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of normal have been observed in many patients (40%) receiving ziconotide; CK concentrations 3 or more times the upper limit of normal have occurred in 11% of patients. These increases generally have been observed during the first 2 months of therapy with ziconotide and have not been associated with treatment-limiting adverse effects. Men, patients receiving concomitant therapy with antidepressants or anticonvulsants, and those who had received intrathecal morphine were more likely to have elevated serum CK values.

Symptomatic myopathy with electromyographic abnormalities has occurred in at least one patient, and acute renal failure with rhabdomyolysis and markedly elevated CK concentrations (17,000–27,000 IU/L) has been reported in at least 2 patients.

Serum CK concentrations should be monitored periodically (e.g., every other week during the first month of therapy and then monthly as appropriate). If neuromuscular symptoms (e.g., myalgias, myasthenia, muscle cramps, asthenia) develop or a reduction in physical activity occurs, the patient should be evaluated (e.g., clinical evaluation, determination of serum CK concentrations). If symptoms persist and CK concentrations remain elevated or continue to rise, dosage reduction or discontinuance of ziconotide should be considered.

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Not known whether ziconotide is distributed into milk. Discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use. Safety and efficacy not established in patients younger than 18 years of age.

Geriatric Use. In clinical studies, 22% of patients were 65 years of age or older and 7% were 75 years of age or older. In all studies, the incidence of confusion was higher in individuals 65 years of age or older than in younger adults. No substantial difference in efficacy in geriatric patients relative to younger adults.

Select dosage with caution, starting at the low end of the dosage range, because of age-related decreases in hepatic, renal, and/or cardiac function and potential for concomitant disease and drug therapy.

■ **Common Adverse Effects** Adverse effects reported in 25% or more of patients receiving ziconotide include dizziness, nausea, confusion, headache, somnolence, nystagmus, asthenia, and pain.

Drug Interactions

■ **Drugs Affecting or Metabolized by Hepatic Microsomal Enzymes** Pharmacokinetic interaction unlikely.

■ **Protein-bound Drugs** Pharmacokinetic interaction unlikely.

■ **CNS Agents** Used concomitantly with anticonvulsants, antidepressants, antipsychotics, anxiolytics, and sedatives in clinical studies. Potential interaction with CNS depressants (increased incidence of adverse CNS effects [e.g., dizziness, confusion, reduced levels of consciousness]). Dosage adjustment or discontinuance of ziconotide or the concomitant CNS depressant may be needed.

Potential interaction with antidepressants or anticonvulsants (elevated serum creatine kinase [CK, creatine phosphokinase, CPK]).

■ **Diuretics** Potential interaction (reduced levels of consciousness).

■ **Opiates** Used concomitantly with systemically administered opiates in clinical studies; concomitant use of ziconotide with intrathecal opiates has not been evaluated in placebo-controlled studies and is not recommended.

Potential interaction in patients who previously had received intrathecal morphine (elevated serum CK).

Description

Ziconotide, a synthetic form of a naturally occurring conopeptide found in the venom of the marine snail *Conus magus*, is a 25-amino acid polybasic peptide containing 3 disulfide bridges. Ziconotide produces potent antinociceptive effects by selectively binding to N-type voltage-sensitive calcium channels on the primary nociceptive afferent nerves in the superficial layers of the spinal cord, thus blocking neurotransmission from primary nociceptive afferents.

Ziconotide does not bind to opiate receptors, and the pharmacologic effects of the drug are not blocked by opiate antagonists. Ziconotide does not potentiate opiate-induced respiratory depression.

Intrathecal administration of ziconotide results in little systemic exposure. Following passage from the CSF into the systemic circulation, ziconotide is expected to be degraded to peptide fragments and their constituent amino acids by endopeptidases and exopeptidases present in most organs.

Advice to Patients

Risk of somnolence: avoid driving, operating machinery, or performing hazardous tasks until effects on individual are known.

Importance of informing clinician if new or worsening muscle pain, soreness, weakness, or brown urine develops.

Importance of promptly reporting any change in mental status (e.g., lethargy, confusion, disorientation, decreased alertness), mood or perception (e.g., hallucinations, unusual tactile sensations in the mouth), and symptoms of depression or suicidal ideation.

Importance of promptly informing clinician if symptoms of meningitis (i.e., nausea, vomiting, seizures, fever, headache, stiff neck) occur.

