

also occur. Diflunisal is distributed into breast milk with concentrations reported to be about 2 to 7% of those in plasma.

#### References.

- Loewen GR, *et al.* Effect of dose on the glucuronidation and sulphation kinetics of diflunisal in man: single dose studies. *Br J Clin Pharmacol* 1988; **26**: 31–9.
- Eriksson L-O, *et al.* Influence of renal failure, rheumatoid arthritis and old age on the pharmacokinetics of diflunisal. *Eur J Clin Pharmacol* 1989; **36**: 165–74.
- Verbeeck RK, *et al.* The effect of multiple dosage on the kinetics of glucuronidation and sulphation of diflunisal in man. *Br J Clin Pharmacol* 1990; **29**: 381–9.
- Macdonald JJ, *et al.* Sex-difference and the effects of smoking and oral contraceptive steroids on the kinetics of diflunisal. *Eur J Clin Pharmacol* 1990; **38**: 175–9.
- Nuernberg B, *et al.* Pharmacokinetics of diflunisal in patients. *Clin Pharmacokinet* 1991; **20**: 81–9.

#### Uses and Administration

Diflunisal is a salicylic acid derivative (see Aspirin, p.23) but it is not hydrolysed to salicylate and its clinical effects resemble more closely those of propionic acid derivative NSAIDs such as ibuprofen (p.65). Diflunisal is given in the acute or long-term management of mild to moderate pain, and pain and inflammation associated with osteoarthritis and rheumatoid arthritis. The usual initial oral dose for pain relief is 1 g followed by a maintenance dose of 500 mg every 12 hours. In some patients 250 mg every 8 to 12 hours may be sufficient but others may require 500 mg every 8 hours. Maintenance doses greater than 1.5 g daily are not recommended. The usual oral dose for arthritis is 500 mg to 1 g daily in 2 divided doses. Doses may need to be reduced in patients with renal impairment, see below.

Diflunisal arginine has been used similarly given by mouth or by intramuscular or intravenous injection.

**Administration in renal impairment.** Diflunisal may need to be given in reduced dosage in patients with significant renal impairment and should not be given when renal impairment is severe.

#### Preparations

**BP 2008:** Diflunisal Tablets;

**USP 31:** Diflunisal Tablets.

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

**Austral.:** Dolobid; **Austria:** Fluniget; **Belg.:** Biartact; **Diflusal:** Denm.; **Donobid;** **Fin.:** Donobid; **Fr.:** Dolobid; **Gr.:** Analeric; **Irl.:** Dolobid; **Israel:** Dolobid; **Ital.:** Artrodol; Dolobid; **Mex.:** Dolobid; **Neth.:** Dolobid; **Dolocid;** **Norw.:** Donobid; **Port.:** Dolobid; **Flunidor;** **Spain:** Dolobid; **Swed.:** Donobid; **Switz.:** Unisalt; **Thai.:** Dolobid; **Turk.:** Dolphir; **UK:** Dolobid; **USA:** Dolobid; **Venez.:** Dolobid.

## Dihydrocodeine Phosphate

(BANM, rINNM)

Dihydrocodéine, Phosphate de; Dihydrocodeini Phosphas; Fosfato de dihidrocodeína; Hydrocodeine Phosphate.

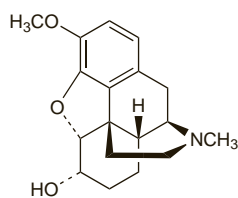
Дигидрокодеина Фосфат

$C_{18}H_{23}NO_3 \cdot H_3PO_4 = 399.4$ .

CAS — 24204-13-5.

ATC — N02AA08.

ATC Vet — QN02AA08.



(dihydrocodeine)

**Pharmacopoeias.** In *Jpn*.

**Dihydrocodeine Tartrate** (BANM, rINNM)

Dihidrokodein-hidrogén-tartrát; Dihidrokodeino-vandenilio tartratas; Dihydrocodeine Acid Tartrate; Dihydrocodeine Bitartrate; Dihydrocodeine Hydrogen Tartrate; Dihydrocodéine, hidrogénotartrate de; Dihydrocodéine, Tartrate de; Dihydrocodeini Bitartras; Dihydrocodeini hydrogenotartras; Dihydrocodeini Tartras; Dihydrokodeinivetytartratti; Dihydrokodein-tartrát; Dihydrokodeinivétetartrát; Dihydrokodeiny wodorowinian; Drocode Bitartrate; Hydrocodeine Bitartrate; Tartrato de dihidrocodeína. 4,5-Epoxy-3-methoxy-17-methylmorphinan-6-ol hydrogen tartrate.

