

intracavernosal methylthionium chloride, particularly in patients with drug-induced priapism; it is thought to act by blocking the vasodilator effects of nitric oxide. However, penile necrosis has occurred³ after the use of methylthionium chloride and it should probably be avoided in patients with corporal fibrosis; aspiration of methylthionium chloride about 5 minutes after injection has been suggested.^{2,3}

1. Steers WD, Selby JB. Use of methylene blue and selective embolization of the pudendal artery for high flow priapism refractory to medical and surgical treatments. *J Urol (Baltimore)* 1991; **146**: 1361-3.
2. deHoll JD, et al. Alternative approaches to the management of priapism. *Int J Impot Res* 1998; **10**: 11-14.
3. Martínez Portillo FJ, et al. Methylene blue as a successful treatment alternative for pharmacologically induced priapism. *Eur Urol* 2001; **39**: 20-3.
4. Hübner J, et al. Methylene blue as a means of treatment for priapism caused by intracavernous injection to combat erectile dysfunction. *Int Urol Nephrol* 2003; **35**: 519-21.
5. Mejean A, et al. Re: Use of methylene blue and selective embolization of the pudendal artery for high flow priapism refractory to medical and surgical treatments. *J Urol (Baltimore)* 1993; **149**: 1149.

Preparations

BP 2008: Methylthionium Injection;
USP 31: Methylene Blue Injection.

Proprietary Preparations (details are given in Part 3)

Hung.: Metienkek; **USA:** Urolene Blue.

Multi-ingredient: **Arg.:** Lagrimas de Santa Lucia; Mictasol Azul; Muelita; Visubril; **Austria:** Methymint; **Braz.:** Acridin; Cystex; Lisian; Pilulas De Witts; Sepurin; Vislin; Visodin; Visolux; **Canad.:** Collyre Bleu; **Fr.:** Collyre Bleu; Pastilles Monleon; **Hong Kong:** Clear Blue; **Israel:** Pronest; **Ital.:** Mictasol Bleu; Visustrin; **NZ:** De Witts Pills; **Pol.:** Ginjal; Mibalin; **Rus.:** Neo-Anusol (Нео-анусол); **Spain:** Argentofenol; Centilux; Tivitis; **Switz.:** Collyre Bleu Laiter; **Turk.:** Buco Bleu; Helmobleu; **USA:** Atrosept; Dolsed; MHP-A; MSP-Blu; Prosed/DS; Trac Tabs 2X; UAA; Urelle; Uret-ron; Uridon Modified; Urimar-T; Urimax; Urised; Uriseptic; UrSym; Uritact; Uro Blue; Urogresic Blue; Utra.

Milk Thistle

Cardo mariano; Chardon marie (milk-thistle fruit); Lady's Thistle; Maarianohdakkeenhedelmä (milk-thistle fruit); Margainių vaisiai (milk-thistle fruit); Marian Thistle; Mariatistelfrukt (milk-thistle fruit); Mariendistel; Plod ostropestřce mariánského (milk-thistle fruit); Silybi mariani fructus (milk-thistle fruit); St Mary's Thistle. **CAS** — 84604-20-6 (milk thistle extract).

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

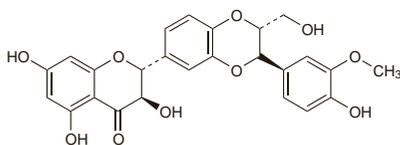
Ph. Eur. 6.2 (Milk-Thistle Fruit). The mature fruit, devoid of the pappus, of *Silybum marianum*. It contains not less than 1.5% of silymarin expressed as silibinin (dried drug). Protect from light. **USP 31** (Milk Thistle). The dried ripe fruit of *Silybum marianum* (Asteraceae), the pappus having been removed. It contains not less than 2% of silymarin, calculated as silibinin, on the dried basis. Store in airtight containers. Protect from light.

Silibinin (rINN)

Silbinina; Silibinine; Silibininum; Silybin; Silybum Substance E₆; Silybinina. 3,5,7-Trihydroxy-2-[3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxan-6-yl]-4-chromanone.

Силибинин

$C_{25}H_{22}O_{10}$ = 482.4.
CAS — 22888-70-6.



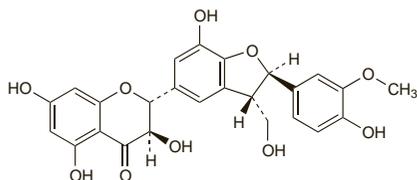
NOTE. The name silymarin has been used for both a mixture of silibinin, silicristin, and silidianin, and for silibinin alone.

Silicristin (rINN)

Silicristina; Silicristine; Silicristinum; Silikrystyna; Silychristin. 2-[2,3-Dihydro-7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-5-benzofuran-7-yl]-3,5,7-trihydroxy-4-chromanone.

