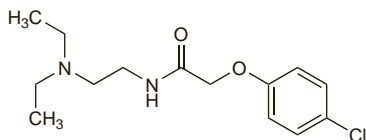


**Clofexamide** (rINN)

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; Clofezina; 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.

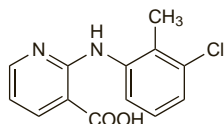
**Profile**

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.

- 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)

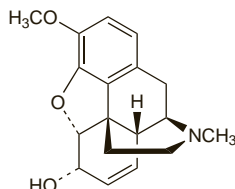
**Arg.:** Clonixil; Diclén; Dolex; Dolnot†; Dorixina; **Braz.:** Dolamin; **Chile:** Blonax; Celex; Clonalgin; Colmax; Dentagesic; Diminon; Dolalgial†; Lafagesic; Medigesic; Nefersil; Traumacid; **Mex.:** Disinal; Donodol; Dorixina; Firac; Lonixer; Prestadol; Sedeproin; **Port.:** Algimate; Clonix; **Spain:** 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; Espadol Compuesto; Firac Plus; Klonaxa; Optium; Pli-dan Compuesto; Prestadol Compuesto; Yuredol; **Venez.:** Dologinex; Dorixina Flex; Migradorixina; Pli-dan Compuesto.

**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, hidrocloreto de; Codéine (chlorhydrate de) dihydrát; Codeini hydrochloridum dihydricum; Kodeinihydroklorididihydrát; 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; Kodeiniinofsaatti; Kodein-fosfát hemihydrát; Kodeinfosfáthem; Kodein-foszfát-hemihidrát; Kodeino fosfatas hemihidratas; Kodeiny fosforan; Kodeiny fosforan potwody; 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>

- Galante RN, et al. Solid-state acetylation of codeine phosphate by aspirin. *J Pharm Sci* 1979; **68**: 1494–8.
- 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>

- 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>

- 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.

- 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>2,5</sup>

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

**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>1</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