For patients receiving ziconotide via an external microinfusion device and catheter, importance of proper handling of the device and proper care of the skin at the catheter exit site.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as concomitant illnesses. Potential for additive CNS effects if used concomitantly with other CNS depressants.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Ziconotide

Parenteral		
Injection, for intrathecal administration via compatible microinfusion device only	25 mcg/mL	**Prialt®**, Elan
	100 mcg/mL	**Prialt®**, Elan

OPIATE ANTAGONISTS 28:10

Naloxone Hydrochloride

N-Allylnoroxymorphone Hydrochloride

■ Naloxone hydrochloride is essentially a pure opiate antagonist.

Uses

■ **Opiate-induced Depression and Acute Opiate Overdosage** Naloxone hydrochloride is used for the complete or partial reversal of opiate-induced depression, including respiratory depression, caused by natural and synthetic opiates (e.g., anileridine, codeine, diphenoxylate, fentanyl citrate, heroin, hydromorphone, levorphanol, meperidine, methadone, morphine, oxymorphone, concentrated opium alkaloids hydrochlorides, propoxyphene) and certain opiate partial agonists (e.g., butorphanol, nalbuphine, pentazocine, cyclazocine). Administration of naloxone should be accompanied by other resuscitative measures such as administration of oxygen, mechanical ventilation, or artificial respiration. Naloxone is effective for the treatment of mild or moderate as well as severe opiate-induced respiratory depression. The drug is not effective in the management of acute toxicity caused by levopropoxyphene. Naloxone is also indicated for the diagnosis of suspected acute opiate overdosage.

There is no conclusive evidence that concomitant use of naloxone with an opiate analgesic will prevent respiratory depression while retaining the analgesic effect; in fact, analgesia and sedation may be decreased if these drugs are administered together.

Naloxone may be used in neonates for the treatment of asphyxia resulting from administration of opiates to the mother during labor and delivery. Naloxone has been given to the mother shortly before delivery†, but many clinicians believe it is preferable to administer an opiate antagonist directly to the neonate if needed after delivery.

■ **Other Uses** Naloxone has been used for detection of chronic opiate abuse†, but it is preferable to use chemical methods to detect the presence of opiates in the urine, since naloxone may precipitate severe withdrawal symptoms in patients who are physically dependent on opiates; however, to avoid precipitating opiate withdrawal following administration of naltrexone, administration of naloxone is recommended as a screening test (the naloxone challenge test) prior to induction of therapy with naltrexone for opiate cessation in patients formerly dependent on opiates who have completed detoxification. (See Naloxone Challenge Test in Dosage and Administration: Dosage, in Naltrexone Hydrochloride 28:10.)

When prolonged vomiting occurs after apomorphine has been used to induce vomiting in the treatment of oral poisonings (apomorphine is no longer used as an emetic), naloxone has been used to terminate the emetic effects and to help diminish respiratory depression induced by apomorphine†; however, it

has been reported that the CNS and respiratory effects of apomorphine may not always be reversed by naloxone.

Naloxone has been used in intoxicated patients to reverse alcohol-induced coma† and to reverse clonidine-induced coma and respiratory depression†.

Naloxone has been used as adjunctive therapy in a limited number of patients to increase blood pressure in the management of septic shock. Treatment with naloxone results in a rise in blood pressure that may last up to several hours; however, this pressor effect has not been demonstrated to improve patient survival. In some studies, use of naloxone for the management of septic shock has been associated with adverse effects, including agitation, nausea, vomiting, pulmonary edema, hypotension, cardiac arrhythmias, and seizures. If a decision is made to use naloxone for management of septic shock, the manufacturers state that the drug should be used with caution, particularly in patients who may have underlying pain or have previously received opiate therapy and may have developed opiate tolerance.

Naloxone also has been used in the management of cardiogenic shock†, high-altitude pulmonary edema†, acute respiratory failure†, senile dementia†, and ischemic neurologic deficits†; however, the safety and efficacy of naloxone in these conditions have not been established and further study is needed.

A combination of pentazocine hydrochloride and naloxone hydrochloride in a ratio of 100:1 is commercially available for oral use as an analgesic. (See Pentazocine 28:08.12.) A combination of buprenorphine hydrochloride and naloxone hydrochloride in a ratio of 4:1 is commercially available for use in the management of opiate dependence. (See Buprenorphine 28:08.12.) A combination of methadone hydrochloride and naloxone hydrochloride in a ratio of 20:1 has also been administered orally in the detoxification or maintenance treatment of opiate addiction in conjunction with appropriate social and medical services. The presence of naloxone in these combinations minimizes the abuse potential of pentazocine, buprenorphine, or methadone, since the antagonistic effect of naloxone will predominate if the combinations are administered parenterally and/or if usual oral doses are exceeded.