Силикристин

$C_{25}H_{22}O_{10}$ = 482.4.
CAS — 33889-69-9.

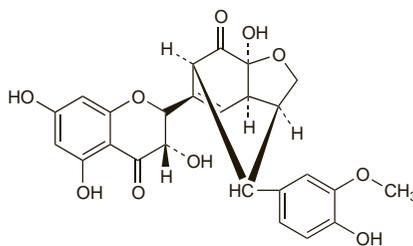


Silidianin (rINN)

Silidianina; Silidianine; Silidianium; Silydianin. (+)-2,3a,3aa,7a-Tetrahydro-7aa-hydroxy-8(R⁺)-(4-hydroxy-3-methoxyphenyl)-4-(3a,5,7-trihydroxy-4-oxo-2β-chroman-yl)-3,6-methanobenzofuran-7(6aH)-one.

Силдианин

$C_{25}H_{22}O_{10}$ = 482.4.
CAS — 29782-68-1.



Silymarin

Silimaring; Silymarinum. A mixture of the isomers silibinin, silicristin, and silidianin.

CAS — 65666-07-1.

ATC — A05BA03.

ATC Vet — QA05BA03.

Profile

Milk thistle (*Silybum marianum*; *Cardus marianus*) is used in herbal medicine, mainly for gastrointestinal and hepatobiliary disorders. The fruit contains the active principle silymarin, a mixture of flavonolignans including the isomers silibinin, silicristin, and silidianin, of which silibinin is the major component. Silymarin is claimed to be a free radical scavenger and to have hepatoprotective properties; it has been used in various liver disorders, as well as to prevent hepatotoxicity associated with poisoning. In *Amanita phalloides* poisoning (p.2349) both silymarin and silibinin (as the disodium dihemisuccinate salt) have been used.

Milk thistle is usually given as a standardised extract containing mainly silymarin, although the herb and fruit have also been used; the strength of the extract is expressed in terms of silymarin or silibinin, although the exact equivalence is not always clear. It is usually given orally since silymarin is poorly water-soluble and therefore unsuitable for intravenous use. A typical oral dose of up to 140 mg of silymarin two or three times daily has been suggested for hepatic disorders. Disodium silibinin dihemisuccinate is water-soluble and is given intravenously; the usual dose in *Amanita phalloides* poisoning is equivalent to silibinin 20 mg/kg daily, given by intravenous infusion in 4 divided doses.

Amanita poisoning. Silymarin and silibinin have been found to be effective in preventing hepatotoxicity after amanita poisoning.^{1,3}

1. Lorenz D. Über die anwendung von silibinin bei der knollenblät-terpilzvergiftung. *Dtsch Arch* 1982; **79**: 43-5.
2. Hruby K, et al. Chemotherapy of *Amanita phalloides* poisoning with intravenous silibinin. *Hum Toxicol* 1983; **2**: 183-90.
3. Enjalbert F, et al. Treatment of amatoxin poisoning: 20-year retrospective analysis. *J Toxicol Clin Toxicol* 2002; **40**: 715-57.

Liver disorders. References to the use of milk thistle or silymarin in patients with liver disorders.

1. Saller R, et al. The use of silymarin in the treatment of liver diseases. *Drugs* 2001; **61**: 2035-63.
2. Jacobs BP, et al. Milk thistle for the treatment of liver disease: a systematic review and meta-analysis. *Am J Med* 2002; **113**: 506-15.

Preparations

USP 31: Milk Thistle Capsules; Milk Thistle Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Benevolus; Laragon; **Austral.:** Biogan Liver-Vite; Herbal Liver Formula; Profl; Silymarin Phytosome; **Austria:** Apilhepar; Ardeyhepar; Legalon; Silyhexal; **Belg.:** Legalon; Legalon SL; **Braz.:** Eleparon; Legalon; Silver; **Chile:** Legalon; **Cz.:** Flavobion; Lagosa; Legalon; Nat Cubetu Benediktu; Silygal; **Fr.:** Legalon; **Ger.:** Alepa; Ardeyhepar; Cefasilymarin; durasilymarin; Hegrimarin; Hepa-Loges; Hepa-Merz Sil; HepaBesch; Hepaduran V; Hepar-Pasc; Heparsy; N; Hepatos; Heplant; Lagosa; Legalon; Legalon SL; Lomacholan; Phytohepar; Poikicholan; Silbene; Silcur; Silymarin; Silmar; Silyvas; Sily-Sabona; **Gr.:** Legalon; **Hong Kong:** Legalon; **Hung.:** Hegrimarin; Legalon; Legalon SL; **India:** Limarin; Silybon; **Ital.:** Legalon; Silmarin; Sillex; Siliver; **Mex.:** Etagem; **Philipp.:** Hepavit; Legalon; Liveraid; **Pol.:** Flexiderm; Lagosa; Legalon; Silmax; Silycaps; Silymarin; Silyverin; **Port.:** Legalon; Legalon SL; **Rus.:** Carsil (Карсил); **S.Afr.:** Legalon; **Spain:** Legalon; Legalon SL; Silanine; Silmazur; **Switz.:** Legalon; Legalon SL; **Thai.:** Legalon; Leveron; Marina; Samarin; Silylar; **Ven.:** Legalon.

