

ROPIDEX- dexamethasone sodium phosphate, ropivacaine hydrochloride, povidine iodine
Asclemed USA, Inc.

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Dexamethasone Sodium Phosphate Injection, USP

For Intravenous or Intramuscular Use Only

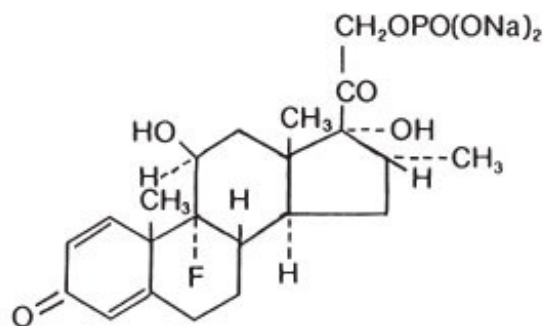
Rx only

DESCRIPTION

Dexamethasone Sodium Phosphate Injection, USP, is a water-soluble inorganic ester of dexamethasone which produces a rapid response even when injected intramuscularly.

Dexamethasone Sodium Phosphate, USP chemically is Pregna-1,4-diene-3,20-dione, 9-fluoro- 11,17-dihydroxy-16-methyl-21-(phosphonooxy)-, disodium salt, (11 β , 16 α).

It occurs as a white to creamy white powder, is exceedingly hygroscopic, is soluble in water and its solutions have a pH between 7.0 and 8.5. It has the following structural formula:



$C_{22}H_{28}FNa_2O_8P$

M.W. 516.41

Each mL of Dexamethasone Sodium Phosphate Injection, USP (**Preservative Free**) contains dexamethasone sodium phosphate, USP equivalent to 10 mg dexamethasone phosphate; 24.75 mg sodium citrate, dihydrate; and Water for Injection, q.s. pH adjusted with citric acid or sodium hydroxide, if necessary. pH: 7.0 to 8.5.

CLINICAL PHARMACOLOGY

Dexamethasone sodium phosphate injection has a rapid onset but short duration of action when compared with less soluble preparations. Because of this, it is suitable for the treatment of acute disorders responsive to adrenocortical steroid therapy.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs, including dexamethasone, are primarily used for their

potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

At equipotent anti-inflammatory doses, dexamethasone almost completely lacks the sodium-retaining property of hydrocortisone and closely related derivatives of hydrocortisone.

INDICATIONS AND USAGE

By intravenous or intramuscular injection when oral therapy is not feasible:

1. Endocrine Disorders

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance).

Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used).

Preoperatively, and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful.

Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected.

Congenital adrenal hyperplasia

Nonsuppurative thyroiditis

Hypercalcemia associated with cancer

2. Rheumatic Disorders

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

Post-traumatic osteoarthritis

Synovitis of osteoarthritis

Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy).

Acute and subacute bursitis

Epicondylitis

Acute nonspecific tenosynovitis

Acute gouty arthritis

Psoriatic arthritis

Ankylosing spondylitis

3. *Collagen Diseases*

During an exacerbation or as maintenance therapy in selected cases of:

Systemic lupus erythematosus

Acute rheumatic carditis

4. *Dermatologic Diseases*

Pemphigus

Severe erythema multiforme (Stevens-Johnson syndrome)

Exfoliative dermatitis

Bullous dermatitis herpetiformis

Severe seborrheic dermatitis

Severe psoriasis

Mycosis fungoides

5. *Allergic States*

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:

Bronchial asthma

Contact dermatitis

Atopic dermatitis

Serum sickness

Seasonal or perennial allergic rhinitis

Drug hypersensitivity reactions

Urticarial transfusion reactions

Acute noninfectious laryngeal edema (epinephrine is the drug of first choice).

6. *Ophthalmic Diseases*

Severe acute and chronic allergic and inflammatory processes involving the eye, such as:

Herpes zoster ophthalmicus

Iritis, iridocyclitis

Chorioretinitis

Diffuse posterior uveitis and choroiditis

Optic neuritis

Sympathetic ophthalmia

Anterior segment inflammation

Allergic conjunctivitis

Keratitis

Allergic corneal marginal ulcers

7. Gastrointestinal Diseases

To tide the patient over a critical period of the disease in:

Ulcerative colitis (systemic therapy)

Regional enteritis (systemic therapy)

8. Respiratory Diseases

Symptomatic sarcoidosis

Berylliosis

Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy.

Loeffler's syndrome not manageable by other means.

Aspiration pneumonitis

9. Hematologic Disorders

Acquired (autoimmune) hemolytic anemia.

Idiopathic thrombocytopenic purpura in adults

(IV only; IM administration is contraindicated).

Secondary thrombocytopenia in adults

Erythroblastopenia (RBC anemia)

Congenital (erythroid) hypoplastic anemia

10. Neoplastic Diseases

For palliative management of:

Leukemias and lymphomas in adults

Acute leukemia of childhood

11. Edematous States

To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

12. Miscellaneous

Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.

Trichinosis with neurologic or myocardial involvement.

13. Diagnostic testing of adrenocortical hyperfunction.

14. Cerebral Edema associated with primary or metastatic brain tumor, craniotomy, or

head injury. Use in cerebral edema is not a substitute for careful neurosurgical evaluation

and definitive management such as neurosurgery or other specific therapy.

CONTRAINDICATIONS

Systemic fungal infections (see **WARNINGS** regarding amphotericin B).

Hypersensitivity to any component of this product (see **WARNINGS**) .

WARNINGS

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug. Anaphylactoid and hypersensitivity reactions have been reported for dexamethasone sodium phosphate injection (see **ADVERSE REACTIONS**).

Corticosteroids may exacerbate systemic fungal infections and, therefore, should not be used in the presence of such infections unless they are needed to control drug reactions due to amphotericin B. Moreover, there have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive failure.