Opiate antagonists (e.g., naloxone, naltrexone) have been used for rapid or ultrarapid detoxification in the management of opiate withdrawal† in opiate-dependent individuals, both in inpatient and outpatient settings. Rapid opiate detoxification involves the administration of opiate antagonists such as naloxone and/or naltrexone to shorten the time period of detoxification. The reported advantage of this technique is to minimize the risk of relapse and to initiate maintenance therapy with naltrexone and psychosocial interventions more quickly. Ultrarapid detoxification is similar, but involves the administration of opiate antagonists (i.e., naloxone, naltrexone) while the patient is sedated or under general anesthesia. However, the risk of adverse respiratory and cardiovascular effects associated with this procedure must be considered as well as the costs of general anesthesia and hospitalization. Safety and efficacy of these therapies have not been established and further study is needed.

Naloxone hydrochloride has been used orally† with some success in the treatment of opiate addiction†. The drug may prevent opiate euphoria and thus decrease the desire for opiates.

Dosage and Administration

■ **Administration** Naloxone hydrochloride may be administered by IV, subcutaneous, or IM injection, or by IV infusion. IV administration is recommended for emergency situations. The American Academy of Pediatrics (AAP) does not endorse subcutaneous or IM administration in children or neonates with opiate intoxication since absorption may be erratic or delayed. When IV access cannot be established in emergency situations, limited evidence suggests that the drug also can be administered effectively via an endotracheal tube† in adults or pediatric patients, by intraosseous† injection for opiate overdosage in pediatric patients, or by the intranasal† route (however, nasal preparations currently are not commercially available in the US) for opiate overdosage in adults. Although naloxone may be administered via an endotracheal tube, some experts state that a specific dose has not been established and IV and other parenteral routes of administration (e.g., IM, subcutaneous) are preferred because of more predictable drug delivery and pharmacologic effect. In addition, these experts do not recommend endotracheal administration of naloxone in neonates.

Continuous IV infusions of naloxone hydrochloride may be most appropriate in patients who require higher doses, continue to experience recurrent respiratory or CNS depression after effective therapy with repeated doses, and/or in whom the effects of long-acting opiates are being antagonized. For continuous IV infusion, 2 mg of naloxone hydrochloride may be diluted in 500 mL of 0.9% sodium chloride or 5% dextrose injection to produce a solution containing 0.004 mg/mL (4 mcg/mL). The rate of IV infusion should be titrated in accordance with the patient's response. Prior to administration, IV solutions of naloxone hydrochloride should be carefully inspected for the presence of particulate matter or discoloration. Diluted solutions of the drug should be used within 24 hours; unused portions should be discarded after 24 hours.

■ **Dosage** ***Postoperative Opiate Depression*** When naloxone hydrochloride is used to partially reverse opiate depression following the use of opiates during surgery, the usual initial dosage recommended by the manufacturers is 0.1–0.2 mg IV in adults or 0.005–0.01 mg IV in children, given at 2- to 3-minute intervals until the desired response (i.e., adequate ventilation and alertness without substantial pain or discomfort) is obtained. Additional doses may be necessary at 1- to 2-hour intervals depending on the response of the patient and the dosage and duration of action of the opiate administered.

Some clinicians have recommended an adult dosage regimen of 0.005 mg/kg administered IV and repeated after 15 minutes if necessary. Alternatively, the initial IV dose may be followed in 15 minutes with an IM dose of 0.01 mg/kg. The manufacturers states that supplemental IM doses of naloxone produce a more prolonged effect than repeated IV doses of the drug. Continuous IV infusions of naloxone in a dosage of 0.0037 mg/kg per hour have also been used in adults to reverse postoperative opiate-induced respiratory depression.

Neonatal Opiate Depression When used to reverse opiate-induced asphyxia neonatorum, the usual initial dosage of naloxone hydrochloride is 0.01 mg/kg, administered into the umbilical vein of the neonate at 2- to 3-minute intervals until the desired response is obtained. Additional doses may be necessary at 1- to 2-hour intervals depending on the response of the neonate and the dosage and duration of action of the opiate administered to the mother. When the IV route cannot be used, the drug may be administered by IM or subcutaneous injection.

