Uses and Administration

Etoricoxib is an NSAID (p.96) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It is used in the symptomatic relief of rheumatoid arthritis, osteoarthritis, and acute gouty arthritis.

In osteoarthritis, etoricoxib is given orally in a usual dose of 30 mg once daily, increased to 60 mg once daily if necessary. The recommended dose in rheumatoid arthritis is 90 mg once daily; higher doses of 120 mg once daily are used in gouty arthritis although such doses should only be used for the acute symptomatic period and for a maximum of 8 days. For dosage recommendations in patients with hepatic impairment, see below.

◊ References.

1. Patrignani P, *et al.* Clinical pharmacology of etoricoxib: a novel selective COX2 inhibitor. *Expert Opin Pharmacother* 2003; **4:** 265–84.
2. Dallob A, *et al.* Characterization of etoricoxib, a novel, selective COX-2 inhibitor. *J Clin Pharmacol* 2003 **43:** 573–85.
3. Martina SD, *et al.* Etoricoxib: a highly selective COX-2 inhibitor. *Ann Pharmacother* 2005; **39:** 854–62.

Administration in hepatic impairment. The maximum oral dose of etoricoxib in patients with mild hepatic impairment (Child-Pugh score of 5 to 6), regardless of indication, is 60 mg once daily; those with moderate impairment (Child-Pugh 7 to 9) should be given a maximum of 60 mg every other day or 30 mg once daily. Etoricoxib should not be given to patients with severe hepatic impairment (Child-Pugh 10 or more).

Musculoskeletal and joint disorders. The selective cyclo-oxygenase-2 (COX-2) inhibitor etoricoxib is used in the treatment of the musculoskeletal disorders osteoarthritis and rheumatoid arthritis (see p.11 and p.11, respectively). However, in the UK, it is recommended that the use of selective COX-2 inhibitors is limited to those patients considered to be at high risk of developing serious gastrointestinal problems if given a non-selective NSAID (see p.97).

Etoricoxib is also used in gouty arthritis (p.552) and has been tried in the treatment of ankylosing spondylitis (see Spondyloarthropathies, p.13).

References.

1. Cochrane DJ, *et al.* Etoricoxib. *Drugs* 2002; **62:** 2637–51.
2. Schumacher HR, *et al.* Randomised double blind trial of etoricoxib and indometacin in treatment of acute gouty arthritis. *BMJ* 2002; **324:** 1488–92.
3. Gottesdiener K, *et al.* Results of a randomized, dose-ranging trial of etoricoxib in patients with osteoarthritis. *Rheumatology (Oxford)* 2002; **41:** 1052–61.
4. Wiesenhutter CW, *et al.* Evaluation of the comparative efficacy of etoricoxib and ibuprofen for treatment of patients with osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2005; **80:** 470–9.
5. van der Heijde D, *et al.* Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study. *Arthritis Rheum* 2005; **52:** 1205–15.
6. Curtis SP, *et al.* Etoricoxib in the treatment of osteoarthritis over 52-weeks: a double-blind, active-comparator controlled trial [NCT00242489]. *BMC Musculoskelet Disord* 2005; **6:** 58. Available at: http://www.biomedcentral.com/content/pdf/1471-2474-6-58.pdf (accessed 01/11/07)
7. Bingham CO, *et al.* Efficacy and safety of etoricoxib 30 mg and celecoxib 200 mg in the treatment of osteoarthritis in two identically designed, randomized, placebo-controlled, non-inferiority studies. *Rheumatology (Oxford)* 2007; **46:** 496–507.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Arcoxia; ***Austria:*** Arcoxia; Auxib; ***Belg.:*** Arcoxia; ***Braz.:*** Arcoxia; ***Cz.:*** Arcoxia; ***Denm.:*** Arcoxia; ***Fin.:*** Arcoxia; ***Fr.:*** Arcoxia; ***Ger.:*** Arcoxia; ***Gr.:*** Arcoxia; ***Hong Kong:*** Arcoxia; ***India:*** Ebov; Ecoxib†; Etoxib; Etozox; Kretos†; Nucoxia; ***Indon.:*** Arcoxia; ***Irl.:*** Arcoxia; ***Israel:*** Arcoxia; ***Ital.:*** Algix; Arcoxia; Tauxib; ***Malaysia:*** Arcoxia; ***Mex.:*** Arcoxia; ***Neth.:*** Arcoxia; Auxib; ***Norw.:*** Arcoxia; ***NZ:*** Arcoxia; ***Philipp.:*** Arcoxia; ***Port.:*** Arcoxia; Exxiv; Turox; ***Singapore:*** Arcoxia; ***Spain:*** Arcoxia; ***Swed.:*** Arcoxia; ***Thai.:*** Arcoxia; ***UK:*** Arcoxia; ***Venez.:*** Arcoxia.