Дигидрокодеина Тартрат

$C_{18}H_{23}NO_3 \cdot C_4H_6O_6 = 451.5$ .

CAS — 125-28-0 (dihydrocodeine); 5965-13-9 (dihydrocodeine tartrate).

**NOTE.** Compounded preparations of dihydrocodeine tartrate may be represented by the following names:

- Co-dydramol (BAN)—dihydrocodeine tartrate 1 part and paracetamol 50 parts (w/w).
- The following terms have been used as 'street names' (see p.vi) or slang names for various forms of dihydrocodeine tartrate:

DFs; Diffis; Duncan Flockharts.

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

**Ph. Eur. 6.2** (Dihydrocodeine Hydrogen Tartrate; Dihydrocodeine Tartrate BP 2008). A white or almost white crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in cyclohexane. A 10% solution in water has a pH of 3.2 to 4.2. Protect from light.

**USP 31** (Dihydrocodeine Bitartrate). pH of a 10% solution in water is between 3.2 and 4.2. Store in airtight containers.

#### Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Dihydrocodeine has been subject to abuse (see under Precautions, below).

#### Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102; adverse effects of dihydrocodeine are less pronounced than those of morphine.

**Overdosage.** A 29-year-old man who had taken 2.1 g of dihydrocodeine had biochemical evidence of acute renal and hepatic impairment when admitted 13 hours after the overdose.<sup>1</sup> Severe life-threatening respiratory depression subsequently developed 36 hours after the overdose and only responded to treatment with naloxone after large doses (a total of 46.6 mg of naloxone) over a long period (106 hours). Commenting on this report some questioned the evidence for hepatic impairment and considered that the raised liver enzyme values were of muscular origin as a result of rhabdomyolysis.<sup>2,4</sup> Rhabdomyolysis may also have contributed to renal failure.

An anaphylactoid reaction after an overdose with an unspecified number of dihydrocodeine tablets<sup>3</sup> appeared to respond to intravenous naloxone.

- Redfern N. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287**: 751–2.
- Buckley BM, Vale JA. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287**: 1547.
- Blain PG, Lane RJM. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287**: 1547.
- Wen P. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287**: 1548.
- Panos MZ, *et al.* Use of naloxone in opioid-induced anaphylactoid reaction. *Br J Anaesth* 1988; **61**: 371.

**Pain.** For reference to increased postoperative pain associated with the use of dihydrocodeine, see under Uses and Administration, below.

#### Precautions

As for Opioid Analgesics in general, p.103.

**Abuse.** Dihydrocodeine has been reported to be widely abused by opiate addicts.<sup>1–4</sup>

- Swadi H, *et al.* Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. *BMJ* 1990; **300**: 1313.
- Robertson JR, *et al.* Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. *BMJ* 1990; **301**: 119.
- Strang J, *et al.* Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. *BMJ* 1990; **301**: 119.
- Seymour A, *et al.* The role of dihydrocodeine in causing death among drug users in the west of Scotland. *Scott Med J* 2001; **46**: 143–6.

**The elderly.** Despite some renal impairment an elderly group of patients<sup>1</sup> appeared to handle dihydrocodeine similarly to healthy young subjects. There was marked variability in all measurements and on the basis of this study no clear conclusions on guidelines for dosage in elderly patients could be drawn. However, the recommendation that small doses be given initially with subsequent doses according to response was endorsed.

- Davies KN, *et al.* The effect of ageing on the pharmacokinetics of dihydrocodeine. *Eur J Clin Pharmacol* 1989; **37**: 375–9.

**Renal impairment.** Caution is necessary when giving dihydrocodeine to patients with severe renal impairment. Severe narcosis occurred in a patient with anuria and on maintenance haemodialysis after she had received dihydrocodeine orally for 4 days.<sup>1</sup> She responded to treatment with naloxone.

See also under Pharmacokinetics, below.

- Barnes JN, Goodwin FJ. Dihydrocodeine narcosis in renal failure. *BMJ* 1983; **286**: 438–9.