Known or Suspected Opiate Overdosage For the treatment of known opiate overdosage or as an aid in the diagnosis of suspected opiate overdosage, the usual initial adult dosage of naloxone hydrochloride is 0.4–2 mg IV, administered at 2- to 3-minute intervals if necessary; if no response is observed after a total of 10 mg of the drug has been administered, the depressive condition may be caused by a drug or disease process not responsive to naloxone. Some experts state that some adults with opiate overdosage may require titration to a total naloxone hydrochloride dosage of 6–10 mg over a short period. In patients with chronic opiate addiction, a lower dose of naloxone should be used and slowly adjusted to minimize adverse cardiovascular effects and withdrawal symptoms. (See Precautions and Contraindications.) When the IV route cannot be used in adults or children, the manufacturer and some experts state that the drug may be administered by IM or subcutaneous injection. In the emergency setting, these experts recommend an IM or subcutaneous adult dose of 0.4–0.8 mg, repeated as necessary. Some experts state that a slightly higher adult dose of naloxone may be needed for the endotracheal† route than that administered by other routes; however, the optimum dose of naloxone administered via an endotracheal tube† remains to be established. (See Dosage and Administration: Administration.)

Children may receive an initial IV naloxone hydrochloride dose of 0.01 mg/kg; if this dose does not produce the desired degree of response, a subsequent dose of 0.1 mg/kg may be administered. Alternatively, an initial 0.1-mg/kg IV dose, repeated every 2–3 minutes as necessary, has been recommended for neonates and children younger than 5 years of age or weighing 20 kg or less. In pediatric patients 5 years of age or older or weighing more than 20 kg, a minimum 2-mg IV dose, repeated as necessary, can be used. However, some experts state that lower doses should be used to reverse respiratory depression associated with therapeutic opiate use in pediatric patients (e.g., 1–15 μg/kg for reversal of peri-arrest respiratory depression, 1–5 μg/kg for respiratory depression during procedural sedation to maintain some opiate analgesia). Some experts suggest an endotracheal† or intraosseous† dose of 0.1 mg/kg in pediatric patients younger than 5 years of age or weighing 20 kg or less or a dose of 2 mg in pediatric patients 5 years of age or older or weighing more than 20 kg; however, the optimum dose of naloxone administered via an endotracheal tube† remains to be established. (See Dosage and Administration: Administration.)

Since the duration of action of the opiate is often greater than that of naloxone, the depressant effects of the opiate may return as the effects of naloxone diminish, and additional doses (or a continuous IV infusion) of naloxone may be required. The patient should be closely observed for a day or longer regardless of the degree of apparent improvement. Continuous IV infusion dosage regimens of naloxone have not been well established, and the rate of administration must be titrated according to the patient's response. In adults, some clinicians recommend an initial IV loading dose of 0.4 mg, followed by a continuous infusion at an initial rate of 0.4 mg/hour. Alternatively, other clinicians have recommended that an IV loading dose of 0.005 mg/kg be given, followed by continuous infusion of 0.0025 mg/kg per hour. Experience with continuous IV infusions of naloxone in children is very limited, but children may require higher infusion rates on a mg/kg basis than adults. In several reports, infusion rates in children have ranged from 0.024–0.16 mg/kg per hour. Some clinicians recommend an initial pediatric infusion rate of 0.4 mg/hour.

Other Uses For information on the use of naloxone as a screening test (the naloxone challenge test) prior to induction of therapy with naltrexone for opiate cessation in patients formerly dependent on opiates who have completed detoxification, see Naloxone Challenge Test in Dosage and Administration: Dosage, in Naltrexone Hydrochloride 28:10.

When naloxone hydrochloride was used in the diagnosis of opiate dependence† in adults, a dose of 0.16 mg was given IM. If no withdrawal symptoms were evident after 20–30 minutes, a second dose of 0.24 mg was given IV. Negative test results were assumed if no withdrawal symptoms were apparent within 30 minutes after the second dose. Withdrawal symptoms induced by naloxone began to diminish 20–40 minutes after injection and were essentially gone within 1.5 hours.

In the treatment of opiate addiction†, naloxone hydrochloride has been administered orally† in dosages of 200 mg to 3 g daily.

Cautions

■ **Adverse Effects** Nausea and vomiting have been reported rarely in postoperative patients who were receiving a parenteral dose of naloxone hydrochloride greater than that usually recommended; however, a causal rela-

tionship has not been established. Tremor and hyperventilation associated with an abrupt return to consciousness has occurred in some patients receiving naloxone for opiate overdosage.

