by slow intravenous injection. In patients already receiving morphine for pain relief the following doses have been suggested:[2]

- mild dyspnoea: 25 to 50% of usual analgesic dose
- moderate dyspnoea: 50 to 100% of usual analgesic dose
- severe dyspnoea: 100% or more of usual analgesic dose

Patients have also obtained relief from subcutaneous injection.[3]

Although it has been reported that a low dose of nebulised morphine (mean dose 1.7 mg) improved exercise endurance in patients with dyspnoea due to advanced chronic lung disease,[4] several subsequent studies[5-7] have failed to obtain significant improvements with doses up to 40 mg. It is considered that current evidence does not support the use of nebulised morphine for breathlessness.[1,8-10] Furthermore, bronchospasm can be a problem, particularly at high doses, and there is no consensus on the optimal dose, schedule, or method of dose titration.

1. Davis CL. ABC of palliative care: breathlessness, cough, and other respiratory problems. *BMJ* 1997; **315:** 931–4.
2. Twycross R, Wilcock A. *Palliative Care Formulary.* 3rd ed. Nottingham, Palliativedrugs.com Ltd, 2007: 280.
3. Bruera E, *et al.* Subcutaneous morphine for dyspnea in cancer patients. *Ann Intern Med* 1993; **119:** 906–7.
4. Young IH, *et al.* Effect of low dose nebulised morphine on exercise endurance in patients with chronic lung disease. *Thorax* 1989; **44:** 387–90.
5. Beauford W, *et al.* Effects of nebulized morphine sulfate on the exercise tolerance of the ventilatory limited COPD patients. *Chest* 1993; **104:** 175–8.
6. Noseda A, *et al.* Disabling dyspnoea in patients with advanced disease: lack of effect of nebulized morphine. *Eur Respir J* 1997; **10:** 1079–83.
7. Jankelson D, *et al.* Lack of effect of high doses of inhaled morphine on exercise endurance in chronic obstructive pulmonary disease. *Eur Respir J* 1997; **10:** 2270–4.
8. Polosa R, *et al.* Nebulised morphine for severe interstitial lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 26/06/08).
9. Foral PA, *et al.* Nebulized opioids use in COPD. *Chest* 2004; **125:** 691–4.
10. Brown SJ, *et al.* Nebulized morphine for relief of dyspnea due to chronic lung disease. *Ann Pharmacother* 2005; **39:** 1088–92.

Preparations

BP 2008: Chloroform and Morphine Tincture; Morphine and Atropine Injection; Morphine Sulphate Injection; Morphine Suppositories; Morphine Tablets; Prolonged-release Morphine Tablets;
USP 31: Morphine Sulfate Extended-Release Capsules; Morphine Sulfate Injection; Morphine Sulfate Suppositories.

