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.

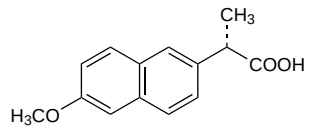
Напроксен

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

Effects on the CNS. Aseptic meningitis has been associated with naproxen therapy;[1,2] attacks may be recurrent and cross-sensitivity with other NSAIDs has occurred.[2]

There has been a report[3] of a patient with Parkinson's disease whose symptoms had previously been well controlled but who deteriorated when she was given naproxen. She improved on withdrawal of naproxen and the effect was confirmed by rechallenge. It was noted that the UK CSM had recorded a case of parkinsonism associated with a combined preparation of naproxen and misoprostol and 12 other reports of tremor or ataxia precipitated by naproxen.

1. Weksler BB, Lehany AM. Naproxen-induced recurrent aseptic meningitis. *DICP Ann Pharmacother* 1991; **25:** 1183–4.
2. Seaton RA, France AJ. Recurrent aseptic meningitis following non-steroidal anti-inflammatory drugs – a reminder. *Postgrad Med J* 1999; **75:** 771–2.
3. Shaunak S, *et al.* Exacerbation of idiopathic Parkinson's disease by naproxen. *BMJ* 1995; **311:** 422.

Effects on the eyes. Keratopathy, characterised by whorl-like corneal opacities, occurred in a woman taking naproxen; complete regression occurred after stopping the drug.[1] There has also been a report of exacerbation of glaucoma in a 65-year-old woman given naproxen.[2]

For reference to effects on the optic nerve associated with naproxen, see p.97.

1. Szmyd L, Perry HD. Keratopathy associated with the use of naproxen. *Am J Ophthalmol* 1985; **99:** 598.
2. Fincham JE. Exacerbation of glaucoma in an elderly female taking naproxen sodium: a case report. *J Geriatr Drug Ther* 1989; **3:** 139–43.

Effects on the gastrointestinal tract. Gastrointestinal adverse effects are among the most frequently reported during short- and long-term treatment with naproxen. Acute proctocolitis associated with the use of naproxen has been reported.[1] Oesophageal ulceration reported in 7 patients[2] may have arisen due to incorrect consumption (such as taking the dosage without fluids or lying down after a dose) but other causes could not be dismissed.

1. Ravi S, *et al.* Colitis caused by non-steroidal anti-inflammatory drugs. *Postgrad Med J* 1986; **62:** 773–6.
2. Kahn LH, *et al.* Over-the-counter naproxen sodium and esophageal injury. *Ann Intern Med* 1997; **126:** 1006.

Effects on the kidneys. Acute renal failure,[1] renal papillary necrosis,[2,3] interstitial nephritis,[4] and hyperkalaemia[1] have been reported in patients receiving naproxen. As with other NSAIDs, renal adverse effects occur more frequently in patients with certain risk factors such as volume depletion, diuretic therapy, heart failure, and pre-existing renal dysfunction.[1]

1. Todd PA, Clissold SP. Naproxen: a reappraisal of its pharmacology, and therapeutic use in rheumatic diseases and pain states. *Drugs* 1990; **40:** 91–137.
2. Caruana RJ, Semble EL. Renal papillary necrosis due to naproxen. *J Rheumatol* 1984; **11:** 90–1.
3. Kovacevic L, *et al.* Renal papillary necrosis induced by naproxen. *Pediatr Nephrol* 2003; **18:** 826–9.
4. Quigley MR, *et al.* Concurrent naproxen- and penicillamine-induced renal disease in rheumatoid arthritis. *Arthritis Rheum* 1982; **25:** 1016–19.

Effects on the liver. There have been a few reports[1,2] of moderate to severe jaundice attributed to naproxen including one in which the patient also had a similar reaction with fenoprofen.[2]

1. Victorino RMM, *et al.* Jaundice associated with naproxen. *Postgrad Med J* 1980; **56:** 368–70.
2. Andrejak M, *et al.* Cross hepatotoxicity between non-steroidal anti-inflammatory drugs. *BMJ* 1987; **295:** 180–1.

Effects on the lungs. See Hypersensitivity, below.

Effects on the salivary glands. For reference to salivary gland swelling associated with naproxen therapy, see Hypersensitivity, below.