In patients on corticosteroid therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. If the patient is receiving steroids already, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Moreover, corticosteroids may affect the nitroblue-tetrazolium test for bacterial infection and produce false negative results.

In cerebral malaria, a double-blind trial has shown that the use of corticosteroids is associated with prolongation of coma and a higher incidence of pneumonia and gastrointestinal bleeding.

Corticosteroids may activate latent amebiasis. Therefore, it is recommended that latent or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses.

Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live virus vaccines, including smallpox, is contraindicated in individuals receiving immunosuppressive doses of corticosteroids. If inactivated viral or bacterial vaccines are administered to individuals receiving immunosuppressive doses of corticosteroids, the expected serum antibody response may not be obtained. However, immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Patients who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. The risk of developing a disseminated infection varies among individuals and can be related to the dose, route and duration of corticosteroid administration as well as to the underlying disease. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered. If exposed to measles, prophylaxis with immune globulin (IG) may be indicated. (See the respective package inserts for VZIG and IG for complete prescribing information).

The use of dexamethasone sodium phosphate injection in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids has not been established, and corticosteroids are not approved for this use.

Usage in Pregnancy

Since adequate human reproduction studies have not been done with corticosteroids, use of these drugs in pregnancy or in women of childbearing potential requires that the anticipated benefits be weighed against the possible hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of

corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. Mothers taking pharmacologic doses of corticosteroids should be advised not to nurse.

PRECAUTIONS

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

Following prolonged therapy, withdrawal of corticosteroids may result in symptoms of the corticosteroid withdrawal syndrome including fever, myalgia, arthralgia, and malaise. This may occur in patients even without evidence of adrenal insufficiency.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction must be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used with caution in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving large doses of corticosteroids may be minimal or absent. Fat embolism has been reported as a possible complication of hypercortisonism.

When large doses are given, some authorities advise that antacids be administered between meals to help prevent peptic ulcer.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Phenytoin, phenobarbital, ephedrine, and rifampin may enhance the metabolic clearance of corticosteroids resulting in decreased blood levels and lessened physiologic activity, thus requiring adjustment in corticosteroid dosage. These interactions may interfere with dexamethasone suppression tests which should be interpreted with caution during administration of these drugs.

False negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be

interpreted with caution in these patients.

The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time because of reports that corticosteroids have altered the response to these anticoagulants. Studies have shown that the usual effect produced by adding corticosteroids is inhibition of response to coumarins, although there have been some conflicting reports of potentiation not substantiated by studies.

When corticosteroids are administered concomitantly with potassium-depleting diuretics, patients should be observed closely for development of hypokalemia.

The slower rate of absorption by intramuscular administration should be recognized.

Information for Patients

Susceptible patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Pediatric Use

Growth and development of infants and children patients on prolonged corticosteroid therapy should be carefully followed.

ADVERSE REACTIONS

Fluid and electrolyte disturbances:

- Sodium retention
- Fluid retention
- Congestive heart failure in susceptible patients
- Potassium loss
- Hypokalemic alkalosis
- Hypertension

Musculoskeletal:

- Muscle weakness
- Steroid myopathy
- Loss of muscle mass
- Osteoporosis
- Vertebral compression fractures
- Aseptic necrosis of femoral and humeral heads
- Tendon rupture
- Pathologic fracture of long bones

Gastrointestinal:

Peptic ulcer with possible subsequent perforation and hemorrhage

Perforation of the small and large bowel; particularly in patients with inflammatory bowel disease

Pancreatitis

Abdominal distention

Ulcerative esophagitis

Dermatologic:

Impaired wound healing

Thin fragile skin

Petechiae and ecchymoses

Erythema

Increased sweating

May suppress reactions to skin tests

Burning or tingling, especially in the perineal area (after IV injection)

Other cutaneous reactions, such as allergic dermatitis, urticaria, angioneurotic edema

Neurologic:

Convulsions

Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment

Vertigo

Headache

Psychic disturbances

Endocrine:

Menstrual irregularities

Development of cushingoid state

Suppression of growth in pediatric patients

Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness

Decreased carbohydrate tolerance

Manifestations of latent diabetes mellitus

Increased requirements for insulin or oral hypoglycemic agents in diabetics

Hirsutism

Ophthalmic:

Posterior subcapsular cataracts

Increased intraocular pressure

Glaucoma

Exophthalmos

Retinopathy of prematurity

Metabolic:

Negative nitrogen balance due to protein catabolism

Cardiovascular:

Myocardial rupture following recent myocardial infarction (see **WARNINGS**)

Hypertrophic cardiomyopathy in low birth weight infants

Other:

Anaphylactoid or hypersensitivity reactions

Thromboembolism

Weight gain

Increased appetite

Nausea

Malaise

Hiccups

The following *additional* adverse reactions are related to parenteral corticosteroid therapy:

Hyperpigmentation or hypopigmentation

Subcutaneous and cutaneous atrophy

Sterile abscess

Charcot-like arthropathy

OVERDOSAGE

Reports of acute toxicity and/or death following overdosage of glucocorticoids are rare. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic.

The oral LD₅₀ of dexamethasone in female mice was 6.5 g/kg. The intravenous LD₅₀ of dexamethasone sodium phosphate in female mice was 794 mg/kg.

DOSAGE AND ADMINISTRATION

Dexamethasone sodium phosphate injection, 10 mg/mL– *For intravenous and intramuscular injection only.*

Dexamethasone sodium phosphate injection can be given directly from the vial, or it can be added to Sodium Chloride Injection or Dextrose Injection and administered by intravenous drip.

Solutions used for intravenous administration or further dilution of this product should be preservative free when used in the neonate, especially the premature infant.

When it is mixed with an infusion solution, sterile precautions should be observed. Since infusion solutions generally do not contain preservatives, mixtures should be used within 24 hours.

DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPONSE OF THE PATIENT.

