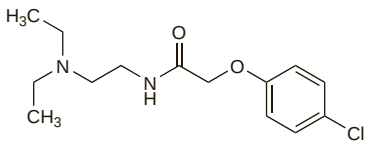
Clofexamide *(rINN)*

ANP-246; Clofexamida; Clofexamidum. 2-(4-Chlorophenoxy)-*N*-(2-diethylaminoethyl)acetamide.

Клофексамид

$C_{14}H_{21}ClN_2O_2$ = 284.8.

CAS — 1223-36-5.



Profile

Clofexamide has been used topically as the hydrochloride in preparations for musculoskeletal, joint, and soft-tissue disorders.

Clofezone *(rINN)*

ANP-3260; Clofezona; Clofézone; Clofezonum. An equimolar combination of clofexamide and phenylbutazone.

Клофезон

$C_{14}H_{21}ClN_2O_2,C_{19}H_{20}N_2O_2,2H_2O$ = 629.2.

CAS — 60104-29-2.

ATC — M01AA05; M02AA03.

ATC Vet — QM01AA05; QM02AA03.

Profile

Clofezone, a combination molecule containing clofexamide (above) and phenylbutazone (p.117), has been given orally and by rectal suppository and applied topically in preparations for musculoskeletal, joint, and soft-tissue disorders.

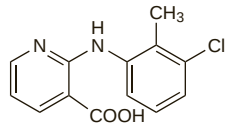
Clonixin *(USAN, rINN)*

CBA-93626; Clonixine; Clonixino; Clonixinum; Sch-10304. 2-(3-Chloro-*o*-toluidino)nicotinic acid.

Клониксин

$C_{13}H_{11}ClN_2O_2$ = 262.7.

CAS — 17737-65-4.



Clonixin Lysine *(rINNM)*

Clonixin Lysinate; Clonixine Lysine; Clonixino lisina; Clonixinum Lysinum; L-104; Lysine Clonixinate; R-173.

Клониксина Лизин

$C_{13}H_{11}ClN_2O_2$, $C_6H_{14}N_2O_2$ = 408.9.

CAS — 55837-30-4.

Profile

Clonixin is an NSAID (p.96). It has been used as the lysine salt in oral doses of up to 250 mg four times daily for the relief of pain. Clonixin lysine has also been given by intramuscular or intravenous injection and as a rectal suppository.

◊ References.

1. Eberhardt R, *et al.* Analgesic efficacy and tolerability of lysine-clonixinate versus ibuprofen in patients with gonarthrosis. *Curr Ther Res* 1995; **56:** 573–80.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Clonixil; Diclen; Dolex; Dolnot†; Dorixina; ***Braz.:*** Dolamin; ***Chile:*** Blonax; Celex; Clonalgin; Colmax; Dentagesic; Diminon; Dolalgial†; Lafigesic; Medigesic; Nefersil; Traumicid; ***Mex.:*** Disinal; Donodol; Dorixina; Firac; Lonixer; Prestodol; Sedepron; ***Port.:*** Algimate; Clonix; ***Spain:*** Dolalgial; ***Venez.:*** Dorixina.

Multi-ingredient: ***Arg.:*** Amplibenzatin Bronquial; Aseptobron Ampicilina†; Dorixina B1 B6 B12; Dorixina Forte; Dorixina Relax; Espasmo Dolex; Migra Dorixina; Mikesan; Nova Paratropina Compositum; Propalgin; Sertal Compuesto; ***Braz.:*** Dolamin Flex; ***Chile:*** Clonalgin Compuesto; Ergonef; Migra-Nefersil; Nefersil B; Neurocam; ***Mex.:*** Donodol Compuesto; Espacil Compuesto; Firac Plus; Klonaza; Optium; Plidan Compuesto; Prestodol Compuesto; Yuredol; ***Venez.:*** Dologinex; Dorixina Flex; Migradorixina; Plidan Compuesto.

Codeine *(BAN)*

Codeína; Codéine; Codeinum; Codeinum Monohydricum; Kodeiini; Kodein; Kodein monohydrát; Kodeina; Kodeinas; Methylmorphine; Metilmorfina; Morphine Methyl Ether. 7,8-Didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol monohydrate.

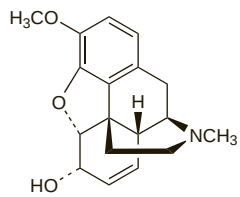
Кодеин

$C_{18}H_{21}NO_3,H_2O$ = 317.4.

CAS — 76-57-3 (anhydrous codeine); 6059-47-8 (codeine monohydrate).

ATC — R05DA04.

ATC Vet — QR05DA04.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of codeine:
AC/DC; Barr; Captain Cody; Cody; Coties; Cough Syrup; Down; Karo; Lean; Nods; School boy; Schoolboy; T3.

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

Ph. Eur. 6.2 (Codeine). White or almost white, crystalline powder or colourless crystals. Soluble in boiling water; freely soluble in alcohol. Protect from light.

USP 31 (Codeine). Colourless or white crystals or white crystalline powder. It effloresces slowly in dry air. Soluble 1 in 120 of water, 1 in 2 of alcohol, 1 in 0.5 of chloroform, and 1 in 50 of ether. Its saturated solution in water is alkaline to litmus. Store in airtight containers. Protect from light.