Effects on the skin. Cutaneous reactions reported in patients receiving naproxen include erythema nodosum,[1] lichen planus,[2] toxic pustular skin eruption,[3] bullous dermatosis,[4] and fixed drug eruption.[5] Photodermatitis, characterised by vesicle formation or increased skin fragility on sun-exposed skin, has been reported in adults[6-8] and children.[9,10]

A relapse of subacute cutaneous lupus erythematosus was reported to be possibly associated with naproxen.[11]

For reference to facial scars of unknown origin developing in children receiving NSAIDs, and in particular naproxen, see under NSAIDs, p.98.

1. Grattan CEH, Kennedy CTC. Naproxen induced erythema nodosum. *BMJ* 1984; **288:** 114.
2. Heymann WR, *et al.* Naproxen-induced lichen planus. *J Am Acad Dermatol* 1984; **10:** 299–301.
3. Page SR, Grattan CEH. Pustular reaction to naproxen with cholestatic jaundice. *BMJ* 1986; **293:** 510.
4. Bouldin MB, *et al.* Naproxen-associated linear IgA bullous dermatosis: case report and review. *Mayo Clin Proc* 2000; **75:** 967–70.
5. Leivo T, Heikkilä H. Naproxen-induced generalized bullous fixed drug eruption. *Br J Dermatol* 2004; **151:** 232.
6. Howard AM, *et al.* Pseudoporphyria due to naproxen. *Lancet* 1985; **i:** 819–20.
7. Rivers JK, Barnetson RS. Naproxen-induced bullous photodermatitis. *Med J Aust* 1989; **151:** 167–8.
8. Levy ML, *et al.* Naproxen-induced pseudoporphyria: a distinctive photodermatitis. *J Pediatr* 1990; **117:** 660–4.
9. Parodi A, *et al.* Possible naproxen-induced relapse of subacute cutaneous lupus erythematosus. *JAMA* 1992; **268:** 51–2.
10. Lang BA, Finlayson LA. Naproxen-induced pseudoporphyria in patients with juvenile rheumatoid arthritis. *J Pediatr* 1994; **124:** 639–42.
11. Cox NH, Wilkinson DS. Dermatitis artefacta as the presenting feature of auto-erythrocyte sensitization syndrome and naproxen-induced pseudoporphyria in a single patient. *Br J Dermatol* 1992; **126:** 86–9.

Hypersensitivity. In an early case-report in 11 aspirin-sensitive asthmatic patients, all developed reactions (rhinorrhoea, tightness of chest, wheezing, dyspnoea) after taking naproxen in doses of 40 to 80 mg.[1] More recently, angioedema occurred after a single dose of naproxen in a patient known to be aspirin-sensitive.[2] Hypersensitivity to individual NSAIDs is believed to be closely linked to the extent to which these drugs inhibit prostaglandin (see under Aspirin, p.21). There may therefore be a dose threshold below which no detectable symptoms occur. Such an effect has been reported[3] in a patient previously stabilised on naproxen for about one year who had a hypersensitivity reaction after a dosage increase.

A hypersensitivity reaction characterised by pulmonary infiltrates with eosinophilia[4,5] has been reported in patients taking naproxen. There has also been a report of a generalised hypersensitivity reaction with acute eosinophilic colitis in a 57-year-old woman treated with naproxen for osteoarthritis.[6] Bilateral swelling of the major salivary glands, a generalised rash, and eosinophilia suggestive of a hypersensitivity response was reported in another patient after use of naproxen.[7] Leukocytoclastic vasculitis with peripheral neuropathy and nephritis has also been noted in a 62-year-old woman after naproxen treatment.[8]

1. Szczeklik A, *et al.* Asthmatic attacks induced in aspirin-sensitive patients by diclofenac and naproxen. *BMJ* 1977; **2:** 231–2.
2. Ghislain P-D, Ghislain E. Oedème de Quincke de la nuque induit par l'acide acétylsalicylique, avec réaction croisée pour le naproxène sodique. *Ann Med Interne (Paris)* 2000; **151:** 227–9.
3. Briscoe-Dwyer L, Etzel JV. Dyspnea and periorbital edema following an increase in naproxen dose. *Ann Pharmacother* 1994; **28:** 1110.
4. Nader DA, Schillaci RF. Pulmonary infiltrates with eosinophilia due to naproxen. *Chest* 1983; **83:** 280–2.
5. Buscaglia AJ, *et al.* Pulmonary infiltrates associated with naproxen. *JAMA* 1984; **251:** 65–6.
6. Bridges AJ, *et al.* Acute eosinophilic colitis and hypersensitivity reaction associated with naproxen therapy. *Am J Med* 1990; **89:** 526–7.
7. Knulst AC, *et al.* Salivary gland swelling following naproxen therapy. *Br J Dermatol* 1995; **133:** 647–9.
8. Schapira D, *et al.* Naproxen-induced leukocytoclastic vasculitis. *Clin Rheumatol* 2000; **19:** 242–4.

