is being investigated in the management of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.

◊ References.

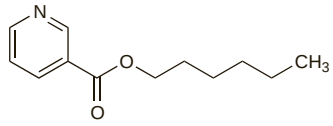
1. Zhou H, *et al.* Pharmacokinetics and safety of golimumab, a fully human anti-TNF-α monoclonal antibody, in subjects with rheumatoid arthritis. *J Clin Pharmacol* 2007; **47:** 383–96.
2. Kay J, *et al.* Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum* 2008; **58:** 964–75.

Hexyl Nicotinate

Heksyylinikotinaatti; Hexylnicotinatum; Hexylnikotinat; Nicotinato de hexilo. *n*-Hexyl nicotinate.

$C_{12}H_{17}NO_2$ = 207.3.

CAS — 23597-82-2.



Profile

Hexyl nicotinate is used in topical preparations as a rubefacient.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Transvane; ***Irl.:*** Transvasin; ***Port.:*** Hipodor†; ***UK:*** Transvasin Heat Rub.

Hydrocodone Hydrochloride *(BANM, rINNM)*

Hidrocloruro de hidrocodona; Hydrocodone, Chlorhydrate d'; Hydrocodoni Hydrochloridum.

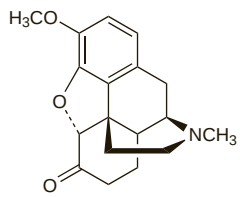
Гидрокодона Гидрохлорид

$C_{18}H_{21}NO_3$,HCl,2 / H_2O = 380.9.

CAS — 25968-91-6 (anhydrous hydrocodone hydrochloride).

ATC — R05DA03.

ATC Vet — QR05DA03.



(hydrocodone)

Hydrocodone Tartrate *(BANM, rINNM)*

Dihydrocodeinone Acid Tartrate; Hydrocodone Acid Tartrate; Hydrocodone Bitartrate *(USAN)*; Hydrocodone, Tartrate d'; Hydrocodoni Bitartras; Hydrocodoni Tartras; Hydrocone Bitartrate; Tartrato de dihidrocodeinona; Tartrato de hidrocodona. 6-Deoxy-3-*O*-methyl-6-oxomorphine hydrogen tartrate hemipentahydrate; (–)-(5*R*)-4,5-Epoxy-3-methoxy-9a-methylmorphinan-6-one hydrogen tartrate hemipentahydrate.

Гидрокодона Тартрат

$C_{18}H_{21}NO_3$,$C_4H_6O_6$,2 / H_2O = 494.5.

CAS — 125-29-1 (hydrocodone); 143-71-5 (anhydrous hydrocodone tartrate); 34195-34-1 (hydrocodone tartrate hemipentahydrate).

ATC — R05DA03.

ATC Vet — QR05DA03.

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

- Co-hycodAPAP (*PEN*)—hydrocodone tartrate and paracetamol.
  The following terms have been used as 'street names' (see p.vi) or slang names for various forms of hydrocodone tartrate:
  Cough Syrup; Vikes.

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

Ph. Eur. 6.2 (Hydrocodone Hydrogen Tartrate 2.5-Hydrate). White or almost white, hygroscopic, crystalline powder. Freely soluble or soluble in water; sparingly soluble in alcohol; practically insoluble in cyclohexane. A 2% solution in water has a pH of 3.2 to 3.8. Store in airtight containers. Protect from light.

USP 31 (Hydrocodone Bitartrate). Fine, white crystals or crystalline powder. Soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 2% solution in water is between 3.2 and 3.8. Store in airtight containers. Protect from light.

Profile

Hydrocodone, a phenanthrene derivative, is an opioid analgesic (p.101) related to codeine (p.37) and has similar actions, but is more potent on a weight-for-weight basis. Hydromorphone (below) is one of the metabolites of hydrocodone.

Hydrocodone is used mainly as the tartrate in combination preparations for the relief of irritant cough, though it has no particular advantage over codeine. Hydrocodone tannate has been used similarly. Hydrocodone tartrate is also used for the relief of moderate to moderately severe pain, usually with paracetamol. The usual oral dose of hydrocodone tartrate in such combination preparations is 5 to 10 mg every 4 to 6 hours.

For details of doses in children, see below.

Hydrocodone hydrochloride is given orally and also by injection. The polistirex derivative (a hydrocodone and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) is used in modified-release preparations.

Hydrocodone has also been used in the treatment of dyspnoea.

Abuse. The abuse or overuse of preparations containing hydrocodone and paracetamol has been associated with *sensorineural hearing loss.*[1,2] Cochlear implants improved the hearing loss in some of the patients.

