	34	(16.4)	21	(8.9)	23	(13.2)
vomiting	18	(7)	33	(11.1)	23	(11.1)	19	(8.1)	14	(8)
headache	12	(4.7)	20	(6.7)	16	(7.7)	13	(5.5)	9	(5.2)
fever	8	(3.1)	5	(1.7)	18	(8.7)	11	(4.7)		
chills	6	(2.3)	7	(2.4)	6	(2.9)	4	(1.7)	3	(1.7)
urinary retention	5	(2)	8	(2.7)	10	(4.8)	10	(4.2)		
paresthesia	5	(2)	10	(3.4)	5	(2.4)	7	(3)		
pruritus			14	(4.7)	3	(1.4)			7	(4)

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 are broken down by gender.

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**Table 5**  
**Effects of Age on Hypotension (Epidural Administration)**  
**Total N: Ropivacaine = 760, Bupivacaine = 410**

AGE	Ropivacaine						Bupivacaine			
	5 mg/mL		7.5 mg/mL		10 mg/mL		5 mg/mL		7.5 mg/mL	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
<65	68	(32.2)	99	(43.2)	87	(51.5)	64	(33.5)	73	(48.3)
≥65	31	(68.9)	47	(69.1)	26	(68.4)	27	(60)	16	(69.6)

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**Table 6**  
**Most Common Adverse Events by Gender (Epidural Administration)**  
**Total N: Females = 405, Males = 355**

Adverse Reaction	Female		Male	
	N	(%)	N	(%)
hypotension	220	(54.3)	138	(38.9)
nausea	119	(29.4)	23	(6.5)
bradycardia	65	(16)	56	(15.8)
vomiting	59	(14.6)	8	(2.3)
back pain	41	(10.1)	23	(6.5)
headache	33	(8.1)	17	(4.8)
chills	18	(4.4)	5	(1.4)
fever	16	(4)	3	(0.8)
pruritus	16	(4)	1	(0.3)
pain	12	(3)	4	(1.1)
urinary retention	11	(2.7)	7	(2)
dizziness	9	(2.2)	4	(1.1)
hypoesthesia	8	(2)	2	(0.6)
paresthesia	8	(2)	10	(2.8)

8

1 ***Systemic Reactions***

2 The most commonly encountered acute adverse experiences that demand immediate  
3 countermeasures are related to the central nervous system and the cardiovascular system.  
4 These adverse experiences are generally dose-related and due to high plasma levels that  
5 may result from overdosage, rapid absorption from the injection site, diminished  
6 tolerance or from unintentional intravascular injection of the local anesthetic solution. In  
7 addition to systemic dose-related toxicity, unintentional subarachnoid injection of drug  
8 during the intended performance of lumbar epidural block or nerve blocks near the  
9 vertebral column (especially in the head and neck region) may result in underventilation  
10 or apnea (“Total or High Spinal”). Also, hypotension due to loss of sympathetic tone and  
11 respiratory paralysis or underventilation due to cephalad extension of the motor level of  
12 anesthesia may occur. This may lead to secondary cardiac arrest if untreated. Factors  
13 influencing plasma protein binding, such as acidosis, systemic diseases that alter protein  
14 production or competition with other drugs for protein binding sites, may diminish  
15 individual tolerance.

16 Epidural administration of ropivacaine has, in some cases, as with other local  
17 anesthetics, been associated with transient increases in temperature to >38.5°C. This  
18 occurred more frequently at doses of ropivacaine >16 mg/h.

19 ***Neurologic Reactions***

20 These are characterized by excitation and/or depression. Restlessness, anxiety, dizziness,  
21 tinnitus, blurred vision or tremors may occur, possibly proceeding to convulsions.  
22 However, excitement may be transient or absent, with depression being the first  
23 manifestation of an adverse reaction. This may quickly be followed by drowsiness

1 merging into unconsciousness and respiratory arrest. Other central nervous system  
2 effects may be nausea, vomiting, chills, and constriction of the pupils.

3         The incidence of convulsions associated with the use of local anesthetics varies  
4 with the route of administration and the total dose administered. In a survey of studies of  
5 epidural anesthesia, overt toxicity progressing to convulsions occurred in approximately  
6 0.1% of local anesthetic administrations.