Proprietary Preparations (details are given in Part 3)
Arg.: Algedol; Amidiaz; Analmorph; Duramorph; GNO; MST Continus; Neocalmans; ***Austral.:*** Anamorph; Kapanol; MS Contin; MS Mono; Ordine; Sevredol; ***Austria:*** Compensan; Kapabloc; Kapanol; M-Dolor; Morapid; Mundidol; Substitol; Vendal; ***Belg.:*** Docmorfine; Kapanol; MS Contin; MS Direct; Oramorph; Stellorphinad; Stellorphine; ***Braz.:*** Dimorf; Dolo Moff; MS-Long†; MST Continus†; ***Canad.:*** Kadian; M-Eslon; Morphitec†; MOS; MS Contin; MSIR; Oramorph†; Statex†; ***Chile:*** M-Eslon; ***Cz.:*** Doltard†; M-Eslon; MST Continus; MST Uno†; Oramorph†; Sevredol; Skenan†; Slovalgin; Vendal; ***Denm.:*** Contalgin; Depolan; Doltard; ***Fin.:*** Depolan; Dolcontin; ***Fr.:*** Actiskenan; Kapanol; Moscontin; Oramorph; Sevredol; Skenan; ***Ger.:*** Capros; Kapanol; M-beta; M-Dolor†; M-long; M-Stada; Mogetic†; Morph; Morphanton; MSI; MSR; MST; Onkomorphin†; Oramorph; Painbreak; Sevredol; ***Hong Kong:*** M-Eslon; MST Continus; ***Hung.:*** M-Eslon; Moretal; MST Continus; Sevredol; ***India:*** Morcontin; ***Indon.:*** MST; ***Irl.:*** Morstel†; MST Continus; MXL; Oramorph; Sevredol; Slo-Morph†; ***Israel:*** Kapanol†; MCR; MIR; Morphex; MSP; ***Ital.:*** MS Contin; Oramorph; Skenan†; Ticinan; Twice; ***Jpn:*** MS Contin; ***Malaysia:*** MST Continus; ***Mex.:*** Analfin; Duralmor†; Graten; ***Neth.:*** Kapanol; MS Contin; Noceptin†; Oramorph; Sevredol; Skenan; ***Norw.:*** Dolcontin; ***NZ:*** Kapanol; LA Morph; M-Eslon; MST Continus†; MST Mono†; RA Morph; Sevredol; ***Philipp.:*** M-Dolor; MST Continus; Relimal; ***Pol.:*** MST Continus; Sevredol; Vendal; ***Port.:*** Ethirfin; MST; MXL†; Oramorph; Sevredol; Skenan; ***S.Afr.:*** MST Continus; SRM-Rhotard; ***Singapore:*** MST Continus; SRM-Rhotard†; Statex; ***Spain:*** MST Continus; MST Unicontinus; Oglos†; Oramorph; Sevredol; Skenan; ***Swed.:*** Depolan; Dolcontin; ***Switz.:*** Kapanol; M-retard; MST Continus; Sevre-Long; Sevredol; ***Turk.:*** M-Eslon; Vendal; ***UK:*** Filnarine; Morcap†; Morphgesic; MST Continus; MXL; Oramorph; Rhotard; Sevredol; Zomorph; ***USA:*** Astramorph; Avinza; DepoDur; Duramorph; Infumorph; Kadian; MS Contin; MSIR; Oramorph; RMS; Roxanol; ***Venez.:*** MS Contin.

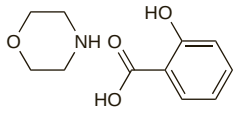
Multi-ingredient: ***Austral.:*** Morphalgin†; ***Austria:*** Modiscop; ***Belg.:*** Spasma†; ***Irl.:*** Cyclimorph; ***Ital.:*** Cardiostenol; ***Pol.:*** Doltard; ***S.Afr.:*** Chloropect; Cyclimorph; Enterodyne; Pectrolyte; ***Swed.:*** Spasmofen; ***Switz.:*** Spasmosol; ***UK:*** Collis Browne's; Cyclimorph; Diocalm Dual Action; Opazimes.

Morpholine Salicylate

Morfoliinsalisylaatti; Morfolinsalicylat; Morpholini Salicylas; Salicilato de morfolinio. 2-Hydroxybenzoic acid compounded with morpholine (1 : 1).

Морфолин Салицилат

$C_{11}H_{15}NO_4$ = 225.2.
CAS — 147-90-0.
ATC — N02BA08.
ATC Vet — QN02BA08.



Profile

Morpholine salicylate is a salicylic acid derivative (see Aspirin, p.20) that has been used for musculoskeletal disorders.

Preparations

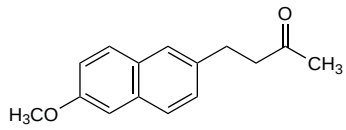
Proprietary Preparations (details are given in Part 3)
Israel: Dolical.

Nabumetone *(BAN, USAN, rINN)*

BRL-14777; Nabumeton; Nabumetona; Nabumetonas; Nabumétone; Nabumetoni; Nabumetonum. 4-(6-Methoxy-2-naphthyl)butan-2-one.

Набуметон

$C_{15}H_{16}O_2$ = 228.3.
CAS — 42924-53-8.
ATC — M01AX01.
ATC Vet — QM01AX01.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Nabumetone). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in acetone; slightly soluble in methyl alcohol. Protect from light.
USP 31 (Nabumetone). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol and in methyl alcohol; freely soluble in acetone. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96. Nabumetone is contra-indicated in patients with severe hepatic impairment.