Codeine Hydrochloride *(BANM)*

Codeína, hidrocloruro de; Codéine (chlorhydrate de) dihydraté; Codeini hydrochloridum dihydricum; Kodeiinihydroklorididihydraatti; Kodein-hidroklorid-dihidrát; Kodein-hydrochlorid dihydrát; Kodeinhydrokloriddihydrat; Kodeino hidrochloridas dihidratas.

Кодеина Гидрохлорид

$C_{18}H_{21}NO_3,HCl,2H_2O$ = 371.9.

CAS — 1422-07-7 (anhydrous codeine hydrochloride).

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

Ph. Eur. 6.2 (Codeine Hydrochloride Dihydrate; Codeine Hydrochloride BP 2008). Small colourless crystals or a white or almost white, crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in cyclohexane. Protect from light.

Codeine Phosphate *(BANM)*

Codeína, fosfato de; Codéine, phosphate de; Codeine Phosphate Hemihydrate; Codeini phosphas; Codeini Phosphas Hemihydricus; Codeinii Phosphas; Kodeiinifosfaatti; Kodein-fosfát hemihydrát; Kodeinfosfathemi; Kodein-foszfát-hemihidrát; Kodeino fosfatas hemihidratas; Kodeiny fosforan; Kodeiny fosforan półwodny; Methylmorphine Phosphate.

Кодеина Фосфат

$C_{18}H_{21}NO_3,H_3PO_4,/H_2O$ = 406.4.

CAS — 52-28-8 (anhydrous codeine phosphate); 41444-62-6 (codeine phosphate hemihydrate); 5913-76-8 (codeine phosphate sesquihydrate).

NOTE. Compounded preparations of codeine phosphate may be represented by the following names:

- Co-codamol *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of codeine phosphate and paracetamol respectively
- Co-codAPAP (*PEN*)—codeine phosphate and paracetamol
- Co-codaprin (*BAN*)—codeine phosphate 1 part and aspirin 50 parts (w/w)
- Co-codaprin (*PEN*)—codeine phosphate and aspirin.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Pharmacopoeias may specify the hemihydrate, sesquihydrate, or both, either under one monograph or as separate monographs.

Ph. Eur. 6.2 (Codeine Phosphate Hemihydrate; Codeine Phosphate BP 2008). A white or almost white, crystalline powder or small, colourless crystals. Freely soluble in water; slightly soluble or very slightly soluble in alcohol. A 4% solution in water has a pH of 4.0 to 5.0. Protect from light.

Ph. Eur. 6.2 (Codeine Phosphate Sesquihydrate; Codeini Phosphas Sesquihydricus). A white or almost white, crystalline powder or small, colourless crystals. Freely soluble in water; slightly soluble in alcohol. A 4% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 31 (Codeine Phosphate). The hemihydrate occurs as fine, white, needle-shaped crystals or white crystalline powder; odourless. Soluble 1 in 2.5 of water, 1 in 0.5 of water at 80°, 1 in 325 of alcohol, and 1 in 125 of boiling alcohol. Its solutions are acid to litmus. Store in airtight containers at a temperature up to 40° as permitted by the manufacturer. Protect from light.

Incompatibility. Acetylation of codeine phosphate by aspirin has occurred in solid dosage forms containing the two drugs, even at a low moisture level.[1] *Animal* work suggested that the analgesic activity of codeine was not affected by acetylation.[2]

1. Galante RN, *et al.* Solid-state acetylation of codeine phosphate by aspirin. *J Pharm Sci* 1979; **68:** 1494–8.
2. Buckett WR, *et al.* The analgesic properties of some 14-substituted derivatives of codeine and codeinone. *J Pharm Pharmacol* 1964; **16:** 174–82.

Codeine Sulfate

Codeína, sulfato de; Codeine Sulphate *(BANM)*.

Кодеина Сульфат

$(C_{18}H_{21}NO_3)_2,H_2SO_4,3H_2O$ = 750.9.

CAS — 1420-53-7 (anhydrous codeine sulfate); 6854-40-6 (codeine sulfate trihydrate).

Pharmacopoeias. In *US*.

USP 31 (Codeine Sulfate). White crystals, usually needle-like, or white crystalline powder. Soluble 1 in 30 of water, 1 in 6.5 of water at 80°, and 1 in 1300 of alcohol; insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Stability. Codeine sulfate solutions appear to be intrinsically more stable than codeine phosphate solutions.[1]

1. Powell MF. Enhanced stability of codeine sulfate: effect of pH, buffer, and temperature on the degradation of codeine in aqueous solution. *J Pharm Sci* 1986; **75:** 901–3.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Codeine is subject to abuse (see under Precautions, below), but produces less euphoria and sedation than morphine.

Neonatal abstinence syndrome. Some of the symptoms characteristic of the neonatal abstinence syndrome were seen in a neonate whose mother had taken about 90 mg of codeine daily during the last 2 months of pregnancy.[1]

1. Khan K, Chang J. Neonatal abstinence syndrome due to codeine. *Arch Dis Child* 1997; **76:** F59–F60.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102.