Although a causal relationship to the drug has not been established, severe cardiopulmonary effects (e.g., hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, cardiac arrest) resulting in death, coma, and encephalopathy have been reported in patients following postoperative administration of naloxone hydrochloride. Adverse cardiopulmonary effects have occurred most frequently in postoperative patients with preexisting cardiovascular disease or in those receiving other drugs that produce similar adverse cardiovascular effects. (See Cautions: Precautions and Contraindications.)

Seizures have occurred rarely following administration of naloxone hydrochloride; however, a causal relationship to the drug has not been established.

When high oral† doses of naloxone have been used in the treatment of opiate addiction†, some patients have experienced mental depression, apathy, inability to concentrate, sleepiness, irritability, anorexia, nausea, and vomiting. These adverse effects usually occurred in the first few days of treatment and abated rapidly with continued therapy or dosage reduction. One case of erythema multiforme cleared promptly after naloxone was discontinued.

■ **Precautions and Contraindications** When naloxone hydrochloride is used in the management of acute opiate overdosage, other resuscitative measures (e.g., maintenance of an adequate airway, artificial respiration, cardiac massage, vasopressor agents) should be readily available and used when necessary. If opiate-induced cardiac arrest occurs, usual guidelines for advanced cardiovascular life support (ACLS) should be followed; an adequate airway should be established before administration of naloxone.

Following the use of opiates during surgery, excessive dosage of naloxone hydrochloride should be avoided, because it may result in excitement, agitation, an increase in blood pressure, and clinically important reversal of analgesia. A reversal of opiate effects achieved too rapidly may induce nausea, vomiting, sweating, tremor, tachycardia, increased blood pressure, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest, which may result in death.

Naloxone should be used with caution in patients with preexisting cardiovascular disease or in those receiving potentially cardiotoxic drugs, since serious adverse cardiopulmonary effects (e.g., ventricular tachycardia and fibrillation, pulmonary edema, cardiac arrest) resulting in death, coma, and encephalopathy have occurred in postoperative patients following administration of naloxone. (See Cautions: Adverse Effects.)

Naloxone should be given with caution to patients known or suspected to be physically dependent on opiates (including neonates born to women who are opiate dependent), particularly in patients with cardiovascular disease, because the drug may precipitate severe withdrawal symptoms. (See Cautions: Pregnancy, Fertility, and Lactation and see Pharmacology.)

Patients who have responded to naloxone should be carefully monitored, since the duration of action of some opiates may exceed that of naloxone; pediatric patients who have responded must be carefully monitored for at least 24 hours. Repeated doses of naloxone should be administered to these patients when necessary.

Safety and efficacy of naloxone in patients with renal or hepatic impairment have not been established in well-controlled clinical trials. Naloxone should be used with caution in these patients.

Some experts state that naloxone should *not* be used in the treatment of meperidine-induced seizures.

Naloxone is contraindicated in patients with known hypersensitivity to the drug.

■ **Pediatric Precautions** Safety and efficacy of naloxone in the management of hypotension associated with septic shock have not been established in pediatric patients. In a study of 2 neonates with septic shock, treatment with naloxone produced positive pressor response; however, one patient subsequently died after intractable seizures.

■ **Geriatric Precautions** Clinical studies of naloxone did not include sufficient numbers of patients 65 years of age and older to determine whether geriatric patients respond differently from younger patients. While other clinical experience has not revealed age-related differences in response, drug dosage generally should be titrated carefully in geriatric patients, usually initiating therapy at the low end of the dosage range. The greater frequency of decreased hepatic, renal, and/or cardiac function and of concomitant disease and drug therapy observed in the elderly also should be considered.

■ **Mutagenicity and Carcinogenicity** Naloxone was weakly positive in the Ames mutagenicity test and the *in vitro* human lymphocyte chromosome aberration test but was negative in the *in vitro* Chinese hamster V79 cell HGPRT mutagenicity assay and the *in vivo* rat bone marrow chromosome aberration study. Studies to determine the carcinogenic potential of naloxone have not been performed to date.

■ **Pregnancy and Lactation** Reproduction studies in mice and rats using naloxone hydrochloride at dosages 4 and 8 times, respectively, the human dosage of 10 mg daily demonstrated no embryotoxic or teratogenic effects. There are no adequate and controlled studies to date using the drug in pregnant women. Naloxone hydrochloride should be used during pregnancy only when clearly needed.

The risk-benefit ratio must be considered before naloxone hydrochloride is administered to a pregnant woman who is known or suspected to be dependent on opiates, since maternal dependence may often be accompanied by fetal dependence. Naloxone crosses the placenta and may precipitate withdrawal symptoms in the fetus as well as in the mother.