Parkinsonism. For a report of a patient whose symptoms of Parkinson's disease were exacerbated by naproxen, see Effects on the CNS, above.

Interactions

For interactions associated with NSAIDs, see p.99.

The excretion of naproxen is delayed by probenecid resulting in raised plasma concentrations of naproxen.

Antiepileptics. For the effect of naproxen on the protein binding of *valproic acid*, see p.510.

Pharmacokinetics

Naproxen and naproxen sodium are readily absorbed from the gastrointestinal tract. Peak plasma concentrations are attained about 1 to 2 hours after ingestion of naproxen sodium and in about 2 to 4 hours after ingestion of naproxen. Food reduces the rate but not the extent of absorption. Naproxen and naproxen sodium are also well absorbed rectally. At therapeutic concentrations naproxen is more than 99% bound to plasma proteins. Plasma concentrations of naproxen increase proportionally with dose up to about 500 mg daily; at higher doses there is an increase in clearance caused by saturation of plasma proteins. Naproxen diffuses into synovial fluid; it crosses the placenta and is distributed into breast milk in small amounts. Naproxen has a plasma elimination half-life of about 12 to 17 hours. About 95% of a dose is excreted in urine as naproxen and 6-*O*-desmethylnaproxen and their conjugates. Less than 5% of a dose appears in the faeces.

◊ References.

1. Bruno R, *et al.* Naproxen kinetics in synovial fluid of patients with osteoarthritis. *Br J Clin Pharmacol* 1988; **26:** 41–4.
2. Bertin P, *et al.* Sodium naproxen: concentration and effect on inflammatory response mediators in human rheumatoid synovial fluid. *Eur J Clin Pharmacol* 1994; **46:** 3–7.
3. Davies NM, Anderson KE. Clinical pharmacokinetics of naproxen. *Clin Pharmacokinet* 1997; **32:** 268–93.
4. Bowalgaha K, *et al.* S-Naproxen and desmethylnaproxen glucuronidation by human liver microsomes and recombinant human UDP-glucuronosyltransferases (UGT): role of UGT2B7 in the elimination of naproxen. *Br J Clin Pharmacol* 2005; **60:** 423–33.

Uses and Administration

Naproxen, a propionic acid derivative, is an NSAID (p.99).

Naproxen is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis. It is also used in dysmenorrhoea, headache including migraine, postoperative pain, soft-tissue disorders, acute gout, and to reduce fever. Naproxen is usually given *orally* as the free acid or as the sodium salt. The doses in the licensed product information are expressed in terms of the free acid or the sodium salt as appropriate for an individual preparation; however, the doses given below are expressed in terms of the equivalent amount of free acid only. Each 550 mg of naproxen sodium is equivalent to about 500 mg of naproxen.

In the treatment of **rheumatic disorders**, the usual dose of naproxen or naproxen sodium is the equivalent of 500 mg to 1 g of naproxen daily either as a single dose or in 2 divided doses. US licensed product information states that patients who tolerate lower doses may have their dosage increased to 1.5 g daily for a period of up to 6 months, if required. For dosage in children, see below.

In **other painful conditions** such as dysmenorrhoea and acute musculoskeletal disorders the usual regimen is the equivalent of 500 mg of naproxen initially, followed by 250 mg every 6 to 8 hours, up to a maximum daily dose of 1.25 g on the first day and 1 g thereafter.

In **acute gout** an initial dose equivalent to 750 mg of naproxen followed by 250 mg every 8 hours is used.

For the treatment of **migraine**, the equivalent of 750 mg of naproxen can be given at the first symptom of an impending attack and, if necessary, this may be followed after at least half an hour by further doses of 250 to 500 mg throughout the day to a total maximum daily dose of 1250 mg. See below for a suggested dose for the prophylaxis of migraine.

Naproxen has been given *rectally* in similar doses to those used orally.