Intravenous and Intramuscular Injection

The initial dosage of dexamethasone sodium phosphate injection varies from 0.5 to 9 mg a day depending on the disease being treated. In less severe diseases doses lower than 0.5 mg may suffice, while in severe diseases doses higher than 9 mg may be required.

The initial dosage should be maintained or adjusted until the patient's response is satisfactory. If a satisfactory clinical response does not occur after a reasonable period of time, discontinue dexamethasone sodium phosphate injection and transfer the patient to other therapy.

After a favorable initial response, the proper maintenance dosage should be determined by decreasing the initial dosage in small amounts to the lowest dosage that maintains an adequate clinical response.

Patients should be observed closely for signs that might require dosage adjustment, including changes in clinical status resulting from remissions or exacerbations of the disease, individual drug responsiveness, and the effect of stress (e.g., surgery, infection, trauma). During stress it may be necessary to increase dosage temporarily.

If the drug is to be stopped after more than a few days of treatment, it usually should be withdrawn gradually.

When the intravenous route of administration is used, dosage usually should be the same as the oral dosage. In certain overwhelming, acute, life-threatening situations, however, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages. The slower rate of absorption by intramuscular administration should be recognized.

Shock

There is a tendency in current medical practice to use high (pharmacologic) doses of corticosteroids for the treatment of unresponsive shock. The following dosages of dexamethasone sodium phosphate injection have been suggested by various authors:

Author	Dosage
Cavanagh ¹	3 mg/kg of body weight per 24 hours by constant intravenous infusion after an initial intravenous injection of 20 mg

Dietzman ²	2 to 6 mg/kg of body weight as a single intravenous injection
Frank ³	40 mg initially followed by repeat intravenous injection every 4 to 6 hours while shock persists
Oaks ⁴	40 mg initially followed by repeat intravenous injection every 2 to 6 hours while shock persists
Schumer ⁵	1 mg/kg of body weight as a single intravenous injection

Administration of high dose corticosteroid therapy should be continued only until the patient's condition has stabilized and usually not longer than 48 to 72 hours.

Although adverse reactions associated with high dose, short-term corticosteroid therapy are uncommon, peptic ulceration may occur.

Cerebral Edema

Dexamethasone sodium phosphate injection is generally administered initially in a dosage of 10 mg intravenously followed by four mg every six hours intramuscularly until the symptoms of cerebral edema subside. Response is usually noted within 12 to 24 hours and dosage may be reduced after two to four days and gradually discontinued over a period of five to seven days. For palliative management of patients with recurrent or inoperable brain tumors, maintenance therapy with 2 mg two or three times a day may be effective.

Acute Allergic Disorders

In acute, self-limited allergic disorders or acute exacerbations of chronic allergic disorders, the following dosage schedule combining parenteral and oral therapy is suggested:

Dexamethasone sodium phosphate injection, *first day*, 4 or 8 mg intramuscularly.

Dexamethasone tablets, 0.75 mg: *second and third days*, 4 tablets in two divided doses each day; *fourth day*, 2 tablets in two divided doses; *fifth and sixth days*, 1 tablet each day; *seventh day*, no treatment; *eighth day*, follow-up visit.

This schedule is designed to ensure adequate therapy during acute episodes, while minimizing the risk of overdosage in chronic cases.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever the solution and container permit.

HOW SUPPLIED

Dexamethasone Sodium Phosphate Injection, USP (**Preservative Free**) equivalent to 10 mg dexamethasone phosphate, is supplied in a single dose vial as follows:

Product No.	NDC No.	Strength	Vial Size
500601	63323-506-01	10 mg per mL	1 mL vial, packaged in twenty-fives.

This container closure is not made with natural rubber latex.

Storage

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Sensitive to heat. Do not autoclave.

Protect from freezing.

Protect from light.

Single dose vials-Store in container until time of use. Discard unused portion.

REFERENCES

1. Cavanagh, D.; Singh, K.B.: Endotoxin shock in pregnancy and abortion, in: "Corticosteroids in the Treatment of Shock", Schumer, W.; Nyhus, L.M., Editors, Urbana, University of Illinois Press, 1970, pp. 86-96.
2. Dietzman, R.H.; Ersek, R.A.; Bloch, J.M.; Lilleheir, R.C.: High-output, low-resistance gram-negative septic shock in man, *Angiology* 20: 691-700, Dec. 1969.
3. Frank, E.: Clinical observations in shock and management (in: Shields, T.F., ed.: Symposium on current concepts and management of shock), *J. Maine Med. Ass.* 59: 195-200, Oct. 1968.
4. Oaks, W. W.; Cohen, H.E.: Endotoxin shock in the geriatric patient, *Geriatr.* 22: 120-130, Mar. 1967.
5. Schumer, W.; Nyhus, L.M.: Corticosteroid effect on biochemical parameters of human oligemic shock, *Arch. Surg.* 100: 405-408, Apr. 1970.



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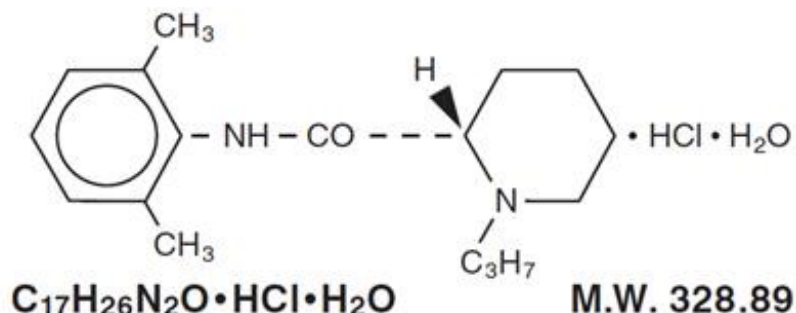
Ropivacaine Hydrochloride Injection, USP Rx only

DESCRIPTION

Ropivacaine hydrochloride injection, USP contains ropivacaine hydrochloride which is a member of the amino amide class of local anesthetics. Ropivacaine hydrochloride injection, USP is a clear, colorless, sterile, isotonic solution free from visible particles that contains the enantiomerically pure drug substance, sodium chloride for isotonicity and water for injection. Sodium hydroxide and/or hydrochloric acid may be used for pH

adjustment. It is administered parenterally.

