NALOXONE Ⓟ

naloxone HCl

Opioid Antagonist

CPhA Monograph

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This monograph has been compiled by CPhA and reviewed by experts. It may contain information different from that found in Health Canada–Approved Product Monographs. The reader is referred to the *CPS* Editorial Policy for more Information.

SUMMARY PRODUCT INFORMATION:

Route of Administration	Dosage Form	Strength
Parenteral (IM, IV, SC)[a]	Solution for injection	0.4 mg/mL, 1 mg/mL
Intranasal[a]	Solution	2 mg/0.1 mL (20 mg/mL), 4 mg/0.1 mL (40 mg/mL)
Sublingual	Tablet	0.5 mg in combination with buprenorphine 2 mg
		2 mg in combination with buprenorphine 8 mg
		3 mg in combination with buprenorphine 12 mg
		4 mg in combination with buprenorphine 16 mg
Oral	Extended-release tablet	2.5 mg in combination with oxycodone 5 mg
		5 mg in combination with oxycodone 10 mg
		10 mg in combination with oxycodone 20 mg
		20 mg in combination with oxycodone 40 mg

[a] Some formulations are available without a prescription.

INDICATIONS AND CLINICAL USE: Health Canada–Approved Indications:
- Complete or partial reversal of opioid effects including respiratory depression.
- Diagnosis of suspected acute opioid overdosage.
- Relief of oxycodone-induced constipation, as part of an oral combination product containing prolonged-release oxycodone/naloxone; for prescribing information consult the Targin product monograph.
- Discourage intravenous misuse of the oral buprenorphine/naloxone combination product; for prescribing information consult the Suboxone product monograph.
- Emergency use for opioid overdose outside hospital settings as take-home naloxone (Schedule II, available without a prescription from the pharmacist). See Dosage and Administration, Recommended Dose and Dosage Adjustment for more information.

Uses Without Health Canada Approval:
- Reduction in the incidence of opioid-induced pruritus and pruritus of cholestasis [*Anesth Analg* 2005;100(4):953-8], [*Anesth Analg* 1994;78(6):1110-3], [*Ann Intern Med* 1995;123(3):161-7].
- Reversal of endorphin-mediated hypotension in patients with septic shock [*Crit Care Med* 1989;17(10):1004-9], [*J Natl Med Assoc* 1989;81(6):669-73], [*Crit Care Med* 1990;18(1):47-51], [*Cochrane Database Syst Rev* 2003;(4):CD004443].
- Relief of opioid-induced constipation in palliative care patients [*J Pain Symptom Manage* 2002;24(1):71-90].

CONTRAINDICATIONS:
- Hypersensitivity to naloxone or to any ingredient in the formulation or component of the container.

WARNINGS AND PRECAUTIONS:

Serious Warnings and Precautions
- Bystanders should immediately request emergency medical assistance (call 911) when an opioid overdose is suspected and before administering naloxone.
- Keep patients who have satisfactorily responded to naloxone under continued surveillance and administer repeat doses as necessary since the duration of action of some opioids may exceed that of naloxone.
- Caregivers administering naloxone should be prepared to assist the patient for potential adverse reactions such as aggressive reactions, convulsions and vomiting (see Warnings and Precautions, Acute Opioid Withdrawal Syndrome). Special attention is warranted if naloxone is administered to a neonate or a pregnant woman (see Warnings and Precautions, Special Populations, Pediatrics and Pregnant Women).
- In patients physically dependent on opioids, including neonates born to opioid-dependent women, naloxone may precipitate symptoms of acute opioid withdrawal such as pain, hypertension, sweating, agitation or irritability. Administer naloxone cautiously in these patients and monitor closely. Titration with smaller than usual doses may be necessary (see Warnings and Precautions, Acute Opioid Withdrawal Syndrome and Table 1).
- Avoid excessive doses of naloxone following the use of opioids during surgery as this may result in excitement, agitation, increased blood pressure or reversal of analgesia. Consequences of reversing the effects of opioids too rapidly may include nausea, vomiting, sweating, tremor, tachycardia, increased blood pressure, seizures, ventricular tachycardia and fibrillation, pulmonary edema or cardiac arrest, resulting in death.

Acute Opioid Withdrawal Syndrome: Naloxone should be administered with caution to persons who are known or suspected to be physically dependent on opioids. In such cases, an abrupt and complete reversal of opioid effects may precipitate an acute opioid withdrawal syndrome depending on the degree of physical dependence, the dose, affinity and potency of the opioid that induced the overdose, as well as the dose of naloxone administered.