Effects on the gastrointestinal tract. Like other NSAIDs nabumetone can produce adverse effects on the gastrointestinal tract, although some studies have produced favourable comparisons with ibuprofen[1] or naproxen.[2] A recent review[3] noted that limited comparative data suggest that nabumetone has a similar gastrointestinal adverse effect profile to that of selective COX-2 inhibitors. It has been suggested[4] that nabumetone may be a preferential inhibitor of cyclo-oxygenase-2 (COX-2) but the significance of this in determining its adverse effects is uncertain.

1. Roth SH, *et al.* A controlled study comparing the effects of nabumetone, ibuprofen, and ibuprofen plus misoprostol on the upper gastrointestinal tract mucosa. *Arch Intern Med* 1993; **153:** 2565–71.
2. Roth SH, *et al.* A longterm endoscopic evaluation of patients with arthritis treated with nabumetone vs naproxen. *J Rheumatol* 1994; **21:** 1118–23.
3. Bannwarth B. Safety of the nonselective NSAID nabumetone: focus on gastrointestinal tolerability. *Drug Safety* 2008; **31:** 485–503.
4. Davies NM. Clinical pharmacokinetics of nabumetone: the dawn of selective cyclo-oxygenase-2 inhibition? *Clin Pharmacokinet* 1997; **33:** 403–16.

Effects on the lungs. Pulmonary fibrosis developed in a 68-year-old woman taking nabumetone 1.5 g; symptoms appeared after 2 weeks of therapy and worsened during the next 6 weeks.[1] There was rapid resolution on stopping nabumetone and treatment with oral corticosteroids.

1. Morice A, *et al.* Pulmonary fibrosis associated with nabumetone. *Postgrad Med J* 1991; **67:** 1021–2.

Effects on the skin. Pseudoporphyria characterised by blistering on the neck and hands developed in a 36-year-old woman taking nabumetone and auranofin for rheumatoid arthritis.[1] Stopping auranofin had no effect on the blistering which only resolved once nabumetone was withdrawn. The authors of the report stated that the UK CSM had received 3 additional reports of pseudoporphyria suspected to be caused by nabumetone.

1. Varma S, Lanigan SW. Pseudoporphyria caused by nabumetone. *Br J Dermatol* 1998; **138:** 549–50. Correction. *ibid.* **139:** 759. [dose]

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Nabumetone is well absorbed from the gastrointestinal tract. Plasma concentrations after oral doses are too small to be measured, as it undergoes rapid and extensive first-pass metabolism in the liver to the principal active compound 6-methoxy-2-naphthylacetic acid (6-MNA) and other inactive metabolites. 6-MNA is more than 99% bound to plasma proteins. It diffuses into synovial fluid, crosses the placenta, and is distributed into breast milk. There is considerable interindividual variation in the plasma elimination half-life of 6-MNA, especially in the elderly; some reported mean values at steady state include 22 to about 27 hours for young adults and about 25 and 34 hours in elderly patients. 6-MNA eventually undergoes further metabolism by *O*-methylation and conjugation. About 80% of a dose is excreted in the urine as inactive or conjugated metabolites and less than 1% as unchanged 6-MNA.

◊ References.

1. Brier ME, *et al.* Population pharmacokinetics of the active metabolite of nabumetone in renal dysfunction. *Clin Pharmacol Ther* 1995; **57:** 622–7.
2. Davies NM. Clinical pharmacokinetics of nabumetone: the dawn of selective cyclo-oxygenase-2 inhibition? *Clin Pharmacokinet* 1997; **33:** 403–16.

Uses and Administration

Nabumetone is a non-active prodrug whose major metabolite is an NSAID (p.99) structurally similar to naproxen (p.92). It is used for the relief of pain and inflammation associated with osteoarthritis and rheumatoid arthritis in a usual oral dose of 1 g taken as a single dose in the evening; if necessary 0.5 to 1 g may be given additionally in the morning. It has been recommended that a dose of 1 g daily should not be exceeded in elderly patients and that 500 mg daily may be satisfactory in some cases.

◊ References.

1. Friedel HA, *et al.* Nabumetone: a reappraisal of its pharmacology and therapeutic use in rheumatic diseases. *Drugs* 1993; **45:** 131–56.
2. Proceedings of a symposium: continuing developments with nabumetone: an investigators' update. *Am J Med* 1993; 95 (suppl 2A): 1S–45S.
3. Dahl SL. Nabumetone: a "nonacidic" nonsteroidal antiinflammatory drug. *Ann Pharmacother* 1993; **27:** 456–63.
4. Hedner T, *et al.* Nabumetone: therapeutic use and safety profile in the management of osteoarthritis and rheumatoid arthritis. *Drugs* 2004; **64:** 2315–43.

