

**Administration in hepatic impairment.** Licensed product information recommends that doses of celecoxib should be reduced by 50% in patients with moderate hepatic impairment (Child-Pugh category B); its use is contra-indicated in those with severe impairment (Child-Pugh category C or a score of 10 or more).

**Familial adenomatous polyposis.** Celecoxib is used in the treatment of familial adenomatous polyposis, an inherited syndrome known to predispose sufferers to the development of colonic cancer (see p.666). A randomised study<sup>1,2</sup> found that treatment with celecoxib reduced the number of colonic polyps; the authors considered celecoxib to be a useful adjunct to the standard therapy of colectomy.

- Steinbach G, *et al.* The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 2000; **342**: 1946–52.
- Phillips RKS, *et al.* A randomised, double blind, placebo controlled study of celecoxib, a selective cyclooxygenase 2 inhibitor, on duodenal polyposis in familial adenomatous polyposis. *Gut* 2002; **50**: 857–60.

**Malignant neoplasms.** Celecoxib is under investigation as adjuvant therapy in the treatment of cancer;<sup>1-9</sup> preliminary results have been variable. It has also been investigated for chemoprevention of malignancy<sup>10-13</sup> (see also Familial Adenomatous Polyposis, above), but a large study for the prevention of colon cancer was terminated early because of increased cardiovascular risk.<sup>11,12</sup>

- Dang CT, *et al.* Phase II study of celecoxib and trastuzumab in metastatic breast cancer patients who have progressed after prior trastuzumab-based treatments. *Clin Cancer Res* 2004; **10**: 4062–7.
- Reardon DA, *et al.* Phase II trial of irinotecan plus celecoxib in adults with recurrent malignant glioma. *Cancer* 2005; **103**: 329–38.
- Nugent FW, *et al.* Docetaxel and cyclooxygenase-2 inhibition with celecoxib for advanced non-small cell lung cancer progressing after platinum-based chemotherapy: a multicenter phase II trial. *Lung Cancer* 2005; **48**: 267–73.
- Gasparini G, *et al.* The combination of the selective cyclooxygenase-2 inhibitor celecoxib with weekly paclitaxel is a safe and active second-line therapy for non-small cell lung cancer: a phase II study with biological correlates. *Cancer J* 2005; **11**: 209–16.
- Prince HM, *et al.* A multicenter phase II trial of thalidomide and celecoxib for patients with relapsed and refractory multiple myeloma. *Clin Cancer Res* 2005; **11**: 5504–14.
- Pan CX, *et al.* A phase II trial of irinotecan, 5-fluorouracil and leucovorin combined with celecoxib and glutamine as first-line therapy for advanced colorectal cancer. *Oncology* 2005; **69**: 63–70.
- Ferrari V, *et al.* Gemcitabine plus celecoxib (GECO) in advanced pancreatic cancer: a phase II trial. *Cancer Chemother Pharmacol* 2006; **57**: 185–90.
- Csik I, *et al.* Targeting cyclooxygenase-2 in recurrent non-small cell lung cancer: a phase II trial of celecoxib and docetaxel. *Clin Cancer Res* 2005; **11**: 6634–40.
- Chow LWC, *et al.* Serum lipid profiles in patients receiving endocrine treatment for breast cancer—the results from the Celecoxib Anti-Aromatase Neoadjuvant (CAAN) Trial. *Biomed Pharmacother* 2005; **59** (suppl 2): S302–S305.
- Limburg PJ, *et al.* Randomized, placebo-controlled, esophageal squamous cell cancer chemoprevention trial of selenomethionine and celecoxib. *Gastroenterology* 2005; **129**: 863–73.
- Solomon SD, *et al.* Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005; **352**: 1071–80.
- Bertagnolli MM, *et al.* Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med* 2006; **355**: 873–84.
- Arber N, *et al.* Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med* 2006; **355**: 885–95.

**Musculoskeletal and joint disorders.** Celecoxib is used in the treatment of osteoarthritis (p.11) and rheumatoid arthritis (p.11) including juvenile idiopathic arthritis (p.10). However, in the UK it is recommended that the use of celecoxib and other selective cyclo-oxygenase-2 (COX-2) inhibitors be limited to those patients considered to be at high risk of developing serious gastrointestinal problems if given a non-selective NSAID and who do not have pre-existing cardiovascular risk factors (see Adverse Effects, above).

Celecoxib is also used in the treatment of ankylosing spondylitis (see Spondyloarthropathies, p.13).