In therapeutic doses codeine is much less liable than morphine to produce adverse effects, although constipation may be troublesome with long-term use. After large doses of codeine, excitement and convulsions may occur.

Codeine, like morphine, has a dose-related histamine-releasing effect. Anaphylactic reactions after intravenous use have been reported rarely.

Effects on mental function. Central effects of codeine phosphate appeared to be limited, but dose-related, in subjects given 30, 60, or 90 mg; visuo-motor coordination was altered with doses of 60 and 90 mg and dynamic visual acuity with 90 mg.[1] Drowsiness reported by subjects given 90 mg of codeine phosphate could not be linked with impaired performance whereas nausea could.

1. Bradley CM, Nicholson AN. Effects of a μ-opioid receptor agonist (codeine phosphate) on visuo-motor coordination and dynamic visual acuity in man. *Br J Clin Pharmacol* 1986; **22:** 507–12.

Effects on the pancreas. A 26-year-old woman developed acute pancreatitis on 2 separate occasions a few hours after taking a single, 40-mg dose of codeine.[1] There was no history of alcohol consumption and her recovery was uneventful. Other cases have been reported.[2-5]

1. Hastier P, *et al.* Pancreatitis induced by codeine: a case report with positive rechallenge. *Gut* 1997; **41:** 705–6.
2. Locher C, *et al.* Pancréatite aiguë après la prise d'une association paracétamol-codéine. *Gastroenterol Clin Biol* 2003; **27:** 124–5.
3. Kohlen K, *et al.* Codein-induzierte Pankreatitis. *Dtsch Med Wochenschr* 2005; **130:** 878–9.
4. Moreno Escobosa MC, *et al.* Pancreatitis due to codeine. *Allergol Immunopathol (Madr)* 2005; **33:** 175–7.
5. Belhassen García M, *et al.* Pancreatitis secundaria a paracetamol-codeína. *An Med Interna* 2006; **23:** 400–401.

Effects on the skin. Pruritus and burning erythemato-vesicular plaques that developed in a patient in response to oral codeine were attributed to a fixed drug eruption.[1] A similar reaction occurred in another patient after taking various analgesics including a combined preparation of paracetamol and codeine;[2] patch testing showed a positive response for codeine only. Maculopapular rash has been seen as part of a hypersensitivity syndrome

associated with oral codeine phosphate;[3] fever, splenomegaly, and lymphadenopathy also occurred.

1. Gonzalo-Garijo MA, Revenga-Arranz F. Fixed drug eruption due to codeine. *Br J Dermatol* 1996; **135:** 498–9.
2. Gastaminza G, *et al.* Erythrodermia caused by allergy to codeine. *Contact Dermatitis* 2005; **52:** 227–8.
3. Enomoto M, *et al.* Codeine phosphate-induced hypersensitivity syndrome. *Ann Pharmacother* 2004; **38:** 799–802.

Hypersensitivity. See Effects on the Skin, above.

Overdosage. Acute codeine intoxication in 430 children, due to accidental ingestion of antitussive preparations, was reviewed.[1] The children were nearly all between 1 and 6 years old. Symptoms in decreasing order of frequency included somnolence, rash, miosis, vomiting, itching, ataxia, and swelling of the skin. Respiratory failure occurred in 8 children and 2 died; all 8 had taken 5 mg/kg or more. Infants are at special risk and there have been fatalities[2,3] and severe adverse effects[4,5] after inappropriate treatment in infants given mixtures containing codeine.

Opioid toxicity, in addition to severe salicylate toxicity, has occurred in adults after overdoses of aspirin and codeine tablets.[6]

1. von Mühlendahl KE, *et al.* Codeine intoxication in childhood. *Lancet* 1976; **ii:** 303–5.
2. Ivey HH, Kattwinkel J. Danger of Actifed-C. *Pediatrics* 1976; **57:** 164–5.
3. Magnani B, Evans R. Codeine intoxication in the neonate. Abstract: *Pediatrics* 1999; **104:** 1379. Full version: http://pediatrics.aappublications.org/cgi/content/full/104/6/e75 (accessed 26/06/08)
4. Wilkes TCR, *et al.* Apnoea in a 3-month-old baby prescribed compound linctus containing codeine. *Lancet* 1981; **i:** 1166–7.
5. Lee AC, *et al.* A case of probable codeine poisoning in a young infant after the use of a proprietary cough and cold medicine. *Hong Kong Med J* 2004; **10:** 285–7.
6. Leslie PJ, *et al.* Opiate toxicity after self poisoning with aspirin and codeine. *BMJ* 1986; **292:** 96.

Precautions

As for Opioid Analgesics in general, p.103.