Preparations

BP 2008: Nabumetone Oral Suspension; Nabumetone Tablets;
USP 31: Nabumetone Tablets.

Proprietary Preparations (details are given in Part 3)
Braz.: Relifex†; ***Canad.:*** Relafen; ***Cz.:*** Relifex; Rodanol S†; ***Denm.:*** Relifex; ***Fin.:*** Relifex; ***Fr.:*** Nabucox; ***Gr.:*** Akratol; Anfer; Ethyfen†; Flogmed; Mevedal; Nabuton; Naditone; Relifex; ***Hong Kong:*** Relifex†; ***Hung.:*** Relifex; Rodanol S†; ***India:*** Nabuflam; ***Indon.:*** Goflex; ***Irl.:*** Relifex; Religer; ***Israel:*** Nabuco; Relifex; ***Ital.:*** Artaxan; Nabuser; ***Jpn:*** Relifen; ***Mex.:*** Naflam; Relifex; ***Neth.:*** Mebutan; ***Norw.:*** Relifex; ***Philipp.:*** Relifex; ***Pol.:*** Coxalgan; Coxeton; Nabuton; Relifex; Rodanol S; ***Port.:*** Balmox; Elitar; ***Rus.:*** Rodanol (Роданол); ***S.Afr.:*** Relifen; Relisan; Relitone; ***Spain:*** Listran; Relif; ***Swed.:*** Relifex; ***Switz.:*** Balmox; ***Thai.:*** Aflex; Anfer†; Bumetone; Nabone; Nabonet; Naflex; Nametone; No-Ton†; Relifex; ***Turk.:*** Relifex; ***UK:*** Relifex; ***USA:*** Relafen†.

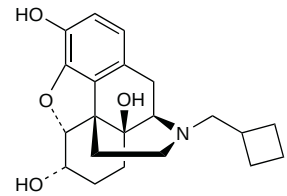
Nalbuphine Hydrochloride

(BANM, USAN, rINNM)

EN-2234A; Hidrocloruro de nalbufina; Nalbufine Hydrochloride; Nalbuphine, Chlorhydrate de; Nalbuphini Hydrochloridum. 17-Cyclobutylmethyl-7,8-dihydro-14-hydroxy-17-normorphine hydrochloride; (−)-(5*R*,6*S*,14*S*)-9a-Cyclobutylmethyl-4,5-epoxymorphinan-3,6,14-triol hydrochloride.

Налбуфина Гидрохлорид

$C_{21}H_{27}NO_4$,HCl = 393.9.
CAS — 20594-83-6 (nalbuphine); 23277-43-2 (nalbuphine hydrochloride).
ATC — N02AF02.
ATC Vet — QN02AF02.



(nalbuphine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of nalbuphine hydrochloride:
Nubian.

Incompatibility. Incompatibility has been reported between injections of nalbuphine hydrochloride and nafcillin sodium,[1] diazepam,[2] pentobarbital sodium,[2] or thiethylperazine maleate.[2] US licensed product information states that nalbuphine is also physically incompatible with ketorolac.

1. Jeglum EL, *et al.* Nafcillin sodium incompatibility with acidic solutions. *Am J Hosp Pharm* 1981; **38:** 462–4.
2. Jump WG, *et al.* Compatibility of nalbuphine hydrochloride with other preoperative medications. *Am J Hosp Pharm* 1982; **39:** 841–3.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

◊ A WHO expert committee considered in 1989 that the likelihood of nalbuphine abuse was low to moderate and was not great enough to warrant international control.[1] Abuse had been reported infrequently and the withdrawal syndrome produced when naloxone was given after continuous nalbuphine dosage was less severe than that in morphine dependence. Subsequently, there have been occasional reports of abuse[2,3] including misuse among athletes.[4,5]

1. WHO. WHO expert committee on drug dependence: twenty-fifth report. *WHO Tech Rep Ser 775* 1989. Also available at: http://libdoc.who.int/trs/WHO_TRS_775.pdf (accessed 26/06/08)
2. Spadari M, *et al.* Pharmacodépendance à la nalbuphine (Nubain): à propos de 2 cas. *Therapie* 2002; **57:** 504–5.
3. Klinzig F, *et al.* Hair analysis by LC-MS as evidence of nalbuphine abuse by a nurse. *J Anal Toxicol* 2007; **31:** 62–5.
4. McBride AJ, *et al.* Three cases of nalbuphine hydrochloride dependence associated with anabolic steroid use. *Br J Sports Med* 1996; **30:** 69–70.
5. Wines JD, *et al.*. Nalbuphine hydrochloride dependence in anabolic steroid users. *Am J Addict* 1999; **8:** 161–4.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102.