Multi-ingredient: **Arg.:** Bibol Leloup; Hepadigenor; Quelodan F; **Austral.:** Antioxidant Forte Tablets; Bupleurum Complex; Bupleurum Compound; Digest; Extralife Liva-Care; Herbal Cleanse; Lifesystem Herbal Formula 7 Liver Tonic; Liver Tonic Herbal Formula 6; Livstim; Livton Complex; Silybum Complex; St Mary's Thistle Plus; **Austria:** Hepabene; **Braz.:** Silamal; **Canad.:** Milk Thistle; Milk Thistle Extract Formula; **Cz.:** Hepabene; Iberogast; Naturland Grosser Swedenbitter; Simepar; Ungolen; **Ger.:** Bilisan Duo; Cheiranthol; Cholhepan N; Cholosom-Tee; Gallex; Galloselect M; Hepaticum-Medice H; Heumann Leber- und Gallentee Solu-Hepar S; Heumann Verdauungstee Solu-Lipar; Heusin; Iberogast; Marianon; Pankreaplex Neu; Paspocankreat novot; Presselin

Hepaticum P; Schwhepan S; Venacton; **Hong Kong:** Hepatofalk Planta; Simepar; **Hung.:** Hepabene; **India:** Livosi-B; **Indon.:** Aptivium Liver Support; Curliv Plus; Hepa-Q; Hepamax; Heparviton; Hepasil; Hepatin; Hepatofalk Planta; Verona; Vionin NF; **Ital.:** Depatox; Epagest; Liverton; Tarassaco (Specie Composta); Venoplus; **Malaysia:** Hepavit; Simepar; **Philipp.:** Liverine; Livermin; **Pol.:** Artechol; Artecholwex; Gastrobonisol; Silycinar; Silyvit; Tabletki Przeciw Niestrawnosci; **Port.:** Cholagutt; Synchrorose; **Rus.:** Hepabene (Гепабене); Silbectan (Силбектан); **Singapore:** Hepatofalk Planta; Hepavit; Noricanex; Simepar; **Switz.:** Demonatur Gouttes pour le foie et la bile; Iberogast; Phytomed Hepato; Simepar; Tisane hepaticque et biliaire.

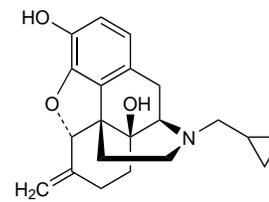
Nalmefene (BAN, USAN, rINN)

6-Desoxy-6-methylene-naltrexone; JF-1; Nalmefène; Nalmefeno; Nalmefenum; Nalmetrene; ORF-11676. 17-(Cyclopropylmethyl)-4,5a-epoxy-6-methylenemorphinan-3,14-diol.

Налмефен

$C_{21}H_{25}NO_3$ = 339.4.

CAS — 55096-26-9.



Nalmefene Hydrochloride (BANM, rINN)

Hydrocloruro de nalmefeno; Nalmefène, Chlorhydrate de; Nalmefeni Hydrochloridum; Nalmetrene Hydrochloride.

Налмефена Гидрохлорид

$C_{21}H_{25}NO_3 \cdot HCl$ = 375.9.

CAS — 58895-64-0.

Adverse Effects

Nausea, vomiting, tachycardia, hypertension, fever, and dizziness have been reported with therapeutic doses of nalmefene. At higher doses or in patients later found to be physically dependent on opioids, symptoms suggestive of opioid withdrawal have been noted; these have included abdominal cramps, chills, dysphoria, myalgia, and joint pain.

Precautions

As for Naloxone, p.1453.

Incremental doses of nalmefene should be given slowly in patients with renal impairment.

Pharmacokinetics

Nalmefene is absorbed after oral doses but bioavailability is not complete owing to significant first-pass metabolism. It is metabolised in the liver, mainly to the inactive glucuronide, and is excreted in the urine. Some of the dose is excreted in the faeces and it may undergo enterohepatic recycling. The plasma elimination half-life is reported to be about 10 hours.