It is not known if naloxone affects the duration of labor and/or delivery. However, published reports indicate that administration of naloxone during labor did not adversely affect maternal or neonatal status. Patients with mild to moderate hypertension who receive naloxone during labor should be carefully monitored, as severe hypertension may occur.

Since it is not known whether naloxone hydrochloride is distributed into milk, the drug should be used with caution in nursing women.

Pharmacology

Naloxone hydrochloride is essentially a pure opiate antagonist. The precise mechanism of action of the opiate antagonist effects of naloxone is not fully understood. Naloxone is thought to act as a competitive antagonist at μ, κ, and σ opiate receptors in the CNS; it is thought that the drug has the highest affinity for the μ receptor. In contrast to levallorphan or nalorphine, naloxone has little or no agonistic activity. When administered in usual doses to patients who have not recently received opiates, naloxone exerts little or no pharmacologic effect. Even extremely high doses of the drug (10 times the usual therapeutic dose) produce insignificant analgesia, only slight drowsiness, and no respiratory depression, psychotomimetic effects, circulatory changes, or miosis.

In patients who have received large doses of morphine or other analgesic drugs with morphine-like effects, naloxone antagonizes most of the effects of the opiate. There is an increase in respiratory rate and minute volume, arterial PCO_2 decreases toward normal, and blood pressure returns to normal if depressed. Unlike nalorphine or levallorphan, naloxone antagonizes mild respiratory depression caused by small doses of opiates. Because the duration of action of naloxone is generally shorter than that of the opiate, the effects of the opiate may return as the effects of naloxone dissipate. Naloxone antagonizes opiate-induced sedation or sleep. Reports are conflicting on whether or not the drug modifies opiate-induced excitement or seizures.

Naloxone does not produce tolerance or physical or psychological dependence. In patients who are dependent on opiates, parenteral administration of naloxone hydrochloride will precipitate opiate withdrawal symptoms, which may appear within minutes of naloxone administration and subside in about 2 hours. The severity and duration of the withdrawal symptoms are related to the dose of naloxone and the degree and type of opiate dependence. Oral administration of naloxone generally does not precipitate withdrawal symptoms unless the dose exceeds 10 mg. Even a 30-mg oral dose of naloxone usually induces only very mild abstinence symptoms.

Naloxone has been shown to increase blood pressure in a limited number of patients with septic shock. (See Uses: Other Uses.)

Pharmacokinetics

■ **Absorption** Naloxone is rapidly inactivated following oral administration. Although the drug is effective orally, doses much larger than those required for parenteral administration are required for complete antagonism. In one study, a single 3-g oral dose of naloxone hydrochloride was required to effectively antagonize the effects of 50 mg of heroin for 24 hours. Naloxone has an onset of action within 1–2 minutes following IV administration and within 2–5 minutes following subcutaneous or IM administration. The duration of action depends on the dose and route of administration and is more prolonged following IM administration than after IV administration. In one study, the duration of action was 45 minutes following IV administration of naloxone hydrochloride 0.4 mg/70kg.

Following administration of 35 or 70 mcg of naloxone hydrochloride into the umbilical vein in neonates in one study, peak plasma naloxone concentrations occurred within 40 minutes and were 4–5.4 ng/mL and 9.2–20.2 ng/mL, respectively. After IM administration of 0.2 mg to neonates in the same study, peak plasma naloxone concentrations of 11.3–34.7 ng/mL occurred within 0.5–2 hours.

■ **Distribution** Following parenteral administration, naloxone is rapidly distributed into body tissues and fluids. In rats, high concentrations are observed in the brain, kidney, spleen, lung, heart, and skeletal muscle. Naloxone is weakly bound to plasma proteins (mainly albumin). In humans, the drug readily crosses the placenta. It is not known whether naloxone is distributed into milk.

■ **Elimination** The half-life of naloxone has been reported to be 30–81 minutes in adults and about 3 hours in neonates.

Naloxone is rapidly metabolized in the liver, principally by conjugation with glucuronic acid. The major metabolite is naloxone-3-glucuronide. Naloxone also undergoes *N*-dealkylation and reduction of the 6-keto group followed by conjugation. Limited studies with radiolabeled naloxone indicate that 25–40% of an oral or IV dose of the drug is excreted as metabolites in urine in 6 hours, about 50% in 24 hours, and 60–70% in 72 hours.

