

parenteral routes may be used, particularly when oral therapy is not possible; the doses stated above may be given orally or parenterally. In the UK, oral treatment is commonly given as a mixture containing 1 mg/mL of methadone hydrochloride.

For details of doses in children, see below.

For the control of intractable cough associated with terminal lung cancer, methadone hydrochloride is usually given in the form of a linctus in a dose of 1 to 2 mg every 4 to 6 hours, but reduced to twice daily on prolonged use.

**Administration.** Although duration of action after single doses of methadone is similar to that of morphine, it increases considerably with multiple dosing of methadone because of the long elimination half-life (see under Pharmacokinetics, above). The minimum effective dose of methadone can be difficult to titrate for the individual patient. A fixed 10-mg oral dose with a flexible patient-controlled dosage interval has been used in patients with chronic cancer pain.<sup>1</sup> Dosage not more frequently than every 4 hours during the first 3 to 5 days, followed by a fixed dose every 8 to 12 hours depending on the patient's requirements, was advised.

A suggested initial dose for patients who need to switch from oral morphine to methadone because of poor pain control is one tenth of the total daily dose of morphine, but not greater than 100 mg, given at intervals determined by the patient, typically every 8 hours.<sup>2</sup>

When switching from oral to parenteral use it was suggested<sup>3</sup> that the dose of methadone should be halved and adjusted thereafter as necessary.

Evidence of the prolonged effect of methadone was demonstrated when a single intravenous bolus dose of 20 mg resulted in postoperative analgesia lasting about 25 hours.<sup>4</sup> An initial 2-hour loading intravenous infusion of methadone 100 to 200 micrograms/kg per hour to provide rapid analgesia followed by infusion at a lower maintenance rate of 10 to 20 micrograms/kg per hour for continuous pain relief has been used in burn patients.<sup>5</sup> Methadone has also been given by continuous subcutaneous infusion for severe cancer pain<sup>6,7</sup> although this route has been associated with local tissue irritation and induration. Epidural methadone has been used successfully in doses of up to 5 mg for analgesia in association with bupivacaine.<sup>8,9</sup> Intermittent and continuous epidural infusion of methadone has also been tried<sup>10</sup> in postoperative analgesia.

A small case series<sup>11</sup> found topical methadone powder to be effective for pain relief of open, exudative wounds.

- Säwe J, *et al.* Patient-controlled dose regimen of methadone for chronic cancer pain. *BMJ* 1981; **282**: 771–3.
- Morley JS, *et al.* Methadone in pain uncontrolled by morphine. *Lancet* 1993; **342**: 1243.
- Säwe J. High-dose morphine and methadone in cancer patients: clinical pharmacokinetic considerations of oral treatment. *Clin Pharmacokinet* 1986; **11**: 87–106.
- Gourlay GK, *et al.* Methadone produces prolonged postoperative analgesia. *BMJ* 1982; **284**: 630–1.
- Denson DD, *et al.* Pharmacokinetics of continuous intravenous infusion of methadone in the early post-burn period. *J Clin Pharmacol* 1990; **30**: 70–5.
- Mathew P, Storey P. Subcutaneous methadone in terminally ill patients: manageable local toxicity. *J Pain Symptom Manage* 1999; **18**: 49–52.
- Makin MK, Morley JS. Subcutaneous methadone in terminally ill patients. *J Pain Symptom Manage* 2000; **19**: 237–8.
- Drenger B, *et al.* Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy. *Br J Anaesth* 1989; **62**: 82–6.
- Martin CS, *et al.* Extradural methadone and bupivacaine in labour. *Br J Anaesth* 1990; **65**: 330–2.
- Prieto-Alvarez P, *et al.* Continuous epidural infusion of racemic methadone results in effective postoperative analgesia and low plasma concentrations. *Can J Anaesth* 2002; **49**: 25–31.
- Gallagher RE, *et al.* Analgesic effects of topical methadone: a report of four cases. *Clin J Pain* 2005; **21**: 190–2.

**Administration in children.** Methadone is not licensed for use in children. However, it has been tried<sup>1</sup> intravenously in children aged 3 to 7 years to prevent postoperative pain; a dose of 200 micrograms/kg was given perioperatively followed postoperatively by 50 micrograms/kg every 10 minutes until the patient was both comfortable and adequately alert. Methadone has also been tried<sup>2</sup> orally for the treatment of severe pain in hospitalised children; daily doses ranged from 200 to 600 micrograms/kg for up to 6 weeks.

Methadone is used for the management of neonatal abstinence syndrome (p.102). The BNFC suggests an initial oral dose of 100 micrograms/kg increased by 50 micrograms/kg every 6 hours until symptoms are controlled; once stabilised, the total daily dose is given in 2 divided doses for maintenance. When withdrawing methadone, the dose should be reduced over 7 to 10 days.