Ropivacaine hydrochloride USP is chemically described as S-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate. The drug substance is a white crystalline powder, with the following structural formula:



At 25°C ropivacaine hydrochloride has a solubility of 53.8 mg/mL in water, a distribution ratio between n-octanol and phosphate buffer at pH 7.4 of 14:1 and a pKa of 8.07 in 0.1 M KCl solution. 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 hydrochloride injection, USP is preservative-free and is available in single dose containers in 5 mg/mL (0.5%) concentrations. The specific gravity of ropivacaine hydrochloride injection, USP solutions range from 1.002 to 1.005 at 25°C.

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 the 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 \pm SD) are 14 ± 7 minutes and 4.2 ± 0.9 h, 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 \pm SD peak plasma concentration of 1.9 ± 0.3 mcg/mL.

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

Route	Epidural Infusion *		Epidural Infusion *	Epidural Block †	Epidural Block †	Plexus Block ‡	IV Infusion §
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 _{max} (mg/L)	2.4 \pm 1 ¶	2.8 \pm 0.5 ¶	2.3 \pm 1.1 ¶	1.1 \pm 0.2	1.6 \pm 0.6	2.3 \pm 0.8	1.2 \pm 0.2 #
T _{max} (min)	n/a ♠	n/a	n/a	43 \pm 14	34 \pm 9	54 \pm 22	n/a
AUC ₀₋ (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 _{1/2} (hr) ♥	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

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

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

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

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

¶ C_{max} measured at the end of infusion (i.e., at 72 hr).

C_{max} measured at the end of infusion (i.e., at 20 minutes).

♠ n/a=not applicable

♥ t_{1/2} is the true terminal elimination half-life. On the other hand, t_{1/2} follows absorption-dependent elimination (flip-flop) after non-intravenous administration.

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

Distribution

After intravascular infusion, ropivacaine has a steady-state volume of distribution of 41 ± 7 liters. Ropivacaine is 94% protein bound, mainly to α_1 -acid glycoprotein. An increase in total plasma concentrations during continuous epidural infusion has been observed, related to a postoperative increase of α_1 -acid glycoprotein. Variations in unbound, i.e., pharmacologically active, concentrations have been less than in total plasma concentration. Ropivacaine readily crosses the placenta and equilibrium 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 1A 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-alkylated (3-OH-PPX) and 4-hydroxy N-de-alkylated (4-OH-PPX) metabolites account for less than 3% of the dose. An additional metabolite, 2-hydroxy-methyl-ropivacaine, has been identified but not quantified in the urine. The N-de-alkylated metabolite of ropivacaine (PPX) and 3-OH-ropivacaine are the major metabolites excreted in the urine during epidural infusion. Total PPX concentration in the plasma was about half as that of total ropivacaine; however, mean 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 vivo* 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 \pm SD total plasma clearance of 387 ± 107 mL/min, an unbound plasma clearance of 7.2 ± 1.6 L/min, and a renal clearance of 1 mL/min. The mean \pm SD terminal half-life is 1.8 ± 0.7 h after intravascular 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 epinephrine has no major effect on either the time of onset or the duration of action of ropivacaine. Likewise, addition of epinephrine 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 atrioventricular block, ventricular arrhythmias and to cardiac arrest, sometimes resulting in fatalities. 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, e.g., visual or

hearing disturbances, perioral numbness, tingling and others. Similar symptoms were seen with both drugs. In 1 study, the mean \pm SD maximum tolerated intravenous dose of ropivacaine infused (124 ± 38 mg) was significantly higher than that of bupivacaine (99 ± 30 mg) while in the other study the doses were not different (115 ± 29 mg of ropivacaine and 103 ± 30 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 blockade 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 cardio-depressant 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 900 patients to evaluate ropivacaine hydrochloride epidural injection for general surgery. Ropivacaine hydrochloride was used in doses ranging from 75 to 250 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 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 muscle relaxation for surgery in all cases.

In addition, 4 active controlled studies for cesarean section were performed in 264 patients at a concentration of 7.5 mg/mL (0.75%) in doses up to 187.5 mg. Median onset measured at T6 ranged from 4 to 15 minutes. Seventy-seven to 96% 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 278 mg as intermittent injections or as a continuous infusion, ropivacaine hydrochloride produced adequate pain relief.

A prospective meta-analysis on 6 of these studies provided detailed evaluation of the delivered newborns 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

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

* p=0.004 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 intravascular 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 intraoperatively 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 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 block at the end of the 21-hour infusion period. Sensory block was also dose rate-dependent and a decrease in spread was observed during the infusion period.

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

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

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

Peripheral Nerve Block

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

In addition, ropivacaine hydrochloride, 7.5 mg/mL (0.75%), was evaluated in 99 ropivacaine hydrochloride-treated patients, in 2 double-blind studies, performed to provide anesthesia for surgery using the techniques of Brachial Plexus Block.

Ropivacaine hydrochloride 7.5 mg/mL was compared to bupivacaine 5 mg/mL. In 1 study, patients underwent axillary brachial plexus block using injections of 40 mL (300 mg) of ropivacaine hydrochloride, 7.5 mg/mL (0.75%) or 40 mL injections of bupivacaine, 5 mg/mL (200 mg). In a second study, patients underwent subclavian perivascular brachial plexus block using 30 mL (225 mg) of ropivacaine hydrochloride, 7.5 mg/mL (0.75%) or 30 mL of bupivacaine 5 mg/mL (150 mg). There was no significant difference between the ropivacaine hydrochloride and bupivacaine groups in either study with regard to onset of anesthesia, duration of sensory blockade, or duration of anesthesia.