Naproxen has also been used as the piperazine, aminobutanol, and lysine salts, and as naproxen cetrimonium. Naproxen is available in a combination pack with misoprostol (p.2013) for patients at risk of NSAID-induced peptic ulceration. Alternatively, packs containing naproxen with lansoprazole capsules are available in some countries for such patients.

◊ Reviews.

1. Todd PA, Clissold SP. Naproxen: a reappraisal of its pharmacology, and therapeutic use in rheumatic diseases and pain states. *Drugs* 1990; **40:** 91–137.
2. Mason L, *et al.* Single dose oral naproxen and naproxen sodium for acute postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 08/11/07).
3. Curran MP, Wellington K. Delayed-release lansoprazole plus naproxen. *Drugs* 2004; **64:** 1915–19.

Administration in children. In the treatment of juvenile idiopathic arthritis (p.10), US licensed product information recommends an oral dose of about 10 mg/kg daily of naproxen in 2 divided doses for children aged 2 years and over. In addition, higher doses may also be used: the *BNFC* suggests a dose of 5 to 10 mg/kg twice daily in children aged 1 month to 18 years which may be increased to 10 to 15 mg/kg twice daily (maximum of 1 g daily) for short-term use in severe disease.

Headache. An NSAID such as naproxen is among the drugs tried first for the symptomatic treatment of various types of headache including migraine (p.616) and tension-type headache (p.617). An NSAID given at the onset of symptoms can successfully treat an acute attack of migraine.[1] Co-treatment with a triptan may provide additional benefit and a preparation containing both sumatriptan succinate and naproxen sodium has recently been developed.[2,3]

NSAIDs also appear to be effective for the prophylaxis of migraine, although propranolol is generally preferred. Studies have indicated that naproxen sodium 550 mg [equivalent to 500 mg of naproxen] given twice daily may be useful for reducing the number of attacks suffered.[4-6]

1. Treves TA, *et al.* Naproxen sodium versus ergotamine tartrate in the treatment of acute migraine attacks. *Headache* 1992; **32:** 280–2.

2. Winner P, *et al.* Twelve-month tolerability and safety of sumatriptan-naproxen sodium for the treatment of acute migraine. *Mayo Clin Proc* 2007; **82:** 61–8.

3. Brandes JL, *et al.* Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA* 2007; **297:** 1443–54.

4. Sargent J, *et al.* A comparison of naproxen sodium to propranolol hydrochloride and a placebo control for the prophylaxis of migraine headache. *Headache* 1985; **25:** 320–4.

5. Welch KMA, *et al.* Successful migraine prophylaxis with naproxen sodium. *Neurology* 1985; **35:** 1304–10.

6. Sances G, *et al.* Naproxen sodium in menstrual migraine prophylaxis: a double-blind placebo controlled study. *Headache* 1990; **30:** 705–9.

Malignant neoplasms. Some NSAIDs such as naproxen may be of value both for the differential diagnosis and the management of neoplastic fever[1-4] as they appear to be more effective in reducing this type of fever than against fever associated with infections. However, the reliability of naproxen in the diagnosis of neoplastic fever has been questioned.[5] In a group of 72 patients, naproxen decreased body temperature in 55% of patients with neoplastic disorders and 38% of patients with other conditions. Thus, the sensitivity of the test was calculated as 55% and its specificity as 62%, which the authors considered to be too low to be reliable.

1. Chang JC, Gross HM. Neoplastic fever responds to the treatment of an adequate dose of naproxen. *J Clin Oncol* 1985; **3:** 552–8.

2. Azeemuddin SK, *et al.* The effect of naproxen on fever in children with malignancies. *Cancer* 1987; **59:** 1966–8.

3. Economos K, *et al.* The effect of naproxen on fever in patients with advanced gynecologic malignancies. *Gynecol Oncol* 1995; **56:** 250–4.

4. Cunha BA, *et al.* Fever of unknown origin (FUO) caused by multiple myeloma: the diagnostic value of the Naprosyn test. *Heart Lung* 2006; **35:** 358–62.

5. Vanderschueren S, *et al.* Lack of value of the naproxen test in the differential diagnosis of prolonged febrile illnesses. *Am J Med* 2003; **115:** 572–5.