Headache may occur. Nausea and vomiting occur less than with other opioids. Hallucinations and other psychotomimetic effects are rare and have been reported less frequently than with pentazocine. As nalbuphine has both antagonist and agonist activity its effects may be only partially reversed by naloxone, but use of the latter is still recommended in nalbuphine overdose.

Effects on the respiratory system. Nalbuphine produces similar respiratory depression to morphine at equianalgesic doses, but there is a ceiling effect with nalbuphine and, unlike morphine, respiratory depression does not increase appreciably with higher doses.[1] In a cumulative-dose study[2] a plateau effect was seen with nalbuphine above a total dose of 30 mg per 70 kg intravenously. Similar ventilatory depression has been noted[3] with single intravenous doses of nalbuphine of 15, 30, or 60 mg per 70 kg; naloxone failed to reverse the depression at the highest dose.

1. Klepper ID, *et al.* Respiratory function following nalbuphine and morphine in anaesthetized man. *Br J Anaesth* 1986; **58:** 625–9.
2. Romagnoli A, Keats AS. Ceiling effect for respiratory depression by nalbuphine. *Clin Pharmacol Ther* 1980; **27:** 478–85.
3. Pugh GC, *et al.* Effect of nalbuphine hydrochloride on the ventilatory and occlusion pressure responses to carbon dioxide in volunteers. *Br J Anaesth* 1989; **62:** 601–9.

Precautions

As for Opioid Analgesics in general, p.103.

Nalbuphine may precipitate withdrawal symptoms if given to patients physically dependent on opioids.

The dose of nalbuphine should be reduced in patients with hepatic or renal impairment.

Abuse. See under Dependence and Withdrawal, above.

Pregnancy. When nalbuphine is used for analgesia during labour there is more placental transfer and sedation in mothers and their infants than with pethidine.[1] There have also been reports of bradycardia and respiratory depression in neonates whose mothers received nalbuphine during labour.[2,3] It was considered that nalbuphine should be given with caution during labour, especially by the intravenous route. Some[2] have recommended subcutaneous dosage and advised that nalbuphine should not be given around the expected time of delivery.

Further references on the transplacental transfer of nalbuphine are given under Pharmacokinetics, below.

1. Wilson CM, *et al.* Transplacental gradient of pethidine and nalbuphine in labour. *Br J Clin Pharmacol* 1986; **21:** 571P–572P.
2. Guillonneau M, *et al.* Perinatal adverse effects of nalbuphine given during parturition. *Lancet* 1990; **335:** 1588.
3. Sgro C, *et al.* Perinatal adverse effects of nalbuphine given during labour. *Lancet* 1990; **336:** 1070.

Interactions

For interactions associated with opioid analgesics, see p.103.

Pharmacokinetics

There appears to be considerable first-pass metabolism of nalbuphine after oral doses. On intramuscular injection nalbuphine has been reported to produce peak plasma concentrations after 30 minutes. It is metabolised in the liver and is excreted in the urine and faeces as unchanged drug and conjugates. Nalbuphine crosses the placenta and small amounts are distributed into breast milk.

◊ References.

1. Sear JW, *et al.* Disposition of nalbuphine in patients undergoing general anaesthesia. *Br J Anaesth* 1987; **59:** 572–5.
2. Kay B, *et al.* Pharmacokinetics of oral nalbuphine in postoperative patients. *Br J Anaesth* 1987; **59:** 1327P.
3. Aitkenhead AR, *et al.* The pharmacokinetics of oral and intravenous nalbuphine in healthy volunteers. *Br J Clin Pharmacol* 1988; **25:** 264–8.
4. Jaillon P, *et al.* Pharmacokinetics of nalbuphine in infants, young healthy volunteers, and elderly patients. *Clin Pharmacol Ther* 1989; **46:** 226–33.