- Berde CB, *et al.* Comparison of morphine and methadone for prevention of postoperative pain in 3- to 7-year-old children. *J Pediatr* 1991; **119**: 136–41.
- Shir Y, *et al.* Oral methadone for the treatment of severe pain in hospitalised children: a report of five cases. *Clin J Pain* 1998; **14**: 350–3.

**Cancer pain.** Methadone is used as an alternative to morphine in the treatment of severe cancer pain (p.5). A better understand-

ing of its pharmacokinetics and of equianalgesic doses may address early concerns about the risk of cumulative toxicity associated with prolonged use. However, its long terminal half-life makes it less suitable for the treatment of breakthrough pain.

Methadone has been given by the oral, rectal, and parenteral routes.

**References.**

- Ayonrinde OT, Bridge DT. The rediscovery of methadone for cancer pain management. *Med J Aust* 2000; **173**: 536–40.
- Bruera E, Sweeney C. Methadone use in cancer patients with pain: a review. *J Palliat Med* 2002; **5**: 127–38.
- Bruera E, *et al.* Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. *J Clin Oncol* 2004; **22**: 185–92.
- Moryl N, *et al.* Methadone in the treatment of pain and terminal delirium [sic] in advanced cancer patients. *Palliat Support Care* 2005; **3**: 311–17.
- Mannino R, *et al.* Methadone for cancer-related neuropathic pain: a review of the literature. *J Opioid Manag* 2006; **2**: 269–76.
- Nicholson AB. Methadone for cancer pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 26/06/08).

**Opioid dependence.** The treatment of opioid dependence is discussed on p.101. In the UK, oral liquid preparations of methadone hydrochloride 1 mg/mL are widely used for this purpose. It is important to note that these preparations are 2.5 times stronger than Methadone Linctus (BP 2008), and although some are licensed for analgesia in severe pain, many are licensed for the treatment of opioid dependence only. Methadone Oral Solution (1 mg/mL) (BP 2008) is available as a ready-to-use solution or may be prepared from Methadone Hydrochloride Oral Concentrate. However, most commercially available preparations in the UK still follow an earlier formula formerly listed in the Drug Tariff Formulary (DTF):

**Methadone Mixture 1 mg/mL**  
methadone hydrochloride 10 mg  
Green S and Tartrazine Solution (BP 1980) 0.02 mL  
Compound Tartrazine Solution (BP 1980) 0.08 mL  
syrup, unpreserved 5 mL  
chloroform water, double-strength to 10 mL.

Some commercially available forms of DTF Methadone Mixture 1 mg/mL use a preservative system based on hydroxybenzoate esters rather than chloroform; however, syrup preserved with hydroxybenzoate esters may be unsuitable for extemporaneous dispensing (see under Incompatibility, above).

**References.**

- Ghodsse AH, *et al.* Comparison of oral preparations of heroin and methadone to stabilise opiate misusers as inpatients. *BMJ* 1990; **300**: 719–20.
- Wolf K, *et al.* Measuring compliance in methadone maintenance patients: use of a pharmacologic indicator to "estimate" methadone plasma levels. *Clin Pharmacol Ther* 1991; **50**: 199–207.
- Wilson P, *et al.* Methadone maintenance in general practice: patients, workload, and outcomes. *BMJ* 1994; **309**: 641–4.
- Farrell M, *et al.* Methadone maintenance treatment in opiate dependence: a review. *BMJ* 1994; **309**: 997–1001.
- Henry JA. Methadone: where are we now? *Hosp Med* 1999; **60**: 161–4.
- Faggioli F, *et al.* Methadone maintenance at different dosages for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 28/08/08).
- Mattick RP, *et al.* Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 26/06/08).
- Amato L, *et al.* Methadone at tapered doses for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 26/06/08).
- NICE. Methadone and buprenorphine for the management of opioid dependence: Technology Appraisal Guidance 114 (issued January 2007). Available at: <http://www.nice.org.uk/nicemedia/pdf/TA114NICEguidance.pdf> (accessed 26/06/08)

## Preparations

**BP 2008:** Methadone Injection; Methadone Linctus; Methadone Oral Solution (1 mg per mL); Methadone Tablets.

**USP 31:** Methadone Hydrochloride Injection; Methadone Hydrochloride Oral Concentrate; Methadone Hydrochloride Oral Solution; Methadone Hydrochloride Tablets; Methadone Hydrochloride Tablets for Oral Suspension.

**Proprietary Preparations** (details are given in Part 3)

**Arg:** Gobbidona; **Austral:** Biodone†; Physseptone; **Austria:** Heptadon; **Belg:** Mephenon; **Braz:** Metadon; Mytedom; **Canad:** Metadol; **Chile:** Amidon†; **Fin:** Dolmed; **Hong Kong:** Physseptone†; **Hung:** Depridol; Metadon; **Ir:** Phymet DTF; Physseptone†; Pinadone DTF; **Israel:** Adolan; **Ital:** Eptadone; **Malaysia:** Aseptone; **Neth:** Symoron; **NZ:** Biodone; Methatabs; Pallidone; **S.Afr:** Physseptone; **Singapore:** Physseptone†; **Spain:** Metasedin; **Switz:** Ketalgine; **UK:** Eptadone; Martindale Methadone Mixture DTF; Methadose; Physseptone; Synastone; **USA:** Diskets; Dolophine; Methadose.