#### References.

- Bensen WG, *et al.* Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. *Mayo Clin Proc* 1999; **74**: 1095–1105.
- Simon LS, *et al.* Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA* 1999; **282**: 1921–28.
- Emery P, *et al.* Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. *Lancet* 1999; **354**: 2106–11.
- Douglas M, *et al.* Efficacy of celecoxib, a cyclooxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal antiinflammatory drug. *Arthritis Rheum* 2001; **44**: 180–5.

- Stengaard-Pedersen K, *et al.* Celecoxib 200 mg qd is efficacious in the management of osteoarthritis of the knee or hip regardless of the time of dosing. *Rheumatology (Oxford)* 2004; **43**: 592–5.
- Schnitzer TJ, *et al.* VACT-1 and VACT-2 (Protocols 106 and 150) Study Groups. Efficacy of rofecoxib, celecoxib, and acetaminophen in patients with osteoarthritis of the knee: a combined analysis of the VACT studies. *J Rheumatol* 2005; **32**: 1093–1105.
- Singh G, *et al.* Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-1 Study. *Am J Med* 2006; **119**: 255–66.
- Barkhuizen A, *et al.* Celecoxib is efficacious and well tolerated in treating signs and symptoms of ankylosing spondylitis. *J Rheumatol* 2006; **33**: 1805–12.
- Luyten FP, *et al.* A prospective randomised multicentre study comparing continuous and intermittent treatment with celecoxib in patients with osteoarthritis of the knee or hip. *Ann Rheum Dis* 2007; **66**: 99–106.

**Palmar-plantar erythrodysesthesia syndrome.** Celecoxib has been investigated in the treatment of capecitabine-induced hand-foot (palmar-plantar erythrodysesthesia) syndrome; for references, see under Adverse Effects and Precautions of Capecitabine, p.692.

## Preparations

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

**Arg.:** Algybrex; Celebrix; Celemax; Cloxib; Coxelt; Coxent; Niflam; Radicaine; Tisorekt; **Austral.:** Celebrix; **Austria:** Celebrix; Solexa; **Belg.:** Celebrix; **Braz.:** Celebra; **Canad.:** Celebrix; **Chile:** Celebra; **Cz.:** Celebrix; **Onsenal; Denm.:** Celebra; **Fin.:** Celebra; **Fr.:** Celebrix; **Onsenal; Ger.:** Celebra; **Gr.:** Adalex; Celebrix; **Hong Kong:** Celebrix; **Hung.:** Celebrix; **India:** Celebri; Celib; Cobix; Orthocel; Ultracel; Zycel; **Indon.:** Celebrix; **Irl.:** Celebrix; **Israel:** Celcox; Celebra; **Ital.:** Artilog; Celebrix; Solexa; **Malaysia:** Celebrix; **Mex.:** Celebrix; **Neth.:** Celebrix; **Onsenal; Solexa; Norw.:** Celebra; **Onsenal; NZ:** Celebrix; **Philipp.:** Celebrix; **Flamar; Pol.:** Celebrix; **Port.:** Celebrix; **Onsenal; Solexa; Rus.:** Celebrix (Левобрекс); **S.Afr.:** Celebrix; **Singapore:** Celebrix; **Spain:** Celebrix; **Onsenal; Swed.:** Celebra; **Onsenal; Switz.:** Celebrix; **Thai.:** Celebrix; **UK:** Celebrix; **USA:** Celebrix; **Venez.:** Celebrix; Cexb.

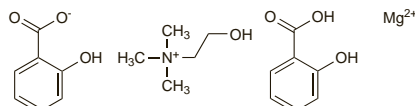
## Choline Magnesium Trisalicylate

Trisalicilato de colina y magnesio.

Холин Магнезиум Трисалицилати

C<sub>26</sub>H<sub>29</sub>O<sub>10</sub>NMg = 539.8.

CAS — 64425-90-7.



## Adverse Effects, Treatment, and Precautions

As for Aspirin, p.20.

The use of aspirin and other acetylated salicylates is generally not recommended for children unless specifically indicated, because of the risk of Reye's syndrome. US licensing information extends this precaution to choline magnesium trisalicylate.

## Effects on the liver. References.

- Cersosimo RJ, Matthews SJ. Hepatotoxicity associated with choline magnesium trisalicylate: case report and review of salicylate-induced hepatotoxicity. *Drug Intell Clin Pharm* 1987; **21**: 621–5.
- Nadkarni MM, *et al.* Eosinophilic hepatitis after ingestion of choline magnesium trisalicylate. *Am J Gastroenterol* 1992; **87**: 151–3.

## Interactions

For interactions associated with salicylates, see Aspirin, p.23.