7         The incidence of adverse neurological reactions associated with the use of local  
8 anesthetics may be related to the total dose and concentration of local anesthetic  
9 administered and are also dependent upon the particular drug used, the route of  
10 administration, and the physical status of the patient. Many of these observations may be  
11 related to local anesthetic techniques, with or without a contribution from the drug.  
12 During lumbar epidural block, occasional unintentional penetration of the subarachnoid  
13 space by the catheter or needle may occur. Subsequent adverse effects may depend  
14 partially on the amount of drug administered intrathecally as well as the physiological  
15 and physical effects of a dural puncture. These observations may include spinal block of  
16 varying magnitude (including high or total spinal block), hypotension secondary to spinal  
17 block, urinary retention, loss of bladder and bowel control (fecal and urinary  
18 incontinence), and loss of perineal sensation and sexual function. Signs and symptoms of  
19 subarachnoid block typically start within 2 to 3 minutes of injection. Doses of 15 and  
20 22.5 mg of ropivacaine resulted in sensory levels as high as T5 and T4, respectively.  
21 Analgesia started in the sacral dermatomes in 2 to 3 minutes and extended to the T10  
22 level in 10 to 13 minutes and lasted for approximately 2 hours. Other neurological  
23 effects following unintentional subarachnoid administration during epidural anesthesia

1 may include persistent anesthesia, paresthesia, weakness, paralysis of the lower  
2 extremities, and loss of sphincter control; all of which may have slow, incomplete or no  
3 recovery. Headache, septic meningitis, meningismus, slowing of labor, increased  
4 incidence of forceps delivery, or cranial nerve palsies due to traction on nerves from loss  
5 of cerebrospinal fluid have been reported (see **DOSAGE AND ADMINISTRATION**  
6 discussion of Lumbar Epidural Block). A high spinal is characterized by paralysis of the  
7 arms, loss of consciousness, respiratory paralysis and bradycardia.

### 8 *Cardiovascular System Reactions*

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

### 14 *Allergic Reactions*

15 Allergic type reactions are rare and may occur as a result of sensitivity to the local  
16 anesthetic (see **WARNINGS**). These reactions are characterized by signs such as  
17 urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema),  
18 tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated  
19 temperature, and possibly, anaphylactoid symptomatology (including severe  
20 hypotension). Cross-sensitivity among members of the amide-type local anesthetic group  
21 has been reported. The usefulness of screening for sensitivity has not been definitively  
22 established.

23

1 **OVERDOSAGE:**

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

6 **MANAGEMENT OF LOCAL ANESTHETIC EMERGENCIES:**

7 Therapy with ropivacaine should be discontinued at the first sign of toxicity. No specific  
8 information is available for the treatment of toxicity with ropivacaine; therefore,  
9 treatment should be symptomatic and supportive. The first consideration is prevention,  
10 best accomplished by incremental injection of ropivacaine, careful and constant  
11 monitoring of cardiovascular and respiratory vital signs and the patient's state of  
12 consciousness after each local anesthetic and during continuous infusion. At the first sign  
13 of change in mental status, oxygen should be administered.

14       The first step in the management of systemic toxic reactions, as well as  
15 underventilation or apnea due to unintentional subarachnoid injection of drug solution,  
16 consists of immediate attention to the establishment and maintenance of a patent airway  
17 and effective assisted or controlled ventilation with 100% oxygen with a delivery system  
18 capable of permitting immediate positive airway pressure by mask. Circulation should be  
19 assisted as necessary. This may prevent convulsions if they have not already occurred.

20       If necessary, use drugs to control convulsions. Intravenous barbiturates,  
21 anticonvulsant agents, or muscle relaxants should only be administered by those familiar  
22 with their use. Immediately after the institution of these ventilatory measures, the  
23 adequacy of the circulation should be evaluated. Supportive treatment of circulatory

1 depression may require administration of intravenous fluids, and, when appropriate, a  
2 vasopressor dictated by the clinical situation (such as ephedrine or epinephrine to  
3 enhance myocardial contractile force).

4       Should cardiac arrest occur, prolonged resuscitative efforts may be required to  
5 improve the probability of a successful outcome.

6       The mean dosages of ropivacaine producing seizures, after intravenous infusion in  
7 dogs, non-pregnant and pregnant sheep were 4.9, 6.1 and 5.9 mg/kg, respectively. These  
8 doses were associated with peak arterial total plasma concentrations of 11.4, 4.3 and 5  
9 mcg/mL, respectively.

10       In human volunteers given intravenous ropivacaine, the mean (min-max)  
11 maximum tolerated total and free arterial plasma concentrations were 4.3 (3.4 to 5.3) and  
12 0.6 (0.3 to 0.9) mcg/mL respectively, at which time moderate CNS symptoms (muscle  
13 twitching) were noted.