Preparations

BP 2008: Gastro-resistant Naproxen Tablets; Naproxen Oral Suspension; Naproxen Suppositories; Naproxen Tablets;
USP 31: Naproxen Delayed-Release Tablets; Naproxen Oral Suspension; Naproxen Sodium Tablets; Naproxen Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Aleve; Algioprux†; Alidase; Bumaflex N; Causalon Pro†; Congex; Debril; Fabralgina; Fadalivio; Flaxvan; Flogocefal†; Melgar; Monarit; Naprofidex; Naprogen; Naprontag; Naprux; Neuralprona; Sicadentol Plus†; Tundra; Veradol†; Xicane†; ***Austral.:*** Aleve†; Anaprox; Chemists Own Period Pain Tablets; Crysanal; Femme Free; Inza; Naprogesic; Naprosyn; Nurolasts†; Proxen; ***Austria:*** Aleve; Miranax; Naprobene; Nycopren; Proxen; ***Belg.:*** Aleve; Apranax; Naproflam; Naprosyne; ***Braz.:*** Flanax; Napronax; Naprosyn; Naprox; ***Canad.:*** Anaprox; Apo-Napro-Na; Naprosyn; Naxen†; Novo-Naprox; Nu-Naprox; Synflex†; ***Chile:*** Atac; Deucoval; Eurogesic; Inveoxel†; Naprogesic; Reprost†; Triox NF; ***Cz.:*** Aleve; Emoxen; Nalgesin; Naprobene†; Naprosyn†; Napsynt†; ***Denm.:*** Bonyl; Miranax†; Naprosyn; ***Fin.:*** Alpoxen; Miranax; Naprometin; Napromex; Naprosyn†; Naxopren; Pronaxen; ***Fr.:*** Aleve; Apranax; Naprosyne; ***Ger.:*** Alacetan NNA; Aleve; Dolormin mit Naproxen; Dysmenalgit; prodolor†; Proxen; ***Gr.:*** Anaprox; Naprosyn; Nycopren-E; ***Hong Kong:*** Apo-Napro-Na; Inza; Naprorex; Naprosyn; Napxen; Noflam-N; Proxen†; Soden; Soren†; Synflex†; ***Hung.:*** Aleve; Apranax; Napmel; Naprosyn; ***India:*** Artagen; Easy Dayz; Naprosyn; Xenobid; ***Indon.:*** Naxen; Synflex; ***Irl.:*** Gerinap; Napmel†; Naprex†; Naprosyn; Synflex; ***Israel:*** Naproxi; Narocin; Naxyn; Point; ***Ital.:*** Aleve; Algonapril; Aperdan; Axer†; Floginax; Flogogin†; Floxalin; Gibixen; Gynestrel; Laser; Momendol; Napreben†; Naprius; Naprocet; Naprorex†; Naprosyn; Neo Eblimon; Nitens; Prexan; Proxagol; Synalgo; Synflex; Ticoflex†; Uninapro; Xenar†; ***Malaysia:*** Apo-Napro-Na; Inza†; Roxyn†; Seladin; Sunprox; Synflex; ***Mex.:*** Actiquim; Analgen; Anapsyl; Arsenal; Artron†; Arxen; Atiflan; Bioxan; Bixen; Dafloxen; Deflamox; Diferbest; Dolxen; Donaprox; Edem; Faraxen; Flanax; Flavoxen; Flaxendol; Flexen†; Flogen; Fuxen; Genalgen†; Inflanox; Iqfasol; Kenaprox†; Lixogan†; Lorexen†; Messelxen; Naflapen; Napoxol; Naprodil; Nasocan†; Navixen; Naxen; Naxopaar; Neonaxil; Nixal†; Novaxen; Pactens; Praxedol; Pronat; Pronax-P†; Pronaxil; Pronoxen; Propional†; Proxalin; Proxem†; Salupran†; Sertrixen; Sodixen; Tandax; Tanizona; Unirelaxed; Vantin; Velsay; ***Neth.:*** Aleve; Femex†; Momendol; Naprelan; Naprocoat; Naprovite; Nycopren†; ***Norw.:*** Alpoxen†; Ledox; Napren; Naprosyn; ***NZ:*** Naprogesic; Naprosyn; Naxen; Noflam; Synflex; ***Philipp.:*** Alpron; Flanax; Naprelan; Naprosyn; Sanomed; ***Pol.:*** Aleve; Anapran; Boloxen; Emochol†; Natrax; ***Port.:*** Momendol; Naprocet; Naprosyn; Reuxen; ***Rus.:*** Nalgesin (Налгезин); ***S.Afr.:*** Acusprain; Aleve; Fibroxyn†; Nafasol; Napflam; Naprel†; Naproscript†; Naprosyn†; Synflex; Traumox; ***Singapore:*** Aleve; Apo-Napro-Na; Bipronyl†; Gesiprox†; Inza; Noflam-N†; Nuprafen†; Seladin; Soden; Soproxen; Zynal†; ***Spain:*** Aleve; Aliviomas; Antalgin; Denaxpren; Lundiran; Momen; Naprosyn; Naproval; Tacron; ***Swed.:*** Alpoxen; Naprosyn; Pronaxen; ***Switz.:*** Aleve; Apranax; Naprosyn†; Nycopren; Proxen; ***Thai.:*** Annoxen; Naproflex; Naprosian; Naprosyn; Napsen†; Napxen†; Narzen†; Polyxen; Proxen; Roxen†; Serviproxan; Sonap; Soproxen; Synflex; U-Proxyn; Vinsen; ***Turk.:*** A-Nox; Aleve; Anaprotab; Apraljin; Apranax; Aprol; Apromed; Aprowell; Bonmin; Kapnax; Karoksen; Naponal; Napradol; Napren; Naprodeva; Naprosyn; Naprotab; Opraks; Relokap; Romaksen; Romatim; Rumazolidin; Synax; Syndol; ***UK:*** Arthrosin†; Arthroxen; Feminax Ultra; Napratec; Naprosyn; Nycopren†; Synflex; Timpron†; ***USA:*** Aleve; Anaprox; Naprelan; Naprosyn; Prevacid NapraPAC; ***Venez.:*** Apranax†; Synaprosyn†.