The median duration of anesthesia varied between 11.4 and 14.4 hours with both techniques. In one study, using the axillary technique, the quality of analgesia and muscle relaxation in the ropivacaine hydrochloride group was judged to be significantly superior to bupivacaine by both investigator and surgeon. However, 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 either the subclavian perivascular approach using 30 mL (225 mg) or via the axillary approach using 40 mL (300 mg) both provided effective and reliable anesthesia.

Local Infiltration

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

INDICATIONS AND USAGE

Ropivacaine hydrochloride injection, USP 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, e.g., postoperative or labor; local infiltration

CONTRAINDICATIONS

Ropivacaine hydrochloride injection 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 intravenous 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 high risk for cardiac arrhythmias, cardiac/circulatory 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 other acute emergencies which might arise from the block to be employed, and then only after insuring the **immediate (without delay)** availability of oxygen, other resuscitative drugs, cardiopulmonary resuscitative equipment, and the personnel resources needed for proper management of toxic reactions and related emergencies (see also **ADVERSE REACTIONS, PRECAUTIONS** and **MANAGEMENT OF LOCAL ANESTHETIC EMERGENCIES**). Delay in proper management of dose-related toxicity, underventilation from any cause, and/or altered sensitivity may lead to the development of acidosis, cardiac arrest and, possibly, death. Solutions of ropivacaine hydrochloride should not be used for the production of obstetrical paracervical block anesthesia, retrobulbar block, or spinal anesthesia (subarachnoid block) due to insufficient data to support such use. Intravenous regional anesthesia (bier block) should not be performed due to a lack of clinical experience and the risk of attaining toxic blood levels of ropivacaine.

Intra-articular infusions 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 infusions. 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 infusions 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. Currently, 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 3 mL injected into the subarachnoid space since this dose represents an incremental epidural volume that could be unintentionally injected. The 15 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 (e.g., amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be additive.

Methemoglobinemia

Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.

Signs of methemoglobinemia may occur immediately or may be delayed some hours after exposure, and are characterized by a cyanotic skin discoloration and/or abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death.

Discontinue ropivacaine hydrochloride and any other oxidizing agents. Depending on the severity of the signs and symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. A more severe clinical presentation may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

PRECAUTIONS

General

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

Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use (see **WARNINGS** and **ADVERSE REACTIONS**). The lowest dosage that

results in effective anesthesia should be used to avoid high plasma levels and serious adverse events. Injections should be made slowly and incrementally, with frequent aspirations before and during the injection to avoid intravascular injection. When a continuous catheter technique is used, syringe aspirations should also be performed before and during each supplemental injection. During the administration of epidural anesthesia, it is recommended that a test dose of a local anesthetic with a fast onset be administered initially and that the patient be monitored for central nervous system and cardiovascular toxicity, as well as for signs of unintended intrathecal administration before proceeding. When 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 serve as a warning sign of unintended intravascular injection. An intravascular injection is still possible even if aspirations for blood are negative. Administration of higher than 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 also be used with caution in patients with hypotension, 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 at such times that restlessness, anxiety, incoherent speech, light-headedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, 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 the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a 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 aspirations should also be performed before and during each supplemental injection in continuous (intermittent) catheter techniques. An intravascular injection is still possible even if aspirations for blood are negative. During the administration of epidural anesthesia, it is

recommended that a test dose be administered initially and the effects monitored before the full dose is given. When 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 45 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 anesthetic such as lidocaine is recommended to detect an unintentional intrathecal administration. This will be manifested within a few minutes by signs of spinal block (e.g., decreased sensation of the buttocks, paresis of the legs, or, in the sedated patient, absent knee jerk). An intravascular 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 when using the 300 mg dose (see **OVERDOSAGE**).

The dose for a major nerve block must be adjusted according to the 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.

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/or 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 seen with unintentional intravascular injections of larger doses. The injection procedures require the utmost care. Confusion, convulsions, respiratory depression, and/or 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 cerebral circulation. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed. Resuscitative 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 in the ropivacaine hydrochloride package insert.

Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath; lightheadedness; or fatigue.

Drug Interactions

Specific trials studying the interaction between ropivacaine and class III antiarrhythmic drugs (e.g., 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. Cytochrome P4501A2 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 fluvoxamine (25 mg bid for 2 days), a selective and potent CYP1A2 inhibitor. Thus strong inhibitors of cytochrome P4501A2, such as fluvoxamine, given concomitantly during administration of ropivacaine hydrochloride, can interact with ropivacaine hydrochloride leading to increased ropivacaine plasma levels. Caution should be exercised when CYP1A2 inhibitors are coadministered. Possible interactions with drugs known to be metabolized by CYP1A2 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 1 hour after ketoconazole) caused a 15% reduction in *in vivo* plasma clearance of ropivacaine.

Patients who are administered local anesthetics are at increased risk of developing methemoglobinemia when concurrently exposed to the following drugs, which could include other local anesthetics:

Examples of Drugs Associated with Methemoglobinemia:

Class	Examples
Nitrates/Nitrites	nitric oxide, nitroglycerin, nitroprusside, nitrous oxide
Local anesthetics	articaine, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, procaine, ropivacaine, tetracaine
Anticoagulant	

Antineoplastic agents	cyclophosphamide, flutamide, hydroxyurea, ifosfamide, rasburicase
Antibiotics	dapsone, nitrofurantoin, para-aminosalicylic acid, sulfonamides
Antimalarials	chloroquine, primaquine
Anticonvulsants	Phenobarbital, phenytoin, sodium valproate
Other drugs	acetaminophen, metoclopramide, quinine, sulfasalazine

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 signs of *in vitro* activity in the mouse lymphoma test were not manifest under diverse *in vivo* conditions.