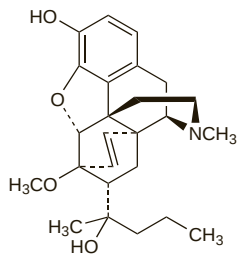
Etorphine Hydrochloride *(BANM, rINNM)*

Étorphine, Chlorhydrate d'; Etorphini Hydrochloridum; Hidrocloruro de etorfina; M-99; 19-Propylorvinol Hydrochloride. (6*R*,7*R*,14*R*)-7,8-Dihydro-7-[(1*R*)-1-hydroxy-1-methylbutyl]-6-*O*-methyl-6,14α-ethenomorphine hydrochloride; (2*R*)-2-[(–)-(5*R*,6*R*,7*R*,14*R*)-4,5-Epoxy-3-hydroxy-6-methoxy-9a-methyl-6,14-ethenomorphinan-7-yl]pentan-2-ol hydrochloride.

Эторфина Гидрохлорид

$C_{25}H_{33}NO_4$,HCl = 448.0.

CAS — 14521-96-1 (etorphine); 13764-49-3 (etorphine hydrochloride).



(etorphine)

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2008 (Etorphine Hydrochloride). A white or almost white microcrystalline powder. Sparingly soluble in water and in alcohol; very slightly soluble in chloroform; practically insoluble in ether. A 2% solution in water has a pH of 4.0 to 5.5. Protect from light.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102. Etorphine is not used therapeutically in humans.

Etorphine hydrochloride is highly potent and rapid acting; minute amounts can exert serious effects leading to coma. It may be absorbed through skin and mucous membranes. It is thus advisable to inject an antagonist *immediately* after contamination of skin or mucous membranes with preparations containing etorphine hydrochloride and to wash the affected areas copiously. Accidental injection or needle scratch injuries should also be treated immediately by injecting an antagonist. Naloxone is preferred as the antagonist in medical treatment. However, veterinary preparations of etorphine are supplied with a preparation (*Revivon*) containing diprenorphine hydrochloride (p.1445) and this should be used for immediate first-aid antagonism if naloxone is not available.

Uses and Administration

Etorphine hydrochloride is a highly potent opioid analgesic (p.104) used for reversible neuroleptanalgesia (see Anaesthetic Techniques, p.1780) in veterinary medicine. It is given with acepromazine maleate or levomepromazine (*Immobilon*) to restrain animals and before minor veterinary surgery. The duration of action of etorphine is up to about 45 to 90 minutes depending on the species but it may be longer in man, especially if the large animal preparation is involved.

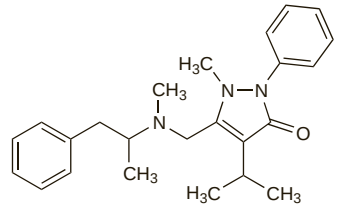
Famprofazone *(BAN, rINN)* ⊗

Famprofazona; Famprofazonum. 4-Isopropyl-2-methyl-3-[methyl(α-methylphenethyl)aminomethyl]-1-phenyl-3-pyrazolin-5-one.

Фампрофазон

$C_{24}H_{31}N_3O$ = 377.5.

CAS — 2288 1-35-2.



Profile

Famprofazone has analgesic and antipyretic properties and has been given orally, usually with other analgesics.

Pharmacokinetics. On ingestion, metabolic products of famprofazone include amfetamine and metamfetamine enantiomers,[1,2] which has led to false positive results on drug testing.[3] For sporting competition famprofazone was classified by the World Anti-Doping Agency as a stimulant.[4]

1. Greenhill B, *et al.* Metabolic profile of amphetamine and methamphetamine following administration of the drug famprofazone. *J Anal Toxicol* 2003; **27:** 479–84.
2. Rodriguez AT, *et al.* Metabolic profile of famprofazone following multidose administration. *J Anal Toxicol* 2004; **28:** 432–8.
3. Musshoff F, Kraemer T. Identification of famprofazone ingestion. *Int J Legal Med* 1998; **111:** 305–8.
4. World Anti-Doping Agency. The world anti-doping code: the 2008 prohibited list international standard. Available at: http://www.wada-ama.org/rtecontent/document/2008_List_En.pdf (accessed 24/07/08)

Felbinac *(BAN, USAN, rINN)*

CL-83544; Felbinaakki; Felbinaco; Felbinacum; Felbinak; LJC-10141. Biphenyl-4-ylacetic acid.