14       Clinical data from patients experiencing local anesthetic induced convulsions  
15 demonstrated rapid development of hypoxia, hypercarbia and acidosis within a minute of  
16 the onset of convulsions. These observations suggest that oxygen consumption and  
17 carbon dioxide production are greatly increased during local anesthetic convulsions and  
18 emphasize the importance of immediate and effective ventilation with oxygen which may  
19 avoid cardiac arrest.

20       If difficulty is encountered in the maintenance of a patent airway or if prolonged  
21 ventilatory support (assisted or controlled) is indicated, endotracheal intubation,  
22 employing drugs and techniques familiar to the clinician, may be indicated after initial  
23 administration of oxygen by mask.

1           The supine position is dangerous in pregnant women at term because of  
2 aortocaval compression by the gravid uterus. Therefore, during treatment of systemic  
3 toxicity, maternal hypotension or fetal bradycardia following regional block, the  
4 parturient should be maintained in the left lateral decubitus position if possible, or manual  
5 displacement of the uterus off the great vessels should be accomplished. Resuscitation of  
6 obstetrical patients may take longer than resuscitation of non-pregnant patients and  
7 closed-chest cardiac compression may be ineffective. Rapid delivery of the fetus may  
8 improve the response to resuscitative efforts.

9           **DOSAGE AND ADMINISTRATION:**

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

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

17          The dose of any local anesthetic administered varies with the anesthetic  
18 procedure, the area to be anesthetized, the vascularity of the tissues, the number of  
19 neuronal segments to be blocked, the depth of anesthesia and degree of muscle relaxation  
20 required, the duration of anesthesia desired, individual tolerance, and the physical  
21 condition of the patient. Patients in poor general condition due to aging or other  
22 compromising factors such as partial or complete heart conduction block, advanced liver  
23 disease or severe renal dysfunction require special attention although regional anesthesia

1 is frequently indicated in these patients. To reduce the risk of potentially serious adverse  
2 reactions, attempts should be made to optimize the patient's condition before major  
3 blocks are performed, and the dosage should be adjusted accordingly.

4 Use an adequate test dose (3 to 5 mL of a short acting local anesthetic solution  
5 containing epinephrine) prior to induction of complete block. This test dose should be  
6 repeated if the patient is moved in such a fashion as to have displaced the epidural  
7 catheter. Allow adequate time for onset of anesthesia following administration of each  
8 test dose.

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

12 The doses in the table are those considered to be necessary to produce a  
13 successful block and should be regarded as guidelines for use in adults. Individual  
14 variations in onset and duration occur. The figures reflect the expected average dose  
15 range needed. For other local anesthetic techniques standard current textbooks should be  
16 consulted.

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**Table 7**  
**Dosage Recommendations**

	Conc. mg/mL	(%)	Volume mL	Dose mg	Onset min	Duration hours
<b>SURGICAL ANESTHESIA</b>						
<b>Lumbar Epidural Administration</b>	5	(0.5%)	15 to 30	75 to 150	15 to 30	2 to 4
Surgery	7.5	(0.75%)	15 to 25	113 to 188	10 to 20	3 to 5
<b>Lumbar Epidural Administration</b>	10	(1%)	15 to 20	150 to 200	10 to 20	4 to 6
Cesarean Section	5	(0.5%)	20 to 30	100 to 150	15 to 25	2 to 4
<b>Thoracic Epidural Administration</b>	7.5	(0.75%)	15 to 20	113 to 150	10 to 20	3 to 5
Surgery	5	(0.5%)	5 to 15	25 to 75	10 to 20	n/a*
<b>Major Nerve Block<sup>†</sup></b>	7.5	(0.75%)	5 to 15	38 to 113	10 to 20	n/a*
(eg, brachial plexus block)	5	(0.5%)	35 to 50	175 to 250	15 to 30	5 to 8
<b>Field Block</b>	7.5	(0.75%)	10 to 40	75 to 300	10 to 25	6 to 10
(eg, minor nerve blocks and infiltration)	5	(0.5%)	1 to 40	5 to 200	1 to 15	2 to 6
<b>LABOR PAIN MANAGEMENT</b>						
<b>Lumbar Epidural Administration</b>						
Initial Dose	2	(0.2%)	10 to 20	20 to 40	10 to 15	0.5-1.5
Continuous infusion <sup>‡</sup>	2	(0.2%)	6 to 14 mL/h	12 to 28 mg/h	n/a*	n/a*
Incremental injections (top-up) <sup>‡</sup>	2	(0.2%)	10 to 15 mL/h	20 to 30 mg/h	n/a*	n/a*
<b>POSTOPERATIVE PAIN MANAGEMENT</b>						
<b>Lumbar Epidural Administration</b>						
Continuous infusion <sup>§</sup>	2	(0.2%)	6 to 14 mL/h	12 to 28 mg/h	n/a*	n/a*
<b>Thoracic Epidural Administration</b>	2	(0.2%)	6 to 14 mL/h	12 to 28 mg/h	n/a*	n/a*
Continuous infusion <sup>§</sup>						
<b>Infiltration</b>	2	(0.2%)	1 to 100	2 to 200	1 to 5	2 to 6
(eg, minor nerve block)	5	(0.5%)	1 to 40	5 to 200	1 to 5	2 to 6