Chemistry and Stability

■ **Chemistry** Naloxone hydrochloride is a semisynthetic opiate antagonist which is derived from thebaine. Naloxone differs structurally from oxymorphone only in that the methyl group on the nitrogen atom of oxymorphone is replaced by an allyl group.

Naloxone hydrochloride occurs as white to slightly off-white powder and is soluble in water, in dilute acids, and in strong alkali; the drug is slightly soluble in alcohol and practically insoluble in ether and chloroform. The drug has a pK_a of 7.94. The commercially available injections are adjusted to pH 3–4.5 with hydrochloric acid or sodium hydroxide; the injections also *may* contain methylparaben and propylparaben as preservatives.

Naloxone hydrochloride may be available either as the anhydrous drug or as the dihydrate; both are defined officially (USP) as simply the hydrochloride salt, and potency is expressed in terms of the salt, calculated on the dried basis. Despite this official designation, some manufacturers calculate potency in terms of the base rather than the salt (e.g., Suboxone®, Reckitt Benckiser).

■ **Stability** Naloxone hydrochloride injections should be stored at 15–30°C and protected from light. The injections are stable at pH 2.5–5. Following dilution in 5% dextrose or 0.9% sodium chloride injection to a concentration of 0.004 mg/mL (4 mcg/mL), naloxone hydrochloride solutions are apparently stable for 24 hours; after 24 hours, any unused solution should be discarded.

Naloxone hydrochloride injection should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high molecular weight anions, or any solution having an alkaline pH. Drugs or chemical agents should not be added to solutions of naloxone hydrochloride unless their effect on the chemical and physical stability of the solution has been established. Specialized references should be consulted for specific compatibility information.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Naloxone Hydrochloride

Parenteral		
Injection	0.4 mg/mL*	**Naloxone Hydrochloride Injection**
		Narcan®, Endo
	1 mg/mL*	**Naloxone Hydrochloride Injection**

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Pentazocine and Naloxone Hydrochlorides

Oral		
Tablets	Pentazocine Hydrochloride 50 mg (of pentazocine) and Naloxone Hydrochloride 0.5 mg (of naloxone)	**Pentazocine and Naloxone Hydrochlorides Tablets** (C-IV)
		Talwin® Nx Caplets (C-IV; scored), Sanofi-Synthelabo

Naloxone Hydrochloride Dihydrate Combinations

Sublingual		
Tablets	0.5 mg (of naloxone) with Buprenorphine Hydrochloride 2 mg (of buprenorphine)	**Suboxone®** (C-III), Reckitt Benckiser
	2 mg (of naloxone) with Buprenorphine Hydrochloride 8 mg (of buprenorphine)	**Suboxone®** (C-III), Reckitt Benckiser

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Naltrexone
Naltrexone Hydrochloride

■ Naltrexone is essentially a pure opiate antagonist.

Uses

■ **Opiate Dependence** Naltrexone hydrochloride is designated an orphan drug by the US Food and Drug Administration (FDA) and is used orally for its opiate antagonist effects as an adjunct to a medically supervised behavior modification program in the maintenance of opiate cessation (opiate-free state) in individuals formerly physically dependent on opiates and who have successfully undergone detoxification. Behavior modification is an integral component in maintaining opiate cessation when naltrexone is used, and such modification involves supervised programs of counseling, psychologic support and therapy, and education, and changes in life-style (social rehabilitation). The theoretical rationale for using naltrexone as an adjunct in opiate cessation therapy is that the drug may diminish or eliminate opiate-seeking behavior by blocking the euphoric reinforcement produced by self-administration of opiates and by preventing the conditioned abstinence syndrome (i.e., heightened sensitivity to stimuli, abnormal autonomic responses, dysphoria, and intense opiate craving) that occurs following opiate withdrawal. There are no data that unequivocally demonstrate a beneficial effect of naltrexone on the tendency to relapse (recidivism) to drug abuse in detoxified, former opiate-dependent individuals; however, by blocking opiate-induced euphoria and potentially preventing the redevelopment of opiate dependence, naltrexone therapy in conjunction with a medically supervised behavior modification program may contribute to the prevention of relapse in the postaddiction period.