Pregnancy. References.

1. Wilson CM, *et al.* Transplacental gradient of pethidine and nalbuphine in labour. *Br J Clin Pharmacol* 1986; **21:** 571P–572P.
2. Dadabhoy ZP, *et al.* Transplacental transfer of nalbuphine in patients undergoing cesarean section: a pilot study. *Acta Anaesthesiol Ital* 1988; **39:** 227–32.
3. Nicolle E, *et al.* Therapeutic monitoring of nalbuphine: transplacental transfer and estimated pharmacokinetics in the neonate. *Eur J Clin Pharmacol* 1996; **49:** 485–9.

Uses and Administration

Nalbuphine hydrochloride, a phenanthrene derivative, is an opioid analgesic (p.104). It has mixed opioid agonist and antagonist activity. It is used for the relief of moderate to severe pain and as an adjunct to anaesthesia. Nalbuphine hydrochloride is reported to act within 15 minutes of subcutaneous or intramuscular injection or within 2 to 3 minutes of intravenous injection and generally to produce analgesia for 3 to 6 hours. It is given subcutaneously, intramuscularly, or intravenously. Intravenous infusion as part of a patient-controlled analgesia system has also been used.

The usual adult dose of nalbuphine hydrochloride for **pain** relief is 10 to 20 mg every 3 to 6 hours as required.

As an adjunct in balanced **anaesthesia** a usual dose is 0.3 to 3 mg/kg given intravenously over 10 to 15 minutes at induction. Maintenance doses of 250 to 500 micrograms/kg may be given as intravenous boluses if required.

Action. Nalbuphine is generally described as a mixed agonist and antagonist acting mainly as an agonist at κ opioid receptors and as an antagonist or partial agonist at μ receptors. It has shown antagonist activity similar to that seen with naloxone in opioid-dependent subjects.[1] Nalbuphine is structurally related to naloxone and oxymorphone. Pharmacologically nalbuphine is qualitatively similar to pentazocine, but nalbuphine is a more potent antagonist at μ opioid receptors, is less likely to produce psychotomimetic effects such as hallucinations, and is reported to produce no significant cardiovascular effects in patients with ischaemic heart disease. It differs from pure μ agonists such as morphine in that its analgesic, sedative, and respiratory depressant actions are subject to a 'ceiling' effect and may not increase proportionately with dose.

1. Preston KL, *et al.* Antagonist effects of nalbuphine in opioid-dependent human volunteers. *J Pharmacol Exp Ther* 1989; **248:** 929–37.

Administration. References to alternative routes or dosage schedules.

1. Krenn H, *et al.* Nalbuphine by PCA-pump for analgesia following hysterectomy: bolus application versus continuous infusion with bolus application. *Eur J Pain* 2001; **5:** 219–26.
2. Woollard M, *et al.* Hitting them where it hurts? Low dose nalbuphine therapy. *Emerg Med J* 2002; **19:** 565–70.
3. Sung KC, *et al.* Transdermal delivery of nalbuphine and its prodrugs by electroporation. *Eur J Pharm Sci* 2003; **18:** 63–70.
4. Gear RW, *et al.* Dose ratio is important in maximizing naloxone enhancement of nalbuphine analgesia in humans. *Neurosci Lett* 2003; **351:** 5–8.
5. Liu KS, *et al.* Antinociceptive effect of a novel long-acting nalbuphine preparation. *Br J Anaesth* 2004; **92:** 712–15.
6. Woollard M, *et al.* Less IS less: a randomised controlled trial comparing cautious and rapid nalbuphine dosing regimens. *Emerg Med J* 2004; **21:** 362–4.
7. Gordon AT, *et al.* Open-label exploration of an intravenous nalbuphine and naloxone mixture as an analgesic agent following gynecologic surgery. *Pain Med* 2007; **8:** 525–30.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Gobbinal; Naltrox; Nubaina; Nubak†; Onfor; ***Austria:*** Nubain; ***Braz.:*** Nubain; ***Canad.:*** Nubain†; ***Cz.:*** Nubain; ***Fr.:*** Nubain†; ***Ger.:*** Nubain†; ***Gr.:*** Nubain; ***Hong Kong:*** Intapan; Nubain†; ***Hung.:*** Nubain; ***Israel:*** Nubain†; ***Malaysia:*** Nubain†; ***Mex.:*** Bufigen; Bufilem; Nalcryn; Nubain†; ***NZ:*** Nubain†; ***Philipp.:*** Nubain; ***S.Afr.:*** Nubain†; ***Singapore:*** Nubain†; ***Switz.:*** Nubain; ***Thai.:*** Nubain; ***UK:*** Nubain†; ***USA:*** Nubain; ***Venez.:*** Bufidol; Nubain†.