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

Pregnancy Category B

Reproduction 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 teratogenic 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 1/3 of the maximum recommended human dose (epidural, 770 mg/24 hours) based on a mg/m² basis. In 2 prenatal 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 late fetal development, parturition, lactation, neonatal viability, or growth of the offspring.

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

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

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

to impaired maternal care due to maternal toxicity.

Labor and Delivery

Local anesthetics, including ropivacaine, rapidly cross the placenta, and when used for epidural block can cause varying degrees of maternal, fetal and neonatal toxicity (see **CLINICAL PHARMACOLOGY** and **PHARMACOKINETICS**). 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.

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

Nursing Mothers

Some local anesthetic drugs are excreted in human milk and caution should be exercised when they are administered to a nursing woman. The excretion of ropivacaine or its metabolites in human milk has not been studied. Based on the milk/plasma concentration ratio in rats, the estimated daily dose to a pup will be about 4% of the dose given to the mother. Assuming that the milk/plasma concentration in humans is of the same order, the total ropivacaine hydrochloride dose to which the baby is exposed by breast-feeding is far lower than by exposure *in utero* in pregnant women at term (see **PRECAUTIONS**).

Pediatric Use

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

Geriatric Use

Of the 2,978 subjects that were administered ropivacaine hydrochloride injection in 71 controlled and uncontrolled clinical studies, 803 patients (27%) were 65 years of age or older which includes 127 patients (4%) 75 years of age and over. Ropivacaine hydrochloride injection was found to be safe and effective in the patients in these studies. 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 blockade increased with age.

This drug and its metabolites are known to be excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

Elderly patients are more likely to have decreased hepatic, renal, or cardiac function, as well as concomitant disease. Therefore, care should be taken in dose selection, starting at the low end of the dosage range, and it may be useful to monitor renal function (see PHARMACOKINETICS, Elimination).

ADVERSE REACTIONS

Reactions to ropivacaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs may be associated with excessive plasma levels, which may be due to overdosage, unintentional intravascular injection or slow metabolic degradation.

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

Incidence \geq 5%

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

Incidence 1 to 5%

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

Incidence in Controlled Clinical Trials

The reported adverse events are derived from controlled clinical studies with ropivacaine hydrochloride (concentrations ranged from 0.125% to 1% for ropivacaine hydrochloride and 0.25% to 0.75% for bupivacaine) in the U.S. and other countries involving 3,094 patients. Table 3A and 3B list adverse events (number and percentage) that occurred in at least 1% of ropivacaine hydrochloride-treated patients in these studies. The majority of patients receiving concentrations higher than 5 mg/mL (0.5%) were treated with ropivacaine hydrochloride.

Table 3A

Adverse Events Reported in \geq 1% of Adult Patients Receiving Regional or Local Anesthesia (Surgery, Labor, Cesarean Section, Postoperative Pain Management, Peripheral Nerve Block and Local Infiltration)

Adverse Reaction	Ropivacaine Hydrochloride 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)

Table 3B

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

Adverse Reaction	Ropivacaine Hydrochloride total N=639		Bupivacaine 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)

Incidence <1%

The following adverse events were reported during the ropivacaine hydrochloride clinical program in more than one patient (N=3988), 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, asthenia, accident and/or injury

Hearing and Vestibular – tinnitus, hearing abnormalities

Heart Rate and Rhythm – extrasystoles, non-specific arrhythmias, atrial fibrillation

Liver and Biliary System – jaundice

Metabolic Disorders – hypomagnesemia

Musculoskeletal System – myalgia

Myo/Endo/Pericardium – ST segment changes, myocardial infarction

Nervous System – tremor, Horner's syndrome, paresis, dyskinesia, neuropathy, vertigo, coma, convulsion, hypokinesia, hypotonia, ptosis, stupor

Psychiatric Disorders – agitation, confusion, somnolence, nervousness, amnesia, hallucination, emotional lability, insomnia, nightmares

Respiratory System – bronchospasm, coughing

Skin Disorders – rash, urticaria

Urinary System Disorders – urinary incontinence, micturition 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)

Adverse Reaction	Ropivacaine Hydrochloride						Bupivacaine			
	5 mg/mL total N=256		7.5 mg/mL total N=297		10 mg/mL total N=207		5 mg/mL total N=236		7.5 mg/mL 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 hydrochloride are broken down by gender.

Table 5

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

AGE	Ropivacaine Hydrochloride						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)

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)

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 overdosage, rapid absorption from the injection site,

diminished tolerance or from unintentional intravascular injection of the local anesthetic solution. In addition to systemic dose-related toxicity, unintentional subarachnoid injection of drug during the intended performance of lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in underventilation or apnea ("Total or High Spinal"). Also, hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia may occur. This may lead to secondary cardiac arrest if untreated. Factors influencing plasma protein binding, such as acidosis, systemic diseases that alter protein production or competition with other drugs for protein binding sites, may diminish individual tolerance.

Epidural administration of ropivacaine hydrochloride has, in some cases, as with other local anesthetics, been associated with transient increases in temperature to $>38.5^{\circ}\text{C}$. This occurred more frequently at doses of ropivacaine hydrochloride $>16\text{ mg/h}$.

Neurologic Reactions

These are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, and constriction of the pupils.

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

The incidence of adverse neurological reactions associated with the use of local anesthetics may be related to the total dose and concentration of local anesthetic administered and are also dependent upon the particular drug used, the route of administration, and the physical status of the patient. Many of these observations may be related to local anesthetic techniques, with or without a contribution from the drug. During lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter or needle may occur. Subsequent adverse effects may depend partially on the amount of drug administered intrathecally as well as the physiological and physical effects of a dural puncture. These observations may include spinal block of varying magnitude (including high or total spinal block), hypotension secondary to spinal block, urinary retention, loss of bladder and bowel control (fecal and urinary incontinence), and loss of perineal sensation and sexual function. Signs and symptoms of subarachnoid block typically start within 2 to 3 minutes of injection. Doses of 15 and 22.5 mg of ropivacaine hydrochloride resulted in sensory levels as high as T5 and T4, respectively. Analgesia started in the sacral dermatomes in 2 to 3 minutes and extended to the T10 level in 10 to 13 minutes and lasted for approximately 2 hours. Other neurological effects following unintentional subarachnoid administration during epidural anesthesia may include persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities, and loss of sphincter control; all of which may have slow, incomplete or no recovery. Headache, septic meningitis, meningismus, slowing of labor, increased incidence of forceps delivery, or cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid have been reported (see **DOSAGE AND ADMINISTRATION** discussion of Lumbar Epidural Block). A high spinal is characterized

by paralysis of the arms, loss of consciousness, respiratory paralysis and bradycardia.