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\* = Not Applicable

<sup>†</sup> = The dose for a major nerve block must be adjusted according to site of administration and patient status. Supraclavicular brachial plexus blocks may be associated with a higher frequency of serious adverse reactions, regardless of the local anesthetic used (see **PRECAUTIONS**).

<sup>‡</sup> = Median dose of 21 mg per hour was administered by continuous infusion or by incremental injections (top-ups) over a median delivery time of 5.5 hours.

<sup>§</sup> = Cumulative doses up to 770 mg of ropivacaine over 24 hours (intraoperative block plus postoperative infusion); Continuous epidural infusion at rates up to 28 mg per hour for 72 hours have been well tolerated in adults, ie, 2016 mg plus surgical dose of approximately 100 to 150 mg as top-up.

1           When prolonged blocks are used, either through continuous infusion or through  
2 repeated bolus administration, the risks of reaching a toxic plasma concentration or  
3 inducing local neural injury must be considered. Experience to date indicates that a  
4 cumulative dose of up to 770 mg ropivacaine administered over 24 hours is well tolerated  
5 in adults when used for postoperative pain management: ie, 2016 mg. Caution should be  
6 exercised when administering ropivacaine for prolonged periods of time, eg, >70 hours in  
7 debilitated patients.

8           For treatment of postoperative pain, the following technique can be  
9 recommended: If regional anesthesia was not used intraoperatively, then an initial  
10 epidural block with 5 to 7 mL ropivacaine is induced via an epidural catheter. Analgesia  
11 is maintained with an infusion of ropivacaine, 2 mg/mL (0.2%). Clinical studies have  
12 demonstrated that infusion rates of 6 to 14 mL (12 to 28 mg) per hour provide adequate  
13 analgesia with nonprogressive motor block. With this technique a significant reduction  
14 in the need for opioids was demonstrated. Clinical experience supports the use of  
15 ropivacaine epidural infusions for up to 72 hours.

16 **HOW SUPPLIED:**

17 **Ropivacaine Hydrochloride Injection, USP Single Dose Vials, in packages of 25, as**  
18 **follows:**

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<b>Product No.</b>	<b>NDC No.</b>	<b>Strength</b>	<b>Size</b>
702720	63323-702-20	7.5 mg/mL (0.75%)	20 mL single dose vial.
703810	63323-703-10	10 mg/mL (1%)	10 mL single dose vial.
703820	63323-703-20	10 mg/mL (1%)	20 mL single dose vial.

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1           The solubility of ropivacaine is limited at pH above 6. Thus, care must be taken  
2 as precipitation may occur if ropivacaine is mixed with alkaline solutions.

3           Disinfecting agents containing heavy metals, which cause release of respective  
4 ions (mercury, zinc, copper, etc.) should not be used for skin or mucous membrane  
5 disinfection since they have been related to incidents of swelling and edema.

6           When chemical disinfection of the container surface is desired, either isopropyl  
7 alcohol (91%) or ethyl alcohol (70%) is recommended. It is recommended that chemical  
8 disinfection be accomplished by wiping the vial stopper thoroughly with cotton or gauze  
9 that has been moistened with the recommended alcohol just prior to use. When a  
10 container is required to have a sterile outside, a Sterile-Pak should be chosen. Glass  
11 containers may, as an alternative, be autoclaved once. Stability has been demonstrated  
12 using a targeted  $F_0$  of 7 minutes at 121°C.

13           Solutions should be stored at 20° to 25°C (68° to 77°F) [see USP Controlled  
14 Room Temperature].

15           This container closure is not made with natural rubber latex.

16           These products are intended for single use and are free from preservatives. Any  
17 solution remaining from an opened container should be discarded promptly. In addition,  
18 continuous infusion bottles should not be left in place for more than 24 hours.

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22 Revised: February 2012