#### Interactions

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

**Quinidine.** Dihydrocodeine is metabolised via the cytochrome P450 isoenzyme CYP2D6 to active metabolites, which may perhaps play a role in its analgesic activity in extensive metabolizers; quinidine impairs this metabolism, but a study in 11 healthy

subjects did not find any reduced analgesic activity when dihydrocodeine was given with quinidine, despite a three- to fourfold reduction in plasma concentrations of the metabolite dihydromorphine.<sup>1</sup>

- Wilder-Smith CH, *et al.* The visceral and somatic antinociceptive effects of dihydrocodeine and its metabolite, dihydromorphine: a cross-over study with extensive and quinidine-induced poor metabolizers. *Br J Clin Pharmacol* 1998; **45**: 575–81.

#### Pharmacokinetics

After oral doses peak concentrations of dihydrocodeine occur after about 1.2 to 1.8 hours; oral bioavailability is only about 20%, probably because of substantial first-pass metabolism in the gut wall or liver. Dihydrocodeine is metabolised in the liver via the cytochrome P450 isoenzyme CYP2D6, to dihydromorphine, which has potent analgesic activity, although the analgesic effect of dihydrocodeine appears to be primarily due to the parent compound; some is also converted via CYP3A4 to nordihydrocodeine. Dihydrocodeine is excreted in urine as unchanged drug and metabolites, including glucuronide conjugates. Elimination half-life is reported to range from about 3.5 to 5 hours.

#### References.

- Rowell FJ, *et al.* Pharmacokinetics of intravenous and oral dihydrocodeine and its acid metabolites. *Eur J Clin Pharmacol* 1983; **25**: 419–24.
- Fromm MF, *et al.* Dihydrocodeine: a new opioid substrate for the polymorphic CYP2D6 in humans. *Clin Pharmacol Ther* 1995; **58**: 374–82.
- Ammon S, *et al.* Pharmacokinetics of dihydrocodeine and its active metabolite after single and multiple dosing. *Br J Clin Pharmacol* 1999; **48**: 317–22.
- Webb JA, *et al.* Contribution of dihydrocodeine and dihydromorphine to analgesia following dihydrocodeine administration in man: a PK-PD modelling analysis. *Br J Clin Pharmacol* 2001; **52**: 35–43.

**Renal impairment.** The pharmacokinetics of dihydrocodeine tartrate, given as a single oral 60-mg dose, were affected in 9 patients with chronic renal failure treated with haemodialysis when compared with 9 healthy subjects.<sup>1</sup> Time to peak plasma concentration in those with renal failure was 3 hours compared with 1 hour in healthy subjects; the area under the plasma concentration-time curve was greater in those with renal failure; and after 24 hours dihydrocodeine was still detectable in the plasma of all renal failure patients, but in only 3 of the healthy subjects.

- Barnes JN, *et al.* Dihydrocodeine in renal failure: further evidence for an important role of the kidney in the handling of opioid drugs. *BMJ* 1985; **290**: 740–2.

#### Uses and Administration

Dihydrocodeine is an opioid analgesic (p.104). It is related to codeine (p.38) and has similar analgesic activity. Dihydrocodeine is used for the relief of moderate to severe pain, often in combination preparations with paracetamol. It has also been used as a cough suppressant.

For **analgesia** the usual oral dose of dihydrocodeine tartrate is 30 mg after food every 4 to 6 hours; up to 240 mg daily may be given for severe pain. Modified-release preparations are available for twice daily dosage in patients with chronic severe pain.

Dihydrocodeine tartrate may also be given by deep subcutaneous or intramuscular injection in doses of up to 50 mg every 4 to 6 hours.

For details of doses in children, see below.

As a **cough suppressant** dihydrocodeine tartrate may be given in oral doses of 10 to 30 mg up to three times daily.

Dihydrocodeine phosphate has also been used. Other salts of dihydrocodeine used, mainly for their antitussive effects, include the hydrochloride, the polistirex, and the thiocyanate. Dihydrocodeine polistirex has also been used in modified-release preparations.

**Administration in children.** In the UK, dihydrocodeine tartrate may be given orally, or by deep subcutaneous or intramuscular injection, for analgesia in children aged from 4 to 12 years in usual doses of 0.5 to 1 mg/kg (to a maximum of 30 mg) every 4 to 6 hours; older children may be given the usual adult dose (see above). Although unlicensed in children under 4 years, the *BNFC* suggests giving those aged 1 to 4 years 500 micrograms/kg every 4 to 6 hours.

**Dyspnoea.** Dihydrocodeine has been reported<sup>1</sup> to have produced benefit in normocapnic patients severely disabled by breathlessness due to chronic airflow obstruction. A dose of