Multi-ingredient: ***Arg.:*** Naprontag Flex; Papasine; ***Ital.:*** Momendol; ***Mex.:*** Acxen†; Analgen Forte; Arsenal Compuesto; Arxen Compositum; Bifardol; Blocacid; Brax; Contraxen; Dafloxen-F; Decosil; Deflamox Plus; Dolotandax; Drunen; Farxen; Febrax; Fiverdol; Flucol; Grifed; Kensedal; Movex; Naprodil Plus; Naxodol; Nedoxal; Neorpan Plus; Onexmol; Pensodil; Polet; Profenlax; Proxalin Plus; Raxenol; Reucortil; Somalgesic; Taxenan; Ulpafie-N; Velsay-S Compuesto; Viplus; ***Rus.:*** Cefecon N (Цефекон Н); Pentalgin-N (Пенталгин-Н).

Nefopam Hydrochloride

(BANM, USAN, rINNM)

Benzoxazocine; Fenazoxine; Hidrocloruro de nefopam; Néfopam, Chlorhydrate de; Nefopami Hydrochloridum; R-738. 3,4,5,6-Tetrahydro-5-methyl-1-phenyl-1*H*-2,5-benzoxazocine hydrochloride.

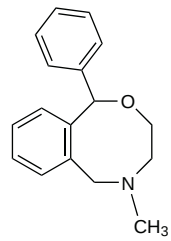
Нефопама Гидрохлорид

$C_{17}H_{19}NO,HCl$ = 289.8.

CAS — 13669-70-0 (nefopam); 23327-57-3 (nefopam hydrochloride).

ATC — N02BG06.

ATC Vet — QN02BG06.



(nefopam)

Pharmacopoeias. In *Chin.*

Adverse Effects and Treatment

Adverse effects occurring with nefopam include gastrointestinal disturbances, such as nausea and vomiting, sweating, drowsiness, insomnia, urinary retention, dizziness, hypotension, tremor, paraesthesia, palpitations, lightheadedness, nervousness, confusion, blurred vision, headache, dry mouth, syncope, angioedema, allergic reactions, and tachycardia. Euphoria, hallucinations, and convulsions have occasionally been reported, as has temporary pink discoloration of the urine. Symptoms of overdosage have included CNS and cardiovascular toxicity.

Effects on the urinary tract. In January 1989, the UK CSM[1] reported that it had received 53 reports in which nefopam was associated with the development of urinary retention or symptoms of hesitancy, poor stream, or dribbling. In one case there was a history of prostatism.

1. CSM. Nefopam hydrochloride (Acupan). *Current Problems 24* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024431&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)

Overdosage. There have been reports of fatal overdoses with nefopam.[1-3] One report[1] also provided details of 9 other patients who recovered with routine supportive treatment.

