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.

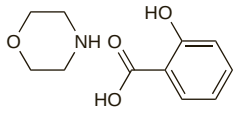
Multi-ingredient: ***Austral.:*** Morphalgin†; ***Austria:*** Modiscop; ***Belg.:*** Spasma†; ***Irl.:*** Cyclimorph; ***Ital.:*** Cardiostenol; ***Pol.:*** Doltard; ***S.Afr.:*** Chloropect; Cyclimorph; Enterodyne; Pectrolyte; ***Swed.:*** Spasmofen; ***Switz.:*** Spasmosol; ***UK:*** Collis Browne's;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

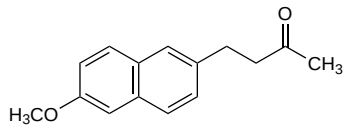
Proprietary Preparations (details are given in Part 3)
Israel: Dolical.

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†.

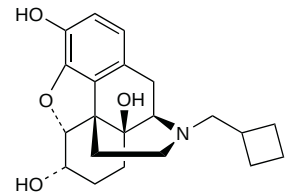
Nalbuphine Hydrochloride

(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.