Abuse. Although the risk of dependence on codeine is low with normal use,[1] it is the subject of deliberate abuse. In France[2] and in the UK linctuses containing codeine have been particularly liable to abuse. Reports in the literature include the use in New Zealand of codeine-containing preparations to produce demethylated products known as "Homebake" containing variable amounts of morphine[3] and abuse of co-codaprin tablets for their codeine content.[4-6]

1. Rowden AM, Lopez JR. Codeine addiction. *DICP Ann Pharmacother* 1989; **23:** 475–7.
2. Armand C, *et al* 10 ans de détournement d'usage du Néocodion entre 1992 et 2002: Neocodion misuse: evolution between 1992 and 2002. *Therapie* 2004; **59:** 547–53.
3. Shaw JP. Drug misuse in New Zealand. *Pharm J* 1987; **238:** 607.
4. Sakol MS, Stark CR. Codeine abuse. *Lancet* 1989; **ii:** 1282.
5. Paterson JR, *et al.* Codeine abuse from co-codaprin. *Lancet* 1990; **335:** 224.
6. Sakol MS, Stark CR. Codeine abuse from co-codaprin. *Lancet* 1990; **335:** 224.

Breast feeding. Breast-fed infants of mothers taking codeine may be at an increased risk of toxicity from its metabolite, morphine, if the mother is an ultrarapid metaboliser of codeine. In a recent report,[1] a 13-day-old infant died from opioid toxicity after being exposed to morphine in his mother's breast milk; the mother had been taking oral codeine 30 mg twice daily as part of a combination preparation with paracetamol for about 2 weeks. Assayed morphine concentrations in the breast milk were found to be 87 nanograms/mL; the usual range is 1.9 to 20.5 nanograms/mL after repeated doses of codeine 60 mg four times daily. Subsequent investigations found that the mother's genotype for the cytochrome P450 isoenzyme CYP2D6 (the enzyme involved in the conversion of codeine to morphine) classified her as an ultrarapid metaboliser of codeine.

Based on this case, the FDA has advised[2] that nursing mothers taking codeine should be informed of the potential risk of morphine overdose and the need to monitor breast-fed infants for signs of toxicity such as increased sleepiness, difficulty feeding or breathing, or limpness. Nursing mothers, themselves, may also experience overdose symptoms including extreme sleepiness, confusion, shallow breathing, and severe constipation. Similar advice has also been issued by the MHRA in the UK.[3] Nonetheless, codeine appears to have been used safely for many years in breast-feeding mothers and several authorities including the American Academy of Pediatrics[4] and the *BNF* consider that it is usually compatible with breast feeding.

1. Koren G, *et al.* Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 2006; **368:** 704.
2. FDA. Information for healthcare professional: use of codeine products in nursing mothers (issued 17th August, 2007). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/codeineHCP.htm (accessed 26/06/08)
3. MHRA/CHM. Codeine: very rare risk of side-effects in breastfed babies. *Drug Safety Update* 2007; **1** (4): 3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2032917&RevisionSelectionMethod=LatestReleased (accessed 26/06/08)
4. 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 26/06/08)

Children. See Overdosage, above, and under Uses and Administration, below.

Driving. Codeine phosphate 50 mg alone and with alcohol had a deleterious effect on driving skills in a simulated driving test.[1]

1. Linnoila M, Häkkinen S. Effects of diazepam and codeine, alone and in combination with alcohol, on simulated driving. *Clin Pharmacol Ther* 1974; **15:** 368–73.

Genetic polymorphism. Life-threatening toxicity in a patient given moderate doses of codeine was thought to be due to a genotype predisposing him to ultrarapid metabolism of the drug into morphine by the cytochrome P450 isoenzyme CYP2D6, coupled with drug-induced inhibition of the usual major metabolic pathway mediated by CYP3A4, and transient reduction in renal function.[1] For a report of the effect of this genotype in a breast-feeding mother, see Breast Feeding, above.

1. Gasche Y, *et al.* Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N Engl J Med* 2004; **351:** 2827–31. Correction. *ibid.* 2005; **352:** 638.

Pregnancy. See Neonatal Abstinence Syndrome under Dependence and Withdrawal, above.

Renal impairment. The renal clearance of codeine and its metabolites is significantly reduced in patients with end-stage renal disease on regular haemodialysis therapy. One such elderly patient developed tonic-clonic seizures 7 days after starting oral codeine phosphate 30 mg 4 times daily; no further seizures occurred after codeine was stopped and naloxone started.[1] The dosage of codeine should be reduced according to renal function in patients with renal impairment but no specific recommendations appear to be given in the literature.

1. Kuo S-C, *et al.* Probable codeine phosphate-induced seizures. *Ann Pharmacother* 2004; **38:** 1848–51.

Interactions

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

Quinidine. For reference to a suggestion that quinidine can inhibit the analgesic effect of codeine, see Metabolism under Pharmacokinetics, below.

Pharmacokinetics

Codeine and its salts are absorbed from the gastrointestinal tract. Rectal absorption of codeine phosphate has been reported. Ingestion of codeine phosphate produces peak plasma-codeine concentrations in about one hour. Codeine is metabolised by *O*- and *N*-demethylation in the liver to morphine, norcodeine, and other metabolites including normorphine and hydrocodone. Metabolism to morphine is mediated by the cytochrome P450 isoenzyme CYP2D6, which shows genetic polymorphism. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid.

The plasma half-life has been reported to be between 3 and 4 hours after an oral or intramuscular dose.

Codeine crosses the placenta and is distributed into breast milk.