1. Piercy DM, *et al.* Death due to overdose of nefopam. *BMJ* 1981; **283:** 1508–9.

2. Urwin SC, Smith HS. Fatal nefopam overdose. *Br J Anaesth* 1999; **83:** 501–2.

3. Tracqui A, *et al.* Fatal overdosage with nefopam (Acupan). *J Anal Toxicol* 2002; **26:** 239–43.

Precautions

Nefopam is contra-indicated in patients with a history of convulsive disorders. It should be used with caution in the elderly and in patients with glaucoma, urinary retention, or impaired hepatic or renal function.

Abuse. Abuse of parenteral nefopam has been reported in 3 patients with a history of chronic pain.[1] Psychostimulant-like symptoms such as agitation, impatience, and violence, were noted in 2 of the patients; antimuscarinic effects were also seen. All 3 patients were found to be psychologically dependent; in 2 who attempted to stop nefopam, withdrawal symptoms were noted.

1. Villier C, Mallaret MP. Nefopam abuse. *Ann Pharmacother* 2002; **36:** 1564–6.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving nefopam, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

Studies in 5 healthy nursing mothers given nefopam for post-episiotomy pain indicated that nefopam was present in human milk in an equivalent concentration to that in plasma.[2] It was calculated that on a body-weight basis a breast-fed infant would receive less than 3% of the maternal dose.

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 10/10/06)

2. Liu DTY, *et al.* Nefopam excretion in human milk. *Br J Clin Pharmacol* 1987; **23:** 99–101.

Interactions

It has been recommended that nefopam should not be given to patients receiving MAOIs and should be used cautiously in those receiving tricyclic antidepressants. The adverse effects of nefopam may be additive to those of other drugs with antimuscarinic or sympathomimetic activity.

Pharmacokinetics

Nefopam is absorbed from the gastrointestinal tract. Peak plasma concentrations occur 1 to 3 hours after a dose by mouth and up to 1 hour after intramuscular injection. About 73% is bound to plasma proteins. Nefopam is distributed into breast milk. It has an elimination half-life of about 4 hours. It is extensively metabolised and excreted mainly in urine, in which less than 5% of a dose is excreted unchanged. About 8% of a dose is excreted via the faeces.

Uses and Administration

Nefopam hydrochloride is a non-opioid analgesic considered to act centrally, although its mechanism of action is unclear. It also has some antimuscarinic and sympathomimetic actions. Nefopam hydrochloride is used for the relief of moderate acute and chronic pain. The usual oral dose range is 30 to 90 mg three times daily; the recommended initial dose is 60 mg (or 30 mg in elderly patients) three times daily. Nefopam hydrochloride may also be given in doses of 20 mg by intramuscular injection, repeated every 6 hours if necessary; it has been recommended that the patient should always be lying down when receiving the injection and should remain so for 15 to 20 minutes afterwards. It has also been given by slow intravenous injection in doses of 20 mg every 4 hours up to a maximum of 120 mg daily.

Hiccup. In two case series[1,2] involving 10 patients in total, hiccups refractory to standard therapy stopped after treatment with intravenous nefopam. For the management of intractable hiccups see under Chlorpromazine, p.976.

1. Bilotta F, Rosa G. Nefopam for severe hiccups. *N Engl J Med* 2000; **343:** 1973–4.

2. Bilotta F, *et al.* Nefopam for refractory postoperative hiccups. *Anesth Analg* 2001; **93:** 1358–60.

Shivering. Nefopam is one of several drugs tried in the prevention of postoperative shivering (p.1779).

References.

1. Bilotta F, *et al.* Nefopam and tramadol for the prevention of shivering during neuraxial anesthesia. *Reg Anesth Pain Med* 2002; **27:** 380–4.

2. Piper SN, *et al.* A comparison of nefopam and clonidine for the prevention of postanaesthetic shivering: a comparative, double-blind and placebo-controlled dose-ranging study. *Anaesthesia* 2004; **59:** 559–64.

3. Bilotta F, *et al.* Nefopam or clonidine in the pharmacologic prevention of shivering in patients undergoing conscious sedation for interventional neuroradiology. *Anaesthesia* 2005; **60:** 124–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Acupan; ***Fr.:*** Acupan; ***Ger.:*** Ajan†; Silentan†; ***Irl.:*** Acupan; ***Ital.:*** Nefam†; Oxadol†; ***NZ:*** Acupan; ***Rus.:*** Oxadol (Оксадол); ***Switz.:*** Acupan†; ***UK:*** Acupan.