Naproxen *(BAN, USAN, rINN)*

Naprokseeni; Naproksen; Naproksenas; Naproxén; Naproxène; Naproxeno; Naproxenum; RS-3540. (+)-2-(6-Methoxy-2-naphthyl)propionic acid.

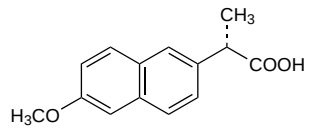
Напроксен

$C_{14}H_{14}O_3$ = 230.3.

CAS — 22204-53-1.

ATC — G02CC02; M01AE02; M02AA12.

ATC Vet — QG02CC02; QM01AE02; QM02AA12.



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

Ph. Eur. 6.2 (Naproxen). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol and in methyl alcohol. Protect from light.

USP 31 (Naproxen). A white to off-white, practically odourless, crystalline powder. Practically insoluble in water; soluble in alcohol, in dehydrated alcohol, and in chloroform; sparingly soluble in ether. Store in airtight containers.

Naproxen Sodium *(BANM, USAN, rINNM)*

Naproksen Sodyum; Naproxène sodique; Naproxeno sódico; Naproxenum natricum; Natrii Naproxenum; RS-3650.

Натрий Напроксен

$C_{14}H_{13}NaO_3$ = 252.2.

CAS — 26159-34-2.

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

Ph. Eur. 6.2 (Naproxen Sodium). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; freely soluble or soluble in methyl alcohol. A 2% solution in water has a pH of 7.0 to 9.8. Store in airtight containers. Protect from light.

USP 31 (Naproxen Sodium). A white to creamy crystalline powder. Soluble in water and in methyl alcohol; sparingly soluble in alcohol; very slightly soluble in acetone; practically insoluble in chloroform and in toluene. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Suppositories containing naproxen may cause rectal irritation and occasional bleeding.

Naproxen should be used with caution in renal impairment, and use is not recommended in patients whose creatinine clearance is less than 20 mL/min.

◊ Reviews.

1. Bansal V, *et al.* A look at the safety profile of over-the-counter naproxen sodium: a meta-analysis. *J Clin Pharmacol* 2001; **41:** 127–38.

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect on the infant associated with the use of naproxen by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding. The *BNF* also considers that the amount of naproxen distributed into breast milk is too small to be harmful to a breast-fed infant; however, some licensed product information recommends that breast feeding should be avoided during naproxen therapy.

In a study[2] of a breast-fed infant only 0.26% of the mother's dose was recovered from the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/07)
2. Jamali F, Stevens DRS. Naproxen excretion in milk and its uptake by the infant. *Drug Intell Clin Pharm* 1983; **17:** 910–11.

Effects on the blood. Haematological adverse effects reported in patients given naproxen include haemolytic anaemia,[1,2] aplastic anaemia,[3] agranulocytosis,[4] and immune thrombocytopenia.[5]

1. Hughes JA, Sudell W. Hemolytic anemia associated with naproxen. *Arthritis Rheum* 1983; **26:** 1054.
2. Lo TCN, Martin MA. Autoimmune haemolytic anaemia associated with naproxen suppositories. *BMJ* 1986; **292:** 1430.
3. McNeil P, *et al.* Naproxen-associated aplastic anaemia. *Med J Aust* 1986; **145:** 53–4.
4. Nygard N, Starkebaum G. Naproxen and agranulocytosis. *JAMA* 1987; **257:** 1732.
5. Bougie D, Aster R. Immune thrombocytopenia resulting from sensitivity to metabolites of naproxen and acetaminophen. *Blood* 2001; **97:** 3846–50.

Effects on the cardiovascular system. For a discussion of the possible cardiovascular effects of naproxen, see p.96.