## Uses and Administration

Choline magnesium trisalicylate is a combination of the salicylic acid derivatives choline salicylate (p.36) and magnesium salicylate (p.79). It has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (p.23). After oral administration, choline magnesium trisalicylate dissociates and the salicylate moiety is rapidly absorbed. Each unit dose of 500 mg of salicylate is provided by about 293 mg of choline salicylate with 362 mg of magnesium salicylate (anhydrous). Choline magnesium trisalicylate has been used in osteoarthritis, rheumatoid arthritis, and other arthritides in oral doses equivalent to 1 or 1.5 g of salicylate twice daily; doses may also be given as a single daily dose if required. A dose of 750 mg given three times daily may be more suitable for elderly patients. Choline magnesium trisalicylate is also used in similar doses in the general management of other forms of pain and for fever.

## Preparations

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

**Canad.:** Trilisate; **USA:** Trilisate.

## Choline Salicylate (BAN, USAN, rINN)

Choline, Salicylate de; Cholini Salicylas; Koliinisalicylaatti; Kolinsalicylat; Salicilato de colina. (2-Hydroxyethyl)trimethylammonium salicylate.

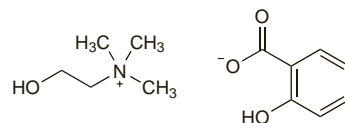
Холина Салицилат

C<sub>12</sub>H<sub>19</sub>NO<sub>4</sub> = 241.3.

CAS — 2016-36-6.

ATC — N02BA03.

ATC Vet — QN02BA03.



**Pharmacopoeias.** *Br.* includes a solution.

**BP 2008** (Choline Salicylate Solution). An aqueous solution containing 47.5 to 52.5% of choline salicylate. It is a clear colourless liquid. It may contain a suitable antimicrobial preservative.

## Profile

Choline salicylate is a salicylic acid derivative (see Aspirin, p.20) used in the treatment of pain and fever, and in the management of rheumatic disorders. In terms of salicylate content, choline salicylate 435 mg is equivalent to about 325 mg of aspirin. Choline salicylate is given orally in doses of 435 to 870 mg every four hours as necessary for pain and fever, and in doses of 4.8 to 7.2 g daily in divided doses for rheumatic disorders.

Choline salicylate is also used as a local analgesic. Solutions containing up to about 20% choline salicylate are used in ear disorders such as the relief of pain in otitis media and externa but are considered to be of doubtful value; they are also used to soften ear wax as an aid to removal (see p.1725). An 8.7% gel is used for lesions of the mouth (p.1700). Choline salicylate has also been applied topically in a rubefacient preparation for the relief of muscular and rheumatic pain.

Choline salicylate is also given in the form of choline magnesium trisalicylate (see above).

**Adverse effects.** A 21-month-old boy developed salicylate poisoning after his mother had rubbed the contents of 3 tubes of *Bonjela* teething ointment (containing a total of 2.61 g of choline salicylate) on his gums over 48 hours.<sup>1</sup>

In another case, an 8-year-old boy with G6PD deficiency developed an oral mucosal burn a few hours after application of about half a tube of *Teelgel* oral gel.<sup>2</sup> He developed mouth ulcers and displayed signs of apathy, lethargy, and nasal congestion 3 days after exposure. His condition improved after a week. The authors felt that G6PD deficiency may have been a contributing factor in the occurrence of adverse effects.

- Paynter AS, Alexander FW. Salicylate intoxication caused by teething ointment. *Lancet* 1979; **ii**: 1132.
- Sapir S, Bimstein E. Cholinisalicylate gel induced oral lesion: report of case. *J Clin Pediatr Dent* 2000; **24**: 103–6.

**REYE'S SYNDROME.** The link between aspirin use in children and the development of Reye's syndrome is established although the evidence for other salicylates could not be adequately evaluated (see p.22). However, a 20-month-old boy who had received a teething gel containing choline salicylate (applied in doses of 1.31 g daily, equivalent to acetylsalicylate 100 mg/kg daily, which exceeds the recommended dose) developed Reye's syndrome following a viral illness.<sup>1</sup> The authors noted that the MHRA in the UK were aware of two earlier reports suggesting an association between choline salicylate and Reye's syndrome.

- Oman TK, *et al.* Topical choline salicylates implicated in Reye's syndrome. *BMJ* 2008; **336**: 1376.