◊ References.

1. Guay DR, *et al.* Pharmacokinetics of codeine after single- and multiple-oral-dose administration to normal volunteers. *J Clin Pharmacol* 1987; **27:** 983–7.
2. Persson K, *et al.* The postoperative pharmacokinetics of codeine. *Eur J Clin Pharmacol* 1992; **42:** 663–6.
3. Lafolie P, *et al.* Urine and plasma pharmacokinetics of codeine in healthy volunteers: implications for drugs-of-abuse testing. *J Anal Toxicol* 1996; **20:** 541–6.
4. Kim I, *et al.* Plasma and oral fluid pharmacokinetics and pharmacodynamics after oral codeine administration. *Clin Chem* 2002; **48:** 1486–96.

Administration. In a comparative study[1] codeine had an oral/intramuscular analgesic relative potency ratio of 6:10. This was high compared with that of morphine and was attributed to protection from rapid first-pass metabolism rather than more efficient absorption after oral doses. In a comparative study in children[2] the absorption rate of codeine from a suppository was found to be similar to that from an intramuscular injection; however, peak plasma concentrations were not as high when given rectally.

1. Beaver WT, *et al.* Analgesic studies of codeine and oxycodone in patients with cancer I: comparisons of oral with intramuscular codeine and of oral with intramuscular oxycodone. *J Pharmacol Exp Ther* 1978; **207:** 92–100.
2. McEwan A, *et al.* A comparison of rectal and intramuscular codeine phosphate in children following neurosurgery. *Paediatr Anaesth* 2000; **10:** 189–93.

Metabolism. The analgesic effect of codeine may be partly due to its metabolite morphine and it has been suggested that its efficacy may be impaired in patients who are poor metabolisers of codeine[1-4] or in those who are also receiving drugs, such as quinidine, that impair its metabolism.[1] However, patients unable to demethylate codeine to produce detectable plasma concentrations of morphine obtained a similar analgesic effect to patients with detectable plasma morphine concentrations.[5] A study[6] involving infants aged 6 to 10 months has indicated that children were capable of demethylating codeine to morphine at the age of 6 months although glucuronidation of the morphine appeared to be impaired when compared with older children.

For a report of severe toxicity thought to be due to altered metabolism of codeine see Genetic Polymorphism, above.

1. Desmeules J, *et al.* Impact of environmental and genetic factors on codeine analgesia. *Eur J Clin Pharmacol* 1991; **41:** 23–6.
2. Chen ZR, *et al.* Disposition and metabolism of codeine after single and chronic doses in one poor and seven extensive metabolisers. *Br J Clin Pharmacol* 1991; **31:** 381–90.
3. Sindrup SH, *et al.* Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of sparteine. *Clin Pharmacol Ther* 1991; **49:** 686–93.
4. Williams DG, *et al.* Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. *Br J Anaesth* 2002; **89:** 839–45.
5. Quiding H, *et al.* Analgesic effect and plasma concentrations of codeine and morphine after two dose levels of codeine following oral surgery. *Eur J Clin Pharmacol* 1993; **44:** 319–23.
6. Quiding H, *et al.* Infants and young children metabolise codeine to morphine: a study after single and repeated rectal administration. *Br J Clin Pharmacol* 1992; **33:** 45–9.

Uses and Administration

Codeine, a phenanthrene derivative, is an opioid analgesic (p.104) obtained from opium or made by methylating morphine. It is much less potent as an analgesic than morphine and has relatively mild sedative effects.

Codeine or its salts, especially the phosphate, are given orally in the form of linctuses for the relief of cough, and as tablets for the relief of mild to moderate pain, often with a non-opioid analgesic such as aspirin, ibuprofen, or paracetamol. The phosphate is also given by intramuscular or subcutaneous injection, in doses similar to those used orally, for the relief of pain; the intravenous and rectal routes have also been used.

For the relief of **pain** codeine phosphate may be given in doses of 30 to 60 mg every 4 hours to a usual maximum of 240 mg daily.

To allay non-productive **cough** codeine phosphate may be given in doses of 15 to 30 mg three or four times daily.

Codeine phosphate is also used as tablets or in mixtures for the symptomatic relief of **acute diarrhoea** in doses of 15 to 60 mg given 3 or 4 times daily.

For details of doses in children, see below.

Other codeine salts used include the hydrochloride, sulfate, camsilate, and hydrobromide. Codeine polistirex (a codeine and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) is used in modified-release preparations.