The signs and symptoms of an acute opioid withdrawal syndrome include, but are not limited to, body aches, pain, fever/pyrexia, sweating/hyperhidrosis, runny nose, sneezing, piloerection, yawning, weakness, asthenia, shivering, chills, tremor/trembling, convulsions/seizures, nervousness, restlessness, irritability, aggressive behaviour, diarrhea, nausea, vomiting, abdominal cramps, increased blood pressure and tachycardia. In the dependent neonate, signs also include excessive crying as well as hyperactive reflexes. The acute withdrawal may be life-threatening if not recognized and properly treated.

Caregivers should be prepared to assist the patient with these potential adverse reactions, e.g., position patient in lateral decubitus (recovery position) to avoid choking if vomiting occurs, move any sharp or dangerous objects away to protect patient from injury if convulsions occur (patient should not be restrained).

Cardiovascular: Use caution when administering naloxone to patients with pre-existing cardiovascular disease or in patients receiving potentially cardiotoxic drugs. Serious adverse cardiopulmonary effects (hypotension, hypertension, ventricular tachycardia and fibrillation, pulmonary edema) have occurred in postoperative patients resulting in encephalopathy, coma and death.

Hepatic/Biliary/Pancreatic: Use caution when administering naloxone to patients with hepatic impairment. Safety and efficacy of naloxone in patients with hepatic impairment has not been established in controlled trials.

Neurologic: Convulsions or seizures have been rarely reported after naloxone use although the relationship with naloxone is unclear. If convulsions or seizures occur, move any sharp or dangerous objects away to protect patient from injury; the patient should not be restrained.

Renal: Use caution when administering naloxone in patients with renal impairment. Safety and efficacy of naloxone in patients with renal impairment has not been established in controlled trials.

Respiratory: Naloxone is not effective against respiratory depression caused by nonopioid drugs. Reversal of respiratory depression induced by partial agonist opioids, such as buprenorphine or pentazocine, or by highly potent opioids, such as fentanyl, may be incomplete and subsequent doses at close intervals may be necessary. Mechanically assist respiration if there is an incomplete response. Vasopressor agents should be employed whenever necessary if available and if a health-care professional is present.

Special Populations: Pregnant Women: Other than reports of naloxone use in labour, information on the fetal effects of naloxone in pregnancy is not available. In 1 report of naloxone use in 18 women during labour, mothers who had received meperidine were administered naloxone to prevent neonatal narcotic depression. Infants whose mothers received naloxone did not have significantly different blood gas values or neurobehavioural examination results compared to the control group whose mothers did not receive meperidine or naloxone [*South Med J* 1976;69(5):570-5]. Consider the benefits to the pregnant mother and risks to the fetus when administering naloxone to opioid-dependent mothers as naloxone may precipitate opioid withdrawal in the fetus and mother (see Warnings and Precautions, Acute Opioid Withdrawal Syndrome), which may precipitate preterm labour or fetal distress. Naloxone should be used only if clearly needed.

Nursing Women: It is not known whether naloxone is transferred into human breast milk. Caution is advised if naloxone is used in breastfeeding women.

Pediatrics: Whether the use of naloxone in neonates exposed to opioids prior to delivery improves outcomes (e.g., admission to neonatal intensive care unit or failure to establish breastfeeding) is unclear [*Cochrane Database Syst Rev* 2013;(2):CD003483]. Administration of naloxone may precipitate an opioid withdrawal syndrome (see Warnings and Precautions Acute Opioid Withdrawal Syndrome), which can be life-threatening in an opioid-dependant neonate if not recognized and treated appropriately. Naloxone should be administered to a neonate only if clearly needed.

ADVERSE REACTIONS: The following adverse reactions have been reported; the incidence is unknown:
Cardiovascular: tachycardia, hypertension, hypotension, ventricular tachycardia, fibrillation.
Central Nervous System: seizures, tremulousness.
Gastrointestinal: nausea, vomiting.
Miscellaneous: reversal of analgesia, excitement, sweating. With intranasal formulation: nasal edema, nasal inflammation, nasal dryness, nasal congestion, toothache, rhinalgia.
Respiratory: pulmonary edema, hyperventilation.

DRUG INTERACTIONS: There are no known significant drug-drug interactions with naloxone.

DOSAGE AND ADMINISTRATION: Dosing Considerations:
- Bystanders should immediately request emergency medical assistance (call 911) when an opioid overdose is suspected and before administering naloxone.
- The most rapid onset of action is achieved by IV administration, although this route of administration should be used only by health-care professionals. The IM route (or intranasal, if nasal formulation is available) is recommended for administration by a bystander.
- The duration of action of some opioids may exceed that of naloxone. Monitor patients and administer repeat doses as necessary.
- If naloxone is administered via endotracheal tube (see Table 1; not a Health Canada–approved route of administration), the dose may need to be doubled or tripled [*Circulation* 2010;122(18 Suppl 3):S876-908].
- When using the intranasal formulation, the lowest available strength of the product should be used as initial dose in all cases.

