at a concentration of 100 micrograms/mL, in an initial dose of 250 nanograms/kg. Further doses of 250 nanograms/kg may be given at intervals of 2 to 5 minutes until the desired level of opioid reversal is reached; cumulative doses above 1 microgram/kg do not provide additional benefit. In patients with an increased cardiovascular risk a concentration of 50 micrograms/mL and doses and increments of 100 nanograms/kg are recommended.

In the management of known or suspected opioid overdosage, nalmefene is given intravenously at a concentration of 1 mg/mL. An initial dose of 500 micrograms per 70 kg is recommended, followed by a second dose of 1 mg per 70 kg after 2 to 5 minutes if necessary. If a total dose of 1.5 mg per 70 kg is not effective then additional doses are unlikely to have an effect. If the patient is suspected of being physically dependent on opioids an initial test dose of 100 micrograms per 70 kg is recommended; if there is no evidence of withdrawal symptoms within 2 minutes the usual dosage may be used.

Although nalmefene has a longer duration of action than naloxone, all patients should be closely observed and if respiratory depression does recur, the dose of nalmefene should be titrated as above to avoid over-reversal of opioid effects.

Alcohol withdrawal and abstinence. For mention of the use of nalmefene in the adjunctive management of patients with alcohol dependence, see under Naltrexone, p.1456.

Pruritus. It has been suggested that because central opioid receptors modulate itch, an opioid antagonist might be useful in pruritus (p.1582). A systematic review[1] found that opioid antagonists are effective in opioid-induced pruritus, and a number have also been reported to be of benefit in pruritus of other causes.

Rapid improvement of severe pruritus was reported after a single oral dose of *nalmefene* 10 or 20 mg in a double-blind study of 80 patients with either chronic urticaria or atopic dermatitis.[2] Pruritus was almost completely eliminated in up to 60% of patients receiving nalmefene. Adverse effects occurred in 67% of patients and included dizziness or lightheadedness, fatigue, and nausea. In another study,[3] 14 patients with resistant pruritus secondary to cholestatic liver disease were treated with oral nalmefene for 2 to 26 months. The initial dose was 2 mg twice daily and the dose was increased gradually as necessary. Although 13 of the patients reported some amelioration of pruritus, 5 found that increasing doses were required to produce any benefit, and in 3 tolerance appeared to develop.

Continuous infusion of *naloxone* 200 nanograms/kg per minute was reported to reduce perception of pruritus and scratching activity in a double-blind study of 29 patients with pruritus due to cholestasis,[4] although the role of continuous infusion in long-term management may be limited.

Benefit has been reported with oral *naltrexone* 50 mg daily in pruritus of various origins,[5] as well as in patients with cholestatic pruritus.[6,7] In uraemic pruritus, conflicting results have been reported;[8,9] a subsequent study[10] suggested that naltrexone might be of benefit in selected patients.

1. Kjellberg F, Tramèr MR. Pharmacological control of opioid-induced pruritus: a quantitative systematic review of randomized trials. *Eur J Anaesthesiol* 2001; **18:** 346–57.
2. Monroe EW. Efficacy and safety of nalmefene in patients with severe pruritus caused by chronic urticaria and atopic dermatitis. *J Am Acad Dermatol* 1989; **21:** 135–6.
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5. Metze D, *et al.* Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases. *J Am Acad Dermatol* 1999; **41:** 533–9.
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7. Terg R, *et al.* Efficacy and safety of oral naltrexone treatment for pruritus of cholestasis, a crossover, double blind, placebo-controlled study. *J Hepatol* 2002; **37:** 717–22.
8. Peer G, *et al.* Randomised crossover trial of naltrexone in uraemic pruritus. *Lancet* 1996; **348:** 1552–4.
9. Pauli-Magnus C, *et al.* Naltrexone does not relieve uremic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. *J Am Soc Nephrol* 2000; **11:** 514–9.
10. Legroux-Crespel E, *et al.* A comparative study on the effects of naltrexone and loratadine on uremic pruritus. *Dermatology* 2004; **208:** 326–30.

Preparations

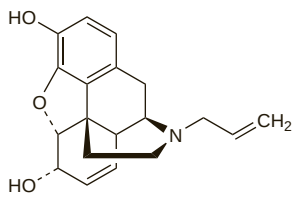
Proprietary Preparations (details are given in Part 3)
Mex.: Nocarex; ***USA:*** Revex.

Nalorphine *(BAN, rINN)*

Nalorfiini; Nalorfin; Nalorfina; Nalorphinum. (–)-(5*R*,6*S*)-9a-Allyl-4,5-epoxymorphin-7-en-3,6-diol; 17-Allyl-17-normorphine.

Налорфин

$C_{19}H_{21}NO_3$ = 311.4.
CAS — 62-67-9.
ATC — V03AB02.
ATC Vet — QV03AB02.



Nalorphine Hydrobromide *(BANM, rINNM)*

Hidrobromuro de nalorfina; Nalorphine, Bromhydrate de; Nalorphini Hydrobromidum.

Налорфина Гидробромид

$C_{19}H_{21}NO_3$,HBr = 392.3.
ATC — V03AB02.
ATC Vet — QV03AB02.

Pharmacopoeias. In *Chin.*

Nalorphine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de nalorfina; Nalorphine, Chlorhydrate de; Nalorphini Hydrochloridum; Nalorphinium Chloride.

Налорфина Гидрохлорид

$C_{19}H_{21}NO_3$,HCl = 347.8.
CAS — 57-29-4.
ATC — V03AB02.
ATC Vet — QV03AB02.