Administration in children. Licensed product information for codeine in the treatment of *pain* often restricts its use to those over 1 year of age, but some authorities consider codeine to be an effective analgesic in neonates and children.[1] In the UK, the *BNFC* suggests that neonates and children aged up to 12 years may be given codeine phosphate 0.5 to 1 mg/kg every 4 to 6 hours for mild to moderate pain up to the usual adult maximum dose of 240 mg daily; these doses can be given orally, rectally, or by the subcutaneous or intramuscular routes. Guidelines[2] for analgesia in children in Accident and Emergency departments in the UK recommend the use of oral codeine as an alternative, or in addition, to diclofenac, for moderate pain such as that associated with small burns or scalds, finger tip injuries, or appendicitis. With a single dose of codeine phosphate 1 mg/kg given orally or by intramuscular injection there was a relatively small risk of respiratory depression in neonates, but significant respiratory depression has occurred with multiple doses and patients should be observed closely.[1] Case reports of adverse reactions such as vasodilatation, severe hypotension, and apnoea in infants and children after intravenous doses of codeine have precluded its use by this route in children of all ages.[3]

Antimotility drugs such as codeine should not be used in infants and young children with acute *diarrhoea*.[4,5]

The *BNFC* advises that *cough* suppressants containing pholcodine or similar opioids (such as codeine) are generally not recommended for children and should be avoided in those under 2 years of age. However, codeine phosphate is licensed to allay non-productive cough and children aged 1 to 5 years may be given 3 mg three or four times daily; and those aged 5 to 12 years, 7.5 to 15 mg three or four times daily.

Children and adolescents aged 12 years and over may be given the usual adult doses of codeine phosphate for all these indications (see above).

1. Lloyd-Thomas AR. Pain management in paediatric patients. *Br J Anaesth* 1990; **64:** 85–104.

2. British Association for Emergency Medicine. Clinical Effectiveness Committee guideline for the management of pain in children (2004). Available at: http://www.emergencymed.org.uk/BAEM/CEC/assets/cec_pain_in_children.pdf (accessed 26/06/08)
3. Marsh DF, *et al.* Opioid systems and the newborn. *Br J Anaesth* 1997; **79:** 787–95.
4. Anonymous. Drugs in the management of acute diarrhoea in infants and young children. *Bull WHO* 1989; **67:** 94–6.
5. Cimolai N, Carter JE. Antimotility agents for paediatric use. *Lancet* 1990; **336:** 874.

Administration in renal impairment. See under Precautions, above.

Cough. A systematic review[1] of over-the-counter preparations for acute cough concluded that codeine appeared no more effective than placebo in reducing cough symptoms in adults or children, although the number of patients in the studies considered was small.

See also Administration in Children, above.

1. Smith SM, *et al.* Over-the-counter medications for acute cough in children and adults in ambulatory settings. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 26/06/08).

Pain. Systematic reviews[1,2] comparing paracetamol-codeine combinations versus paracetamol alone concluded that in single-dose studies addition of codeine to paracetamol produced a comparatively small but statistically significant increase in analgesic effect; however, there was an increased incidence of adverse effects with the combination.

1. de Craen AJM, *et al.* Analgesic efficacy and safety of paracetamol-codeine combinations versus paracetamol alone: a systematic review. *BMJ* 1996; **313:** 321–5.
2. Moore A, *et al.* Single dose paracetamol (acetaminophen), with and without codeine, for postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1998 (accessed 26/06/08).

Preparations

BP 2008: Co-codamol Capsules; Co-codamol Tablets; Co-codaprin Tablets; Codeine Linctus; Codeine Phosphate Injection; Codeine Phosphate Oral Solution; Codeine Phosphate Tablets; Dispersible Co-codaprin Tablets; Effervescent Co-codamol Tablets; Paediatric Codeine Linctus;
USP 31: Acetaminophen and Codeine Phosphate Capsules; Acetaminophen and Codeine Phosphate Oral Solution; Acetaminophen and Codeine Phosphate Oral Suspension; Acetaminophen and Codeine Phosphate Tablets; Aspirin and Codeine Phosphate Tablets; Bromodiphenhydramine Hydrochloride and Codeine Phosphate Oral Solution; Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules; Carisoprodol, Aspirin, and Codeine Phosphate Tablets; Codeine Phosphate Injection; Codeine Phosphate Tablets; Codeine Sulfate Tablets; Guaifenesin and Codeine Phosphate Syrup; Terpin Hydrate and Codeine Elixir.

Proprietary Preparations (details are given in Part 3)
Austral.: Actacode; ***Austria:*** Codipertussin; Codipront Mono; Coditard; Makatussin-Hustentropfen; Tricodein; ***Belg.:*** Bromophar; Bronchodine; Bronchosedal; Eulyptan†; Gloceda†; Glottyl; Toularynx; ***Canad.:*** Codeine Contin; ***Fr.:*** Codedrill; Codenfan; Neo-Codion; Paderyl; ***Ger.:*** Antitussivum Burger; Bronchicum Mono Codein; codi OPT; Codicaps mono; Codicaps N†; Codicaps Neo; Codicompren; Codipertussin; Codipront Mono†; Makatussin Codein; Melrosum Codein Hustensirup†; Neo-Codion NN†; Optipect Kodein; Tryasol; Tussoret; ***Gr.:*** Codipront N†; ***Hong Kong:*** Codipront N†; ***India:*** Codifos; ***Irl.:*** Codant; Codinex; ***Israel:*** Codical; Rekod; ***Malaysia:*** Setlinctus†; ***Neth.:*** Bronchicum Extra Sterk; ***Port.:*** Toseina; ***Rus.:*** Neo-Codion (Нео-Кодион); ***Spain:*** Bisoltus; Codeisan; Codulin; Fludan Codeina; Histaverin; Notusin; Perduretas Codeina; Toseina; ***Switz.:*** Makatussin nouvelle formule; Tricodein†; ***UK:*** Bepro; Galcodine; ***Venez.:*** Codipront Mono.