References

1. Dixon R, et al. Nalmefene: intravenous safety and kinetics of a new opioid antagonist. *Clin Pharmacol Ther* 1986; **39**: 49-53.
2. Dixon R, et al. Nalmefene: safety and kinetics after single and multiple oral doses of a new opioid antagonist. *J Clin Pharmacol* 1987; **27**: 233-9.
3. Frye RF, et al. The effect of age on the pharmacokinetics of the opioid antagonist nalmefene. *Br J Clin Pharmacol* 1996; **42**: 301-6.
4. Frye RF, et al. Effects of liver disease on the disposition of the opioid antagonist nalmefene. *Clin Pharmacol Ther* 1997; **61**: 15-23.

Uses and Administration

Nalmefene is a derivative of naltrexone and is a specific opioid antagonist with actions and uses similar to those of naloxone (p.1454), but with a longer duration of action. It is given as the hydrochloride but doses are expressed in terms of the base. Nalmefene hydrochloride 111 micrograms is equivalent to about 100 micrograms of nalmefene. It is usually given intravenously for a rapid onset of action; subcutaneous or intramuscular administration is also effective but has a slower onset. Nalmefene has also been given orally.

For the reversal of postoperative central depression due to the use of opioids, nalmefene is given intravenously,

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 review¹ 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 study¹⁰ suggested that naltrexone might be of benefit in selected patients.

- Kjellberg F, Tramèr MR. Pharmacological control of opioid-induced pruritus: a quantitative systematic review of randomized trials. *Eur J Anaesthesiol* 2001; **18**: 346–57.
- 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.
- Bergasa NV, et al. Open-label trial of oral nalmefene therapy for the pruritus of cholestasis. *Hepatology* 1998; **27**: 679–84.
- Bergasa NV, et al. Effects of naloxone infusions in patients with the pruritus of cholestasis. *Ann Intern Med* 1995; **123**: 161–7.
- 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.
- Wolffhagen FH, et al. Oral naltrexone treatment for cholestatic pruritus: a double-blind, placebo-controlled study. *Gastroenterology* 1997; **113**: 1264–9.
- 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.
- Peer G, et al. Randomised crossover trial of naltrexone in uraemic pruritus. *Lancet* 1996; **348**: 1552–4.
- Pauli-Magnus C, et al. Naltrexone does not relieve uraemic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. *J Am Soc Nephrol* 2000; **11**: 514–9.
- Legroux-Crespel E, et al. A comparative study on the effects of naltrexone and loratadine on uraemic pruritus. *Dermatology* 2004; **208**: 326–30.

Preparations

Proprietary Preparations (details are given in Part 3)

Mex.: Nocarex; **USA:** Revex.

Nalorphine (BAN, rINN)

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

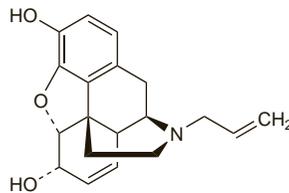
Налорфин

C₁₉H₂₁NO₃ = 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

C₁₉H₂₁NO₃·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

C₁₉H₂₁NO₃·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; Naloksonihidroklorid; Naloksono hidrochlorid; Naloksonu chlorowodorek dwuwodny; Naloxone, Chlorhydrate de; Naloxone (chlorhydrate de) dihydrate; Naloxon-hidroklorid; Naloxon-hydrochlorid; Naloxonhydrochlorid; Naloxoni Hydrochloridum; Naloxoni hydrochloridum dihydricum. 17-Allyl-6-deoxy-7,8-dihydro-14-hydroxy-6-oxo-17-normorphine hydrochloride dihydrate; (–)-(5R,14S)-9a-Allyl-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate.

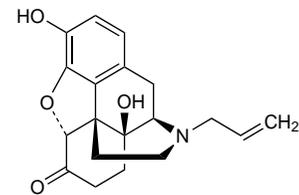
Налоксона Гидрохлорид

C₁₉H₂₁NO₄·HCl·2H₂O = 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 fibrillation⁴ 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).

- Tanaka GY. Hypertensive reaction to naloxone. *JAMA* 1974; **228**: 25–6.
- Azar I, Turndorf H. Severe hypertension and multiple atrial premature contractions following naloxone administration. *Anesth Analg* 1979; **58**: 524–5.
- Flacke JW, et al. Acute pulmonary edema following naloxone reversal of high-dose morphine anesthesia. *Anesthesiology* 1977; **47**: 376–8.
- 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.
- 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.
- Taff RH. Pulmonary edema following naloxone administration in a patient without heart disease. *Anesthesiology* 1983; **59**: 576–7.
- Barsan WG, et al. Use of high dose naloxone in acute stroke: possible side effects. *Crit Care Med* 1989; **17**: 762–7.
- Cuss FM, et al. Cardiac arrest after reversal of effects of opiates with naloxone. *BMJ* 1984; **288**: 363–4.
- Barret L, et al. Cardiac arrest following naloxone. *BMJ* 1984; **288**: 936.
- 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-