A case of *palatal perforation* associated with intranasal abuse of a crushed preparation of hydrocodone and paracetamol has also been reported.[3]

1. Friedman RA, *et al.* Profound hearing loss associated with hydrocodone/acetaminophen abuse. *Am J Otol* 2000; **21:** 188–91.
2. Ho T, *et al.* Hydrocodone use and sensorineural hearing loss. *Pain Physician* 2007; **10:** 467–72.
3. Jewers WM, *et al.* Palatal perforation associated with intranasal prescription narcotic abuse. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **99:** 594–7.

Administration in children. Hydrocodone tartrate may be given as part of a combination preparation for the relief of irritant cough in children aged from 6 to 12 years in usual oral doses of 2.5 mg every 4 to 6 hours. Older children may be given the usual adult dose (see above).

Pharmacokinetics. References.

1. Hutchinson MR, *et al.* CYP2D6 and CYP3A4 involvement in the primary oxidative metabolism of hydrocodone by human liver microsomes. *Br J Clin Pharmacol* 2004; **57:** 287–97.

Preparations

USP 31: Hydrocodone Bitartrate and Acetaminophen Tablets; Hydrocodone Bitartrate and Homatropine Methylbromide Tablets; Hydrocodone Bitartrate Tablets.

Proprietary Preparations (details are given in Part 3)

Belg.: Biocodone; ***Canad.:*** Hycodan; ***Ger.:*** Dicodid; ***Switz.:*** Dicodid†; Hydrocodeinon.

Multi-ingredient: ***Arg.:*** Hidronovag Complex; ***Canad.:*** Coristine-DH†; Dalmacol; Dimetane Expectorant DC; Hycomine; Novahistex DH; Novahistine DH; ratio-Calmydone; ratio-Coristex-DH; Tussionex; Vasofrinic DH; ***India:*** Cardiazol-Dicodid†; ***USA:*** Alor; Anaplex HD; Anexsia; Atuss EX†; Atuss G; Atuss HC; Atuss HD; Atuss HS; Atuss HX; Bancap HC; Ceta Plus; Co-Gesic; Co-Tuss V; Codal-DH; Codiclear DH; Codimal DH; Cophene XP; Cordron-HC; Cyndal HD†; Cytuss HC; Cytuss-HC NR; Damason-P; De-Chlor G; De-Chlor HC; De-Chlor HD†; De-Chlor MR; De-Chlor NX; Deconamine CX; Dolacet; Donatussin DC; Drocon-CS; Duocet; Duratuss HD; Dytan-HC; ED Tuss HC; ED-TLC; Endagen-HD; Endal-HD; Endal-HD Plus; Entex HC; Entuss Expectorant; Entuss-D; Entuss-D Jr; H-Tuss-D†; Histex HC; Histinex D; Histinex HC; Histinex PV; Histussin D†; Histussin HC; Hy-KXP; Hy-Phen; Hycet; HycoClear Tuss; Hycodan; Hycomine Compound; Hycotuss; Hydex PD; Hydro DP; Hydro PC†; Hydro-GP; Hydro-Tussin HD; Hydro-Tussin HG; Hydrocet; Hydrocodone CP; Hydrocodone GF; Hydrocodone HD; Hydrogesic; Hydromet; Hydron CP; Hydron EX; Hydron KGS; Hydron PSC; Hydropane; Hyphed; HyTan; Ibudone; Iodal; Iotussin HC; Kwelcof; Levall 5.0; Liquicet; Lorcet 10/650; Lorcet Plus; Lorcet-HD; Lortab; Lortab ASA; Lortuss HC; Marcof; Margesic H; Maxi-Tuss HCG; Maxi-Tuss HCX; Maxidone; Nalex DH; Nalex Expectorant; Narcof; Nariz HC; Neo HC; Norco; Notuss PD; Notuss-Forte; Oncet; P-V-Tussin; Pancof XP; Pancof-HC; Pancof-XL; Para-Hist HD; Pneumotussin; Poly-Tussin; Pro-Red; Protuss-D†; Protuss†; Relacon-HC; Relasin-HCX; Reprexain; S-T Forte 2; SRC Expectorant; Stagesic; Su-Tuss HD; T-Gesic; Tusana-D; Tusdec-HC; Tusnel-HC; Tussafed HC†; Tussafed-HCG; Tussafin Expectorant; Tussanil DH; Tussend; Tussigon; Tussionex Pennkinetic; Tusso-DF; Tusso-HC; Tussplex; Tyrodone; Unituss HC; Vanex Expectorant; Vanex-HD; Vazotuss HC; Vicodin; Vicodin Tuss; Vicoprofen; Vitussin; Xodol; Z-Cof HC; Zamicet; Zydone; Zymine HC.