Multi-ingredient: numerous preparations are listed in Part 3.

Croton Oil

Aceite de crotón; Oleum Crotonis; Oleum Tiglii.

CAS — 8001-28-3.

Pharmacopoeias. *Chin.* includes fruits of *Croton tiglium*.

Profile

Croton oil is an oil expressed from the seeds of *Croton tiglium* (Euphorbiaceae). Externally, it is a powerful counter-irritant and vesicant. Croton oil is also used with phenol in cosmetic chemical peeling of the skin.

Croton oil has such a violent purgative action that it should not be used as a laxative. Croton oil contains phorbol esters, which are carcinogenic.

Homoeopathy. Croton has been used in homoeopathic medicines under the following names: Croton tiglium; Crot. tig.

Preparations

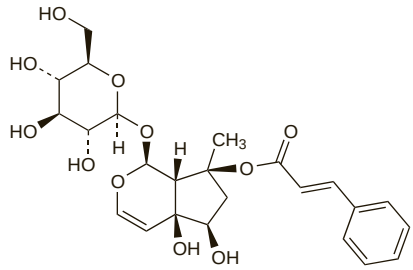
Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Canad.:*** Rheumalan†.

Devil's Claw Root

Djävulsklorot; Harpagofytový kořen; Harpagonjuuri; Harpagophyti radix; Harpagophyton; Harpagophyton, racine d'; Harpagophytum; Inkaruočių šaknys; Ördögcsáklya gyökér; Raíz de harpagofito; Teufelskrallenwurzel.

CAS — 19210-12-9 (harpagoside).



(harpagoside)

Pharmacopoeias. In *Eur.* (see p.vii), which also includes the dry extract.
Ph. Eur. 6.2 (Devil's Claw Root; Devil's Claw BP 2008). The cut and dried tuberous, secondary roots of *Harpagophytum procumbens* and/or *H. zeyheri*. Greyish-brown to dark brown with a bitter taste. Contains not less than 1.2% harpagoside ($C_{24}H_{30}O_{11}$ = 494.5), calculated with reference to the dried drug. Protect from light.

Profile

Devil's claw root is used in herbal remedies for musculoskeletal and joint disorders. Its activity is attributed in part to the plant's content of iridoid glycosides, notably harpagoside.

Pain. Preparations containing devil's claw root have been tried with some success in the treatment of musculoskeletal disorders such as low back pain and osteoarthritis. There is some evidence of efficacy for daily doses standardised to 50 to 100 mg harpagoside but the quality of reporting in trials is generally poor and further studies are needed to establish its place in therapy.[1,2]

1. Gagnier JJ, *et al.* Harpgophytum [sic] procumbens for osteoarthritis and low back pain: a systematic review. *BMC Complement Altern Med* 2004; **4:** 13.
2. Gagnier JJ, *et al.* Herbal medicine for low back pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 05/10/06).

Preparations

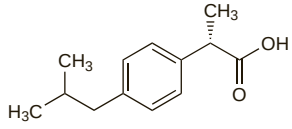
Proprietary Preparations (details are given in Part 3)
Arg.: Herbaccion Flex†; ***Braz.:*** Tenitrat; ***Fr.:*** Elusanes Harpagesic; Harpadol; Harpagocid; ***Ger.:*** Ajuta; Allya; Arthrosetten H; Arthrotabs; Bomarthros; Cefatec; Dolo-Arthrodynat†; Dolo-Arthrosetten H; Doloteffin; flexi-loges; Harpagoforte; HarpagoMega†; Harpagosan†; Herbadon†; Jucurba; Matai†; Pargo†; Rheuferm Phyto; Rheuma-Sern; Rivoltan; Sogoon; Teltonal; Teufelskralle; ***Pol.:*** Reumaphyt; ***Spain:*** Fitokey Harpagophytum; Harpagofito Orto; ***UK:*** Atrosan; Flexiherb.

Multi-ingredient: ***Austral.:*** Arthriforte; Arthritic Pain Herbal Formula 1; Bioglan Arthri Plus; Boswellia Compound; Devils Claw Plus; Extralife Arthri-Care; Guaiacum Complex†; Herbal Arthritis Formula†; Lifesystem Herbal Formula 1 Arthritic Aid†; Prost-1†; ***Belg.:*** Algi-Cool; ***Cz.:*** Antirevmaticky Caj; ***Fr.:*** Arkophytum†; ***Ger.:*** Dr Wiemanns Rheumatonikum; ***Ital.:*** Bodyguard; Cartago; Flodolor; Nevril; Pik Gel; Reumafort; ***Malaysia:*** Celery Plus†; ***Mex.:*** Rodan; ***Pol.:*** Reumaherb; ***Spain:*** Dolosul†; Natusor Harpagosinol†.

Dexibuprofen *(BAN, USAN, rINN)*

Deksibuprofeeni; Dexibuprofène; Dexibuprofeno; Dexibuprofenum; *S*-(+)-Ibuprofen.