Recommended Dose and Dosage Adjustment: Adults: See Table 1.

Table 1: NALOXONE
Dose in Adult Patients

Indication	Route	Dose	Dose Titration	Clinical Comment
Opioid-induced CNS/respiratory depression	Intermittent: IV (IM, SC, ET[a] routes may be used if IV route unavailable)	0.4–2 mg	Repeat dose every 2–3 min as needed	May need to repeat doses every 20–60 min. If no response is seen after 10 mg,[b] consider other causes of respiratory depression.
	Continuous: IV infusion	0.4 mg/h	Adjust infusion rate based on clinical response	Administer as a 0.004 mg/mL solution (see Administration). Infusion required rarely.
Opioid-induced CNS/respiratory depression in opioid-dependent patients	IV (IM, SC, ET[a] routes may be used if IV route unavailable)	0.1–0.2 mg	Repeat dose every 2–3 min as needed; titrate dose to avoid precipitating acute opioid withdrawal	May need to repeat doses every 20–60 min. If no response is seen after 10 mg, consider other causes of respiratory depression.
Emergency use for opioid overdose outside hospital setting as take-home naloxone	IM, intranasal	IM: 0.4 mg Intranasal: 1 spray in 1 nostril of lowest available strength	Repeat dose every 2–3 min as needed	Caregiver should be prepared to give more naloxone if necessary while waiting for ambulance to arrive. See Administration for more information. Use an additional spray device for additional nasal doses; device contains a single dose only. Administer in alternate nostrils with each dose.
Postoperative opioid-induced CNS/respiratory depression	IV (IM, SC, ET[a] routes may be used if IV route unavailable)	0.1–0.2 mg	Repeat dose every 2–3 min as needed	May need to repeat doses every 1–2 h. Supplemental IM dose provides longer duration of effect.
Opioid-induced pruritus (not a Health Canada–approved use)	IV infusion	0.25–2.4 mcg/kg/h	Adjust infusion rate based on clinical response	Doses ≥2 mcg/kg/h may decrease pain control and may necessitate an increase in opioid dose. Monitor pain control closely.

(cont'd)

Table 1: NALOXONE *(cont'd)*
Dose in Adult Patients

Indication	Route	Dose	Dose Titration	Clinical Comment
Septic shock (not a Health Canada–approved use)	IV	0.03–0.2 mg/kg bolus over 5 min followed by infusion of 0.03 mg/kg/h	Optimal dose and duration of therapy have not been established	If a response occurs, continue infusion for 1–24 h or longer, depending on clinical response.
Opioid-induced constipation in palliative care (not a Health Canada–approved use)	PO	1 mg BID of injectable formulation given PO	Increase dose gradually to effect (usual dose: 2–18 mg/day)	Monitor for symptoms of opioid withdrawal.

[a] ET: via endotracheal tube (not an approved route in Canada); dose may need to be doubled or tripled.
[b] According to some experts, certain patients may require higher doses, e.g., 10–20 mg, especially when carfentanil is involved.

Geriatrics: See Adults.
Pediatrics: See Table 2.

Table 2: NALOXONE
Dose in Pediatric Patients

Indication	Route	Age/Weight	Initial Dose	Dose Titration
Opioid-induced CNS depression	IV (IM, SC, ET[a] routes may be used if IV route unavailable)	Birth to 5 y (or ≤20 kg)	0.1 mg/kg Maximum dose: 2 mg	Repeat doses every 2–3 min as needed.
		>5 y or >20 kg	2 mg	Repeat doses every 2–3 min as needed.
Neonatal opioid-induced CNS depression (due to maternal exposure before delivery)	IV (IM or SC routes may be used if IV route unavailable)	Neonates	0.01 mg/kg	Repeat doses every 2–3 min as needed based on patient response. Additional doses may be administered every 1–2 h.
Postoperative opioid-induced CNS depression	IV (IM, SC, ET[a] routes may be used if IV route unavailable)	Infants and children	0.001–0.005 mg/kg	Repeat at 2–3 min intervals as needed.

[a] ET: via endotracheal tube (not an approved route in Canada); dose may need to be doubled or tripled.

Administration: Naloxone can be administered by IV, IM or SC injection, by continuous IV infusion or by intranasal route. IV administration is the preferred route of administration and is recommended in emergency situations; however, IM, SC or intranasal route can be used if IV administration is not possible. IV infusion may be useful in cases of opioid overdose with long-acting drugs such as methadone. IM and SC administration can result in erratic absorption in hypotensive patients and patients with peripheral vasoconstriction or hypoperfusion.