In individuals formerly dependent on opiates, naltrexone reportedly decreases opiate craving within 3–5 weeks of initiation of therapy; however, decreased opiate craving has occurred during the first week of naltrexone therapy in some individuals, with further decreases occurring in subsequent weeks. The efficacy of opiate cessation therapy that includes naltrexone on long-term cessation rates appears to be low, and poor compliance appears to be the major limiting factor in opiate cessation therapy that includes naltrexone. Because noncompliance with naltrexone therapy, unlike methadone or levomethadyl acetate (LAAM; no longer commercially available in the US because of potentially severe adverse cardiac effects) maintenance therapy, is not associated with unpleasant symptoms of withdrawal, compliance with opiate cessation therapy that includes naltrexone depends more on the voluntary efforts of the individual, and successful cessation appears to be more likely in highly motivated individuals. Repeated attempts at opiate cessation therapy may increase efficacy in terms of the amount of time the individual remains opiate-free; complete cessation may not be an obtainable goal in some individuals, and cycles of relapse to opiate use and cessation may be likely.

Behavioral therapy, as a component of opiate cessation therapy, allows the patient to undergo a social and psychologic rehabilitation that will aid in maintaining opiate cessation. Naltrexone therapy in combination with behavioral therapy has been shown to be more effective than naltrexone or behavioral therapy alone in prolonging opiate cessation in patients formerly physically dependent on opiates. Individuals who are highly motivated, employed, and in a stable married or other relationship appear to be most successful with naltrexone therapy and able to maintain opiate cessation. Strong external support from family and/or employer also contributes to the success of opiate cessation therapy that includes naltrexone. Because naltrexone is used as an adjunct to the individual's own cessation efforts, individuals should be highly motivated to develop a life-style free of opiate dependence. Individuals who are psychologically healthier generally are more successful in opiate cessation than those with more baseline psychologic disturbances, including mood disorders. Potential candidates for opiate cessation therapy that involves naltrexone include former opiate-dependent individuals who are employed and socially functioning, were recently detoxified from methadone maintenance, are leaving prison or residential treatment settings, are sporadically abusing opiates but are not yet dependent, are physically dependent on opiates secondary to medical use of the drugs, and/or are ineligible for methadone maintenance; naltrexone therapy may also be useful when the waiting period for admission into a methadone maintenance program is long. Naltrexone may be particularly useful as maintenance therapy in the prevention of relapse in former opiate-dependent individuals during times of stress when relapse to drug abuse may be most likely. Adolescents who have only recently become physically dependent on opiates may benefit particularly well from opiate cessation therapy that includes naltrexone. Opiate cessation therapy that includes naltrexone may also be especially beneficial in health-care professionals physically dependent on opiates. However, individuals may differ in their specific needs for behavioral therapy (e.g., psychotherapy, counseling) or additional pharmacologic support (e.g., sedatives and hypnotics, GI drugs). Individuals from lower socioeconomic groups who have recently been detoxified from methadone maintenance appear to benefit less from naltrexone therapy than health-care professionals and white-collar workers; however, behavioral therapy in the form of strong family external support improves the beneficial results of naltrexone therapy observed in individuals from lower socioeconomic groups.

Most clinical experience with naltrexone therapy in detoxified, former opiate-dependent individuals has been reported to date in uncontrolled studies. In controlled studies, patients receiving naltrexone therapy generally appeared to decrease their consumption of opiates, participated in opiate cessation programs longer, and had greater decreases in craving for opiates than did patients receiving placebo.

Opiate antagonists (e.g., naltrexone, naloxone) have been used for rapid or ultrarapid detoxification in the management of opiate withdrawal† in opiate-dependent individuals, both in inpatient and outpatient settings. Rapid opiate detoxification involves the administration of opiate antagonists such as naltrexone and/or naloxone to shorten the time period of detoxification. When used for this purpose, naltrexone sometimes has been given in combination with clonidine, guanabenz, or lofexidine (not currently available in the US). The reported advantage of rapid detoxification is to minimize the risk of relapse and to initiate maintenance therapy with naltrexone and psychosocial interventions more quickly. Ultrarapid detoxification is similar, but involves the administration of opiate antagonists (i.e., naltrexone, naloxone) while the patient is sedated or under general anesthesia. However, the risk of adverse respiratory and cardiovascular effects associated with this procedure must be considered as well as the costs of general anesthesia and hospitalization. Safety and efficacy of these therapies have not been established and further study is needed.

Parenteral naltrexone is not approved for use for its opiate antagonist effects or for the treatment of opiate dependence.

■ **Alcohol Dependence** Naltrexone is used orally or IM in the management of alcohol dependence in conjunction with a comprehensive management program that includes psychosocial support. Naltrexone is used IM in patients with alcohol dependence who are able to abstain from alcohol in an outpatient setting prior to initiation of naltrexone therapy and are abstinent at the time such therapy is initiated. Individuals who are willing to use pharmacologic ther-