Дексибупрофен
CAS — 51146-56-6.
ATC — M01AE14.
ATC Vet — QM01AE14.



Profile

Dexibuprofen is the *S*(+)-enantiomer of ibuprofen (p.64) and is used similarly in the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache, postoperative pain, dental pain, sprains, and soft-tissue rheumatism. It is also used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis. It may be used as an antipyretic to reduce fever.

The usual adult dose is 600 to 900 mg daily by mouth in up to 3 divided doses, adjusted according to response, to a usual maximum of 1.2 g daily. Elderly patients should be started at the lower end of the dose range; dosage may then be increased according to tolerance. Dose reductions are also recommended in patients with hepatic or renal impairment, see below.

For doses in children, see below.

◊ References.

1. Phleps W. Overview on clinical data of dexibuprofen. *Clin Rheumatol* 2001; **20** (suppl 1): S15–S21.
2. Mayrhofer F. Efficacy and long-term safety of dexibuprofen [S(+)-ibuprofen]: a short-term efficacy study in patients with osteoarthritis of the hip and a 1-year tolerability study in patients with rheumatic disorders. *Clin Rheumatol* 2001; **20** (suppl 1): S22–S29.
3. Hawel R, *et al.* Comparison of the efficacy and tolerability of dexibuprofen and celecoxib in the treatment of osteoarthritis of the hip. *Int J Clin Pharmacol Ther* 2003; **41:** 153–64.

Administration in children. Although dexibuprofen is not licensed for use in children under 18 years of age in the UK, some countries permit such use. For example, in Switzerland, dexibuprofen has been given to children aged 6 years and over; usual oral doses are 10 to 15 mg/kg daily in 2 to 4 divided doses. Licensed product information for one preparation recommends a maximum dose of 300 mg daily for those weighing less than 30 kg.

Administration in hepatic and renal impairment. UK licensed product information specifies that the initial dose of dexibuprofen should be reduced in patients with mild to moderate hepatic or renal impairment; it should not be used in those with severe impairment.

Pharmacokinetics. For mention of the metabolism of dexibuprofen, see p.65.

Further references.

1. Eller N, *et al.* Pharmacokinetics of dexibuprofen administered as 200 mg and 400 mg film-coated tablets in healthy volunteers. *Int J Clin Pharmacol Ther* 1998; **36:** 414–17.

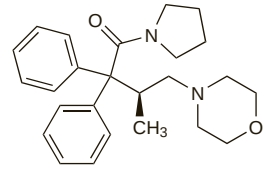
Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Dextropirac†; Dolomin†; ***Austria:*** Actifen; Eu-Med Neu; Monactil; Movone; Seractil; ***Chile:*** Dexelle; ***Cz.:*** Seractil; ***Denm.:*** Seractiv; ***Fin.:*** Dexit; ***Ger.:*** Deltaran; ***Gr.:*** Seractil; ***Hung.:*** Seractil; ***India:*** Sibet; ***Ital.:*** Seractil; ***Neth.:*** Seractil; ***Norw.:*** Seractiv; ***Pol.:*** Dexprofen; Seractil; ***Port.:*** Seractil; ***Spain:*** Atriscal; Seractil; ***Swed.:*** Tradil; ***Switz.:*** DexOptifen; Seractil; ***UK:*** Seractil.

Dextromoramide *(BAN, plNN)* ⊗

Dekstromoramidi; Dextrodiphenopyrine; Dextromoramid; Dextromoramida; Dextromoramidum; *d*-Moramid; Pyrrolamidol. (+)-1-(3-Methyl-4-morpholino-2,2-diphenylbutyryl)pyrrolidine.

Декстроморамид
$C_{25}H_{32}N_2O_2$ = 392.5.
CAS — 357-56-2.
ATC — N02AC01.
ATC Vet — QN02AC01.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of dextromoramide: Palf.

Dextromoramide Tartrate *(BANM, plNNM)* ⊗

Bitartrate de Dextromoramide; Dekstromoramiditartraatti; Dekstromoramido tartratas; Dextromoramide Acid Tartrate; Dextromoramide Hydrogen Tartrate; Dextromoramide, tartrate de; Dextromoramidi tartras; Dextromoramid-tartarát; Dextromoramidtartrat; Tartrato de dextromoramida.

Декстроморамида Тартрат
$C_{25}H_{32}N_2O_2,C_4H_6O_6$ = 542.6.
CAS — 2922-44-3.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Dextromoramide Tartrate). A white or almost white, crystalline or amorphous powder. Soluble in water; sparingly soluble in alcohol. A 1% solution in water has a pH of 3.0 to 4.0.

Profile

Dextromoramide is an opioid analgesic (p.104) structurally related to methadone (p.82). It has been used in the treatment of severe pain although it was not recommended for use in obstetric analgesia because of an increased risk of neonatal depression. Dextromoramide is subject to abuse.

Dextromoramide has been given orally as the tartrate. It has also been given rectally as suppositories and by subcutaneous or intramuscular injection.

Preparations

BP 2008: Dextromoramide Tablets.

Proprietary Preparations (details are given in Part 3)
Irl.: Palfium; ***Neth.:*** Palface; Palfium.