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, 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, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly, anaphylactoid symptomatology (including severe hypotension). Cross-sensitivity among members of the amide-type local anesthetic group has been reported. The usefulness of screening for sensitivity 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**).

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.

The first step in the management of systemic toxic reactions, as well as underventilation or apnea due to unintentional subarachnoid injection of drug solution, consists of immediate attention to the establishment and maintenance of a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting 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 ventilatory 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 ephedrine or epinephrine to enhance myocardial contractile force).

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 infusion in dogs, nonpregnant and pregnant sheep were 4.9, 6.1 and 5.9 mg/kg, respectively. These doses were associated with peak arterial total plasma concentrations of 11.4, 4.3 and 5 mcg/mL, respectively.

In human volunteers given intravenous ropivacaine hydrochloride, the mean (min-max) maximum tolerated total and free arterial plasma concentrations were 4.3 (3.4 to 5.3) and 0.6 (0.3 to 0.9) mcg/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 avoid cardiac arrest.

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

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

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 chondrolysis 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 anesthetized, the vascularity of the tissues, the number of neuronal

segments to be blocked, the depth of anesthesia and degree of muscle relaxation required, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient. Patients in poor general condition due to aging or other compromising factors such as partial or complete heart conduction block, advanced liver disease or severe renal dysfunction require special attention although regional anesthesia is frequently indicated in these patients. To reduce the risk of potentially serious adverse reactions, attempts should be made to optimize the patient's condition before major blocks are performed, and the dosage should be adjusted accordingly.

Use an adequate test dose (3 mL 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 such a fashion as 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.

Table 7 Dosage Recommendations

	Conc.		Volume mL	Dose mg	Onset min	Duration hours
	mg/mL	(%)				
SURGICAL ANESTHESIA						
Lumbar Epidural	5	(0.5%)	15 to 30	75 to 150	15 to 30	2 to 4
Administration	7.5	(0.75%)	15 to 25	113 to 188	10 to 20	3 to 5
Surgery	10	(1%)	15 to 20	150 to 200	10 to 20	4 to 6
Lumbar Epidural	5	(0.5%)	20 to 30	100 to 150	15 to 25	2 to 4
Administration	7.5	(0.75%)	15 to 20	113 to 150	10 to 20	3 to 5
Cesarean Section						
Thoracic Epidural	5	(0.5%)	5 to 15	25 to 75	10 to 20	n/a *
Administration	7.5	(0.75%)	5 to 15	38 to 113	10 to 20	n/a *
Surgery						
Major Nerve Block †	5	(0.5%)	35 to 50	175 to 250	15 to 30	5 to 8
(e.g., brachial plexus block)	7.5	(0.75%)	10 to 40	75 to 300	10 to 25	6 to 10
Field Block	5	(0.5%)	1 to 40	5 to 200	1 to 15	2 to 6
(e.g., minor nerve blocks and infiltration)						
LABOR PAIN MANAGEMENT						
Lumbar Epidural						

Administration						
Initial Dose	2	(0.2%)	10 to 20	20 to 40	10 to 15	0.5 to 1.5
Continuous infusion ‡	2	(0.2%)	6 to 14 mL/h	12 to 28 mg/h	n/a *	n/a *
Incremental injections (top-up) ‡	2	(0.2%)	10 to 15 mL/h	20 to 30 mg/h	n/a *	n/a *
POSTOPERATIVE PAIN MANAGEMENT						
Lumbar Epidural Administration						
Continuous infusion §	2	(0.2%)	6 to 14 mL/h	12 to 28 mg/h	n/a*	n/a*
Thoracic Epidural Administration	2	(0.2%)	6 to 14 mL/h	12 to 28 mg/h	n/a*	n/a*
Continuous infusion §						
Infiltration	2	(0.2%)	1 to 100	2 to 200	1 to 5	2 to 6
(e.g., minor nerve block)	5	(0.5%)	1 to 40	5 to 200	1 to 5	2 to 6

* = Not Applicable

† = 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**).

‡ = 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.

§ = Cumulative doses up to 770 mg of ropivacaine hydrochloride 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, i.e., 2016 mg plus surgical dose of approximately 100 mg to 150 mg as top-up.

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 variations 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 ropivacaine hydrochloride injection administered over 24 hours is well tolerated in adults when used for postoperative pain management: i.e., 2016 mg. Caution should be exercised when administering ropivacaine hydrochloride injection 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 intraoperatively, then an initial epidural block with 5 mL to 7 mL ropivacaine hydrochloride injection is induced via an epidural catheter. Analgesia is maintained with an infusion of ropivacaine hydrochloride injection, 2 mg/mL (0.2%). Clinical studies have demonstrated that infusion rates of 6 mL to 14 mL (12 mg to 28 mg) per hour provide adequate analgesia with nonprogressive motor block. With this technique a significant reduction in the need for opioids was demonstrated. Clinical

experience supports the use of ropivacaine hydrochloride epidural infusions for up to 72 hours.