Hydromorphone Hydrochloride

(BANM, rINNM) ⊗

Dihydromorphinone Hydrochloride; Hidrocloruro de dihidromorfinona; Hidrocloruro de hidromorfona; Hidromorfono hidrochloridas; Hydromorfon-hydrochlorid; Hydromorfonhydroklorid; Hydromorfonihydrokloridi; Hydromorphone, chlorhydrate d'; Hydromorphoni hydrochloridum. 6-Deoxy-7,8-dihydro-6-oxomorphine hydrochloride; (–)-(5*R*)-4,5-Epoxy-3-hydroxy-9a-methylmorphinan-6-one hydrochloride.

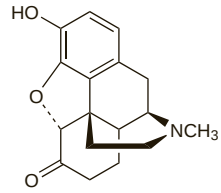
Гидроморфона Гидрохлорид

$C_{17}H_{19}NO_3$,HCl = 321.8.

CAS — 466-99-9 (hydromorphone); 71-68-1 (hydromorphone hydrochloride).

ATC — N02AA03.

ATC Vet — QN02AA03.



(hydromorphone)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of hydromorphone:
Dillies; HillBilly Heroin; Hospital heroin.

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

Ph. Eur. 6.2 (Hydromorphone Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. Protect from light.

USP 31 (Hydromorphone Hydrochloride). A fine white, or practically white, odourless, crystalline powder. Soluble 1 in 3 of water; sparingly soluble in alcohol; practically insoluble in ether. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Colour change from pale yellow to light green occurred when solutions of minocycline hydrochloride or tetracycline hydrochloride were mixed with hydromorphone hydrochloride in 5% glucose injection.[1] Mixtures of hydromorphone hydrochloride and dexamethasone sodium phosphate exhibited concentration-dependent incompatibility.[2] White cloudiness, haziness, or precipitation developed 4 hours after mixing thiopental sodium and hydromorphone hydrochloride.[3]

Stability of mixtures of fluorouracil and hydromorphone hydrochloride in 0.9% sodium chloride or 5% glucose depended on the concentration of fluorouracil present.[4] Hydromorphone hydrochloride 0.5 mg/mL with fluorouracil 1 mg/mL was stable for at least 7 days at 32° and for at least 35 days at 23°, 4°, or –20°. When the concentration of fluorouracil was increased to 16 mg/mL, hydromorphone was noted to decompose incurring unacceptable losses after 3 days at 32° or after 7 days at 23°, but was stable for at least 35 days at 4° or –20°.

1. Nieves-Cordero AL, *et al.* Compatibility of narcotic analgesic solutions with various antibiotics during simulated Y-site injection. *Am J Hosp Pharm* 1985; **42:** 1108–9.
2. Walker SE, *et al.* Compatibility of dexamethasone sodium phosphate with hydromorphone hydrochloride or diphenhydramine hydrochloride. *Am J Hosp Pharm* 1991; **48:** 2161–6.
3. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
4. Xu QA, *et al.* Stability and compatibility of fluorouracil with morphine sulfate and hydromorphone hydrochloride. *Ann Pharmacother* 1996; **30:** 756–61.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p.102.

UK licensed product information contra-indicates the use of hydromorphone hydrochloride in patients with hepatic impairment; however, product information in the USA permits its cautious use although doses may need to be reduced. It should also be used with caution and given in reduced doses to those with renal impairment.

Effects on the nervous system. Myoclonus has been reported[1] in a 55-year-old man given relatively low doses of intravenous hydromorphone with a total daily dose of 4 mg on day 1 and 6 mg on day 2; symptoms resolved when the drug was stopped on day 3. A chart review[2] for neuroexcitatory symptoms in 48 patients with terminal illnesses on hydromorphone found 13 cases of agitation, 9 of myoclonus, and 4 of seizures; maximal dose and treatment duration were noted to increase the risk of neurotoxicity.

1. Patel S, *et al.* A myoclonic reaction with low-dose hydromorphone. *Ann Pharmacother* 2006; **40:** 2068–70.
2. Thwaites D, *et al.* Hydromorphone neuroexcitation. *J Palliat Med* 2004; **7:** 545–50.

Interactions

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

Alcohol. The FDA received data from pharmacokinetic studies in healthy subjects which showed that significantly higher peak plasma concentrations of hydromorphone were achieved, as a result of dose-dumping, when alcohol was ingested with once-daily hydromorphone modified-release capsules (*Palladone;*