## Methyl Butetisaliclylate

Butetisalicilato de metilo; Methyl Diethylacetylalsalicylate. Methyl O-(2-ethylbutyryl)salicylate.

$C_{14}H_{18}O_4 = 250.3$ .

### Profile

Methyl butetisaliclylate is a salicylic acid derivative that has been used similarly to methyl salicylate (p.85) as a rubefacient for the relief of musculoskeletal, joint, and soft-tissue pain.

## Preparations

**Proprietary Preparations** (details are given in Part 3)

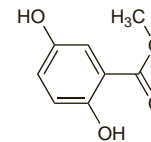
**Ital:** Doloderm.

## Methyl Gentisate

Gentisato de metilo, 2,5-Dihydroxybenzoic acid methyl ester:

$C_8H_8O_4 = 168.1$ .

CAS — 2150-46-1.



### Profile

Methyl gentisate has been used topically for the relief of musculoskeletal and joint pain.

### Preparations

**Proprietary Preparations** (details are given in Part 3)

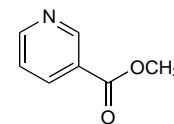
**Multi-ingredient: Ital:** Reumacort.

## Methyl Nicotinate (USAN)

Méthyle, nicotinate de; Methyl Nicotinas; Methylis nicotinas; Methyl-nikotinát; Metilo nikotinatás; Metylnikotinát; Metylinikotinatti; Nicotinato de metilo, Methyl pyridine-3-carboxylate.

$C_7H_7NO_2 = 137.1$ .

CAS — 93-60-7.



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

**Ph. Eur. 6.2** (Methyl Nicotinate). A white or almost white powder. M.p. 40° to 42°. Very soluble in water, in alcohol, and in dichloromethane. Protect from light.

### Profile

Methyl nicotinate is used in topical preparations as a rubefacient.

### Preparations

**Proprietary Preparations** (details are given in Part 3)

**UK:** Pickles Chlilain Cream.

**Multi-ingredient: Arg:** Infrarub†; Medex Rub; **Austral:** Deep Heat; **Austria:** Berggest; **Belg:** Alipgan; Emerxil; Percutalgine; Rado-Spray†; **Canad:** Arthricare for Women Multi-Action†; Arthricare Triple Medicated†; Midalgan†; **Chile:** Frixio; Konirub; Mentobalsam; **Fr:** Alipgan; Capsic; Clipol Sport†; Decontractyl; Gel Rubefiant; Percutalgine; Sedarby†; **Ger:** Doloneuro†; Forapin E†; Kytta-Balsam f. Rheuma Bad; Spondylon; Tetesept Badkonzentrat Rheuma Bad†; **Gr:** Faragel-For†; **India:** Alipgan; Flamar; Medicreme; Relaxyl; **Indon:** Remakrim; **Ir:** Alipgan; **Israel:** Deep Heat Spray; **Ital:** Altadrine; Balsamo Sifcamina; Relaxar; Sedalpan; **Neth:** C. Cremer capsi comp; Cremer Capsi compositus; Kruidvat Spierbalsem; **Pol:** Deep Heat; **Port:** Midalgan; **S.Afr:** Deep Heat Spray; Infrarub; Sloan's Heat Rub; **Singapore:** Deep Heating Spray†; **Spain:** Doctofril Antinflammat; Doctomil†; Radio Sali; **Switz:** Kytta Baume; Midalgan; Radalgan; **Thai:** Percutalgine†; **UK:** Crealgan; Deep Heat Spray; Dubam; Fiery Jack; Radlan-B Red Oil; Raigex; Raigex Heat Spray (low-odour); Red Oil; Transvian Heat Spray; **USA:** Arthricare Odor Free; Arthricare Triple Medicated; Mlusterole.

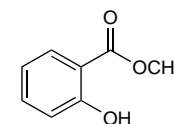
## Methyl Salicylate

Methyl Sal; Méthyle, salicylate de; Methyli Salicylas; Methylis salicylas; Methyl-salicylát; Metilsalicylatas; Metilsalicylat; Metil-szalicylát; Metylsalicylat; Metylu salicylan; Metyylisalisylaatii; Salicylato de metilo, Methyl 2-hydroxybenzoate.

МЕТИЛСАЛИЦИЛАТ

$C_8H_8O_3 = 152.1$ .

CAS — 119-36-8.



**NOTE.** Methyl salicylate and methyl salicylate liniment have been known previously as oil of wintergreen, wintergreen, and wintergreen oil. Wintergreen oil has also been known as sweet birch oil.

**Pharmacopoeias.** In *Eur.* (see p.vii), *Jpn.* and *Viet.* Also in *USNF.*

**Ph. Eur. 6.2** (Methyl Salicylate). A colourless or slightly yellow