Endotracheal tube (ET) administration can also be employed in children and adults for opioid overdosage but optimal doses are unknown. Following administration of ET naloxone, the endotracheal tube should be flushed with 5 mL of normal saline followed by 5 ventilations [*Circulation* 2010;122(18 Suppl 3):S876-908]. The ET route is not a preferred or Health Canada–approved route of administration for naloxone, and is not recommended for neonates [*Circulation* 2005;112(24 Suppl):IV1-203].

Naloxone may be administered by direct IV undiluted or diluted in sterile water for injection (e.g., into a 10-mL syringe) at a rate of 0.4 mg/15 seconds.

For IV infusion, dilute naloxone preparations to a concentration of 0.004 mg/mL in dextrose 5% for injection or sodium chloride 0.9% for injection.

For emergency use for opioid overdose outside hospital setting as take-home naloxone (Schedule II), it is recommended that the pharmacist dispense naloxone as a bundle. Pre-assembled kits are available for ordering. Regulation of take-home naloxone will vary according to province; most Canadian provinces and territories now have a publicly funded take-home naloxone kit program at no cost to patients.

Components of injectable naloxone kit:
- A minimum of 2 ampoules or vials of naloxone 0.4 mg/mL with a minimum 6-month expiry date (ampoules preferred)
- A minimum of 2 safety syringes (3 mL) with 25 gauge × 1-in. needle
- Nitrile gloves (non-latex)
- Alcohol swabs
- Ampoule breakers (not necessary if vials are used)
- Naloxone identifier card (name of person trained in responding to opioid overdose, expiry date and date naloxone supplied)
- Instructions for use
- Breathing mask or rescue breathing barrier (used when administering CPR)

The trained caregiver should draw up the entire contents of the ampoule/vial and administer IM into thigh, buttocks or shoulder. CPR should be continued throughout the process and while waiting for the ambulance to arrive. The caregiver should be prepared to give more naloxone if necessary (see Table 1).

Components of nasal spray naloxone kit:
- A minimum of 2 devices of naloxone nasal spray
- Nitrile gloves (non-latex)
- Naloxone identifier card (name of person trained in responding to opioid overdose, expiry date and date naloxone supplied)
- Breathing mask or rescue breathing barrier (used when administering CPR)
- Instructions for use

The trained caregiver should place the patient on his or her back, insert the device nozzle in either nostril (alternate with each dose) and provide support to the back of the neck to allow the head to tilt back. Do not test or prime the device. To administer, press firmly on the device plunger. Do not reuse the device; each device contains a single dose. CPR should be continued throughout the process and while waiting for the ambulance to arrive. The caregiver should be prepared to give more naloxone if necessary (see Table 1).

For more information, tutorial videos and infographics, visit the Canadian Pharmacists Association website: www.pharmacists.ca/advocacy/opioid-crisis.

OVERDOSAGE:

For management of a suspected drug overdose, contact your regional Poison Control Centre. See the *CPS* Directory section for a list of Poison Control Centres.

ACTION AND CLINICAL PHARMACOLOGY: Mechanism of Action: Naloxone is a pure opioid antagonist that appears to competitively antagonize kappa-, sigma- and mu-opioid receptor sites in the CNS. This agent competes with and displaces opioids from opioid receptor sites and antagonizes the effect of the opioid. Naloxone has little agonist activity and when administered in usual doses to patients who have not received opioids, naloxone exerts little or no pharmacologic effect.

Pharmacokinetics: Adults: Naloxone has an onset of action of 1–2 minutes following IV administration and 2–5 minutes following IM or SC administration. The intranasal route has shown a similar onset of action as the IM route. The duration of action depends on the route of administration and can range from 30–120 minutes; IV naloxone has a shorter duration of action compared to IM administration.

Distribution: Naloxone is rapidly distributed into body tissues and fluids following parenteral administration. The drug is weakly bound to plasma proteins and crosses the placenta. The nasal formulation can deliver a dose with approximately 50% of the bioavailability of the IM route.

Metabolism: Naloxone is rapidly metabolized in the liver primarily via glucuronidation to form the major metabolite naloxone-3-glucuronide.

Excretion: Naloxone is excreted in urine as metabolites. After parenteral administration, the elimination half-life of naloxone has been reported as 30–81 minutes in adults and 3.1 hours in neonates. After intranasal administration, the elimination half-life of naloxone is 2 hours.

STORAGE AND STABILITY: Store injectable naloxone between 15–30°C and protect from light. Store the nasal formulation between 15–25°C (excursions permitted up to 40°C), protect from light and keep in the blister and cartons provided.

SUPPLIED: Please refer to Summary Product Information section.