HOW SUPPLIED

Ropivacaine hydrochloride injection, USP is a clear, colorless, sterile, isotonic solution free from visible particles and is supplied as follows:

Ropivacaine hydrochloride injection USP, 0.5 %

100 mg/20 mL (5 mg/mL): 20 mL Single Dose Vials
in a Carton of 25 NDC 55150-197-20

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

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

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 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. Stability has been demonstrated using a targeted F_0 of 7 minutes at 121°C.

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

The vial stoppers are not made with natural rubber latex.

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

Distributed by:

AuroMedics Pharma LLC
279 Princeton-Hightstown Rd.
E. Windsor, NJ 08520

Manufactured by:

Aurobindo Pharma Limited Hyderabad - 500038
India

Revised: March 2019

Povidone Iodine Swabsticks

Active Ingredient

Povidone Iodine 10% w/v (9.85% w/w/) Antiseptic

Purpose

Purpose:

Purpose:

- First aid antiseptic to help prevent skin infection in minor cuts, scrapes and burns.
- For preparation of the skin prior to surgery.
- Helps reduce bacteria that can potentially cause skin infections.

Warnings:

- **FOR EXTERNAL USE ONLY**

Do not use:

- As a first aid antiseptic for more than 1 week.
- In the eyes.
- Over large areas of the body.

Ask a doctor before use if you have:

- Deep puncture wounds
- Animal bites
- Serious burns

Stop Use:

- If irritation and redness develop
- If condition persists for more than 72 hours, consult a physician.

Keep Out Of Reach Of Children

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center.

Directions Povidone iodine:

Tear at notch, remove applicator, use only once.

As a first aid antiseptic

- clean affected area
- apply 1 to 3 times daily
- may be covered with a sterile bandage, if bandaged let dry.

For preoperative patient skin preparation

- clean area
- apply to operative site prior to surgery using the applicator

Other information:

Store at room temperature.

Avoid excessive heat

For use as an

- first aid antiseptic
- pre-operative skin preparation

Inactive Ingredients

Inactive ingredients: Citric acid, glycerin, polysorbate 80, sodium citrate USP, sodium phosphate dibasic, water

Principal Display Panel - Ropidex Kit Label

NDC: 76420-219-01 RX Only

Ropidex™**Kit Contains**

- 1 Dexamethasone Sodium Phosphate Inj., USP 10mg/mL (1mL)
- 1 Ropivacaine Hydrochloride Injection, USP 0.5% (20mL)
- 1 Povidone-Iodine Swabsticks (3 Swabs)
- 2 Isopropyl Alcohol 70% Prep Pads
- 1 Pair Nitrile Powder Free Sterile Gloves (M)
- 1 Drape
- 1 Adhesive Bandage
- 5 Non Sterile 4x4 Gauze
- Needles and Syringes Not Included
- 1 Dose

Single Use Only
Distributed by
Enovachem™
PHARMACEUTICALS
Torrance, CA 90501



NDC: 76420-219-01

Rx Only

Ropidex™

	Kit Contains
1	Dexamethasone Sodium Phosphate Inj., USP 10mg/mL (1mL)
1	Ropivacaine Hydrochloride Injection, USP 0.5% (20mL)
1	Povidone-Iodine Swabsticks (3 Swabs)
2	Isopropyl Alcohol 70% Prep Pads
1	Pair Nitrile Powder Free Sterile Gloves (M)
1	Drape
1	Adhesive Bandage
5	Non Sterile 4x4 Gauze
	 Needles and Syringes Not Included
	 1 Dose Single Use Only

Distributed by  **Enovachem™**
PHARMACEUTICALS
Torrance, CA 90501



ROPIDEX				
dexamethasone sodium phosphate, ropivacaine hydrochloride, povidine iodine kit				
Product Information				
Product Type	HUMAN PRESCRIPTION DRUG		Item Code (Source)	NDC:76420-219
Packaging				
#	Item Code	Package Description	Marketing Start	Marketing End

#	Item Code	Package Description	Date	Date
1	NDC:76420-219-01	1 in 1 CARTON; Type 1: Convenience Kit of Co-Package	06/10/2019	

Quantity of Parts		
Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL	1 mL
Part 2	1 VIAL, SINGLE-DOSE	20 mL
Part 3	1 PACKET	0.9 mL

Part 1 of 3
DEXAMETHASONE SODIUM PHOSPHATE dexamethasone sodium phosphate injection, solution

Product Information	
Item Code (Source)	NDC:63323-506
Route of Administration	INTRAMUSCULAR, INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
DEXAMETHASONE SODIUM PHOSPHATE (UNII: AI9376Y64P) (DEXAMETHASONE - UNII: 7S5I7G3JQL)	DEXAMETHASONE PHOSPHATE	10 mg in 1 mL

Inactive Ingredients	
Ingredient Name	Strength
SODIUM CITRATE (UNII: 1Q73Q2JULR)	24.75 mg in 1 mL
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63323-506-01	25 in 1 TRAY		
1		1 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date

ANDA	ANDA040491	05/29/2003	
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Part 2 of 3

ROPIVACAINE HYDROCHLORIDE

ropivacaine hydrochloride injection, solution

Product Information

Item Code (Source)	NDC:55150-197
Route of Administration	INFILTRATION, PERINEURAL, EPIDURAL

Active Ingredient/Active Moiety

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

Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55150-197-20	25 in 1 CARTON		
1		20 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA205612	09/15/2016	

Part 3 of 3

POVIDINE IODINE

povidine iodine swab

Product Information

Route of Administration	TOPICAL
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Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
POVIDONE-IODINE (UNII: 85H0HZ U99M) (IODINE - UNII:9679TC07X4)	IODINE	10 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
GLYCERIN (UNII: PDC6A3C0OX)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
SODIUM CITRATE (UNII: 1Q73Q2JULR)	
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS (UNII: 22ADO53M6F)	
CITRIC ACID ACETATE (UNII: DSO12WL7AU)	
WATER (UNII: 059QF0KOOR)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67777-419-02	0.9 mL in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
OTC Monograph Drug	M003	09/13/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other		06/10/2019	

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