Pharmacopoeias. In *US.*
USP 31 (Nalorphine Hydrochloride). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects and Precautions
As for Naloxone (below). Nalorphine also has some opioid agonist properties and adverse effects such as drowsiness, respiratory depression, miosis, dysphoria, and lethargy may occur if it is given to patients who have not received opioids.

Uses and Administration
Nalorphine is an opioid antagonist with properties similar to those of naloxone (below); in addition it also possesses some agonist properties. It has been used as the hydrobromide or hydrochloride in the treatment of opioid-induced respiratory depression; it reverses severe opioid-induced respiratory depression but may exacerbate respiratory depression such as that induced by alcohol or other non-opioid central depressants.

Preparations
USP 31: Nalorphine Hydrochloride Injection.

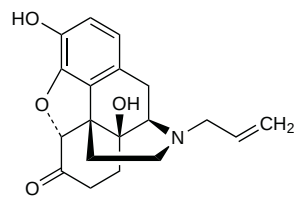
Naloxone Hydrochloride

(BANM, USAN, rINNM)

N-Allylnoroxymorphone Hydrochloride; Cloridrato de Naloxona; EN-15304; Hidrocloruro de naloxona; Nalokson Hidroklorür; Naloksonihydrokloridi; Naloksono hidrochloridas; Naloksonu chlorowodorek dwuwodny; Naloxone, Chlorhydrate de; Naloxone (chlorhydrate de) dihydraté; Naloxon-hidroklorid; Naloxon-hydrochlorid; Naloxonhydroklorid; Naloxoni Hydrochloridum; Naloxoni hydrochloridum dihydricum. 17-Allyl-6-deoxy-7,8-dihydro-14-hydroxy-6-oxo-17-normorphine hydrochloride dihydrate; (–)-(5*R*,14*S*)-9a-Allyl-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate.

Налоксона Гидрохлорид

$C_{19}H_{21}NO_4$,HCl,2H_2O = 399.9.
CAS — 465-65-6 (naloxone); 357-08-4 (anhydrous naloxone hydrochloride); 51481-60-8 (naloxone hydrochloride dihydrate).
ATC — V03AB15.
ATC Vet — QV03AB15.



(naloxone)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*. Forms specified may be anhydrous, dihydrate, or both.
Ph. Eur. 6.2 (Naloxone Hydrochloride Dihydrate; Naloxone Hydrochloride BP 2008). It contains two molecules of water of hydration. A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in toluene. Store in airtight containers. Protect from light.
USP 31 (Naloxone Hydrochloride). It is anhydrous or contains two molecules of water of hydration. A white to slightly off-white powder. Soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Its aqueous solution is acidic. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Infusions of naloxone hydrochloride should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high-molecular-weight anions, or solutions with an alkaline pH.

Adverse Effects
Nausea and vomiting have occurred with naloxone. Some adverse effects may be associated with opioid withdrawal. There have been individual reports of hypotension, hypertension, cardiac arrhythmias, and pulmonary oedema, generally in patients given naloxone postoperatively. Seizures have also been reported infrequently.

◊ Hypertension,[1,2] pulmonary oedema,[3] and cardiac arrhythmias including ventricular tachycardia and fibrillation[4] have been reported after the postoperative use of naloxone, generally in patients with pre-existing heart disease undergoing cardiac surgery. However, there have also been reports in healthy patients,[5,6] including some fatalities.[5]

Hypotension, bradycardia, and precipitation of focal seizures have been reported in patients given high-dose naloxone for acute ischaemic stroke.[7]

Ventricular fibrillation has been observed in an opioid addict given naloxone to reverse the effects of diamorphine.[8] However, this patient was later shown to have hepatic cirrhosis and alcoholic cardiomyopathy and the National Poisons Information Service in London noted that it had never been informed of such a suspected adverse reaction despite being contacted in about 800 cases of opioid poisoning each year.[9] In a later report severe adverse effects were noted in 6 of 453 subjects given naloxone to reverse diamorphine intoxication.[10] The effects were: asystole (1 case), generalised convulsions (3), pulmonary oedema (1), and violent behaviour (1).

1. Tanaka GY. Hypertensive reaction to naloxone. *JAMA* 1974; **228:** 25–6.
2. Azar I, Turndorf H. Severe hypertension and multiple atrial premature contractions following naloxone administration. *Anesth Analg* 1979; **58:** 524–5.
3. Flacke JW, *et al.* Acute pulmonary edema following naloxone reversal of high-dose morphine anesthesia. *Anesthesiology* 1977; **47:** 376–8.
4. Michaelis LL, *et al.* Ventricular irritability associated with the use of naloxone hydrochloride: two case reports and laboratory assessment of the effects of the drug on cardiac excitability. *Ann Thorac Surg* 1974; **18:** 608–14.
5. Wride SRN, *et al.* A fatal case of pulmonary oedema in a healthy young male following naloxone administration. *Anaesth Intensive Care* 1989; **17:** 374–7.
6. Taff RH. Pulmonary edema following naloxone administration in a patient without heart disease. *Anesthesiology* 1983; **59:** 576–7.
7. Barsan WG, *et al.* Use of high dose naloxone in acute stroke: possible side effects. *Crit Care Med* 1989; **17:** 762–7.
8. Cuss FM, *et al.* Cardiac arrest after reversal of effects of opiates with naloxone. *BMJ* 1984; **288:** 363–4.
9. Barret L, *et al.* Cardiac arrest following naloxone. *BMJ* 1984; **288:** 936.
10. Osterwalder JJ. Naloxone—for intoxications with intravenous heroin and heroin mixtures—harmless or hazardous? A prospective clinical study. *Clin Toxicol* 1996; **34:** 409–16.

Precautions
Naloxone should be used with caution in patients physically dependent on opioids, or who have received large doses of opioids, as an acute withdrawal syndrome may be precipitated (see Dependence and With-