## Preparations

**BP 2008:** Choline Salicylate Ear Drops; Choline Salicylate Oromucosal Gel.

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

**Arg.:** Dercolina; **Austral.:** Applacaine; Herron Baby Teething Gel; Ora-Sed Jel; **Belg.:** Teejel; **Ger.:** Audax; **Hong Kong:** Ora-Sed; **India:** Gelora; **Zytec; Irl.:** Audax; Teejel; **Israel:** Teejel; **NZ:** Ora-Sed; **Pol.:** Choline; **Otinum; Port.:** Bucage; **Rus.:** Otinum (Отинум); **Singapore:** Ora-Sed; **UK:** Audax; **Dinnefords Teejel; USA:** Arthropant.

**Multi-ingredient Arg.:** Pansoral; **Austral.:** Bonjela; Seda-Gel; **Austria:** Mundisal; **Belg.:** Givalex; **Cz.:** Mundisal; **Fr.:** Givalex; Pansoral; **Ger.:** Givalex; **India:** Mundisal; **Gr.:** Mundisal; **Hong Kong:** Bonjela; Dermojela; **Hung.:** Mundisal; **Irl.:** Bonjela; **Israel:** Baby Gum; Bonjela; **Malaysia:** Bonjela; **Oregel; NZ:** Bonjela; **Pol.:** Sachol zel Stomatologiczny; **Rus.:** Cholisal (Холисал); Pansoral (Пансорал); **S.Afr.:** Bonjela; **Singapore:** Bonjela; **Soragel; Spain:** Aldo Otico; **Switz.:** Mundisal; Pansoral; Tenderdol; **Thai.:** Bonjela; **UK:** Bonjela; Earex Plus.

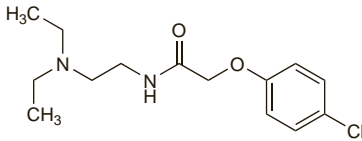
**Clofexamide** (rINN)

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

Клофексамида

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

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

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

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.

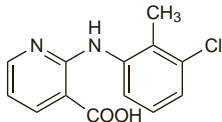
**Clonixin** (USAN, rINN)

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** (rINN)

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

Клониксина Лизин

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

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; Diclén; Dolex; Dolnot†; Dorixina; **Braz.:** Dolamin; **Chile:** Blonax; Celex; Clonalgin; Colmax; Dentagesic; Diminon; Dolalgial†; Lafagesic; Medigesic; Nefersil; Traumacid; **Mex.:** Disinal; Donodol; Dorixina; Firac; Lonixer; Prestadol; 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; Propalgín; Sertal Composto; **Braz.:** Dolamin Flex; **Chile:** Clonalgin Composto; Ergonef; Migra-Nefersil; Nefersil B; Neurocam; **Mex.:** Donodol Composto; Espacil Composto; Firac Plus; Klonaza; Optium; Plián Composto; Prestadol Composto; Yuredol; **Venez.:** Dologinex; Dorixina Flex; Migradorixina; Plián Composto.

**Codeine** (BAN)

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

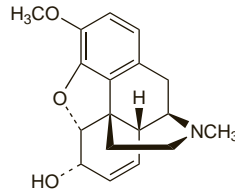
Кодеин

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

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; Kodeinihydroklorididihydraatti; Kodein-hidroklorid-dihidrát; Kodein-hydrochlorid dihydrát; Kodeinhydroklorididihydrát; Kodeino hydrochloridas dihidratas.

Кодеина Гидрохлорид

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

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; Kodeiniinofosfaatti; Kodein-fosfát hemihydrát; Kodeinofosfathemi; Kodein-foszfát-hemihidrát; Kodeino fosfatas hemihidratas; Kodeiny fosforan; Kodeiny fosforan półwodny; Methylmorphine Phosphate.

Кодеина Фосфат

$C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot H_2O = 406.4$ .

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.<sup>1</sup> *Animal* work suggested that the analgesic activity of codeine was not affected by acetylation.<sup>2</sup>

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

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

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.<sup>1</sup>

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.<sup>1</sup>

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.<sup>1</sup> 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  $\mu$ -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.<sup>1</sup> There was no history of alcohol consumption and her recovery was uneventful. Other cases have been reported.<sup>2,3</sup>

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-codeine. *Gastroenterol Clin Biol* 2003; **27**: 124–5.
3. Kohlen K, *et al.* Codein-induzierte Pankreatitis. *Dtsch Med Wochenschr* 2005; **130**: 878–9.
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**Effects on the skin.** Pruritus and burning erythematous-vesicular plaques that developed in a patient in response to oral codeine were attributed to a fixed drug eruption.<sup>4</sup> A similar reaction occurred in another patient after taking various analgesics including a combined preparation of paracetamol and codeine;<sup>2</sup> patch testing showed a positive response for codeine only. Maculopapular rash has been seen as part of a hypersensitivity syndrome