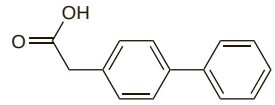
Фелбинак

$C_{14}H_{12}O_2$ = 212.2.

CAS — 5728-52-9.

ATC — M02AA08.

ATC Vet — QM02AA08.



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

Ph. Eur. 6.2 (Felbinac). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in methyl alcohol.

Adverse Effects and Precautions

Mild local reactions such as erythema, dermatitis, and pruritus have occurred in patients using felbinac topically. More serious adverse effects including bullous dermatoses such as epidermal necrolysis and erythema multiforme, photosensitivity, anaphylaxis, and bronchospasm or wheeziness have also been reported. Gastrointestinal disturbances may occur.

Felbinac preparations should be avoided in patients with a history of hypersensitivity reactions to aspirin or other NSAIDs.

Incidence of adverse effects. The UK CSM had received 49 reports of adverse reactions associated with felbinac by October 1989, about 11 months after it was released on the UK market.[1] Bronchospasm or wheeziness was reported in 8 patients using felbinac gel. Four of these patients had a history of asthma of whom 3 were reported to have had a similar reaction to aspirin or other NSAIDs. Other reported reactions included skin rashes (17 cases), local application site reactions (7), and dyspepsia (6).

1. CSM. Felbinac (Traxam) and bronchospasm. *Current Problems 27* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024444&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)

Uses and Administration

Felbinac, an active metabolite of fenbufen (below), is an NSAID (p.99). It is used topically in the symptomatic treatment of musculoskeletal pain including that due to soft-tissue injuries. It is applied as a 3% gel or a 3.17% foam to unbroken skin over affected areas 2 to 4 times daily. The total daily dose of gel or foam should not exceed 25 g regardless of the size or number of affected areas. Therapy should be reviewed after 14 days.

Diisopropanolamine felbinac has been used similarly.

◊ References.

1. Hosie GAC. The topical NSAID, felbinac, versus oral ibuprofen: a comparison of efficacy in the treatment of acute lower back injury. *Br J Clin Res* 1993; **4:** 5–17.

Preparations

BP 2008: Felbinac Cutaneous Foam; Felbinac Gel.

Proprietary Preparations (details are given in Part 3)

Austria: Target†; ***Belg.:*** Flexfree; ***Ger.:*** Spalt Schmerz-Gel†; ***Irl.:*** Traxam; ***Ital.:*** Dolinac; Traxam; ***Jpn:*** Seltouch; ***Switz.:*** Dolo Target†; ***UK:*** Traxam.

Fenbufen *(BAN, USAN, rINN)*

CL-82204; Fenbufeeni; Fenbufén; Fenbufenas; Fenbufène; Fenbufenum. 4-(Biphenyl-4-yl)-4-oxobutyric acid.

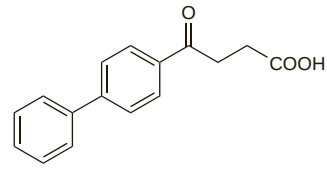
Фенбуфен

$C_{16}H_{14}O_3$ = 254.3.

CAS — 36330-85-5.

ATC — M01AE05.

ATC Vet — QM01AE05.



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

Ph. Eur. 6.2 (Fenbufen). A white or almost white, fine crystalline powder. Very slightly soluble in water; slightly soluble in alcohol, in acetone, and in dichloromethane.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96, although the commonest adverse effects of fenbufen are skin rashes,

usually occurring within the first 2 weeks of therapy, and particularly in women and in patients with seronegative rheumatoid arthritis or psoriatic arthritis. Disorders such as epidermal necrolysis, erythema multiforme, and Stevens-Johnson syndrome have also been reported. A small number of patients who develop rash may go on to develop a severe illness characterised by pulmonary eosinophilia or allergic alveolitis. Treatment with fenbufen should be stopped immediately if a rash appears.

Breast feeding. UK licensed product information advises that fenbufen should be avoided in breast-feeding mothers, because of the presence of its metabolites in breast milk.

Effects on the blood. Haemolytic anaemia[1] and aplastic anaemia[2] have been reported in patients receiving fenbufen.

1. Martland T, Stone WD. Haemolytic anaemia associated with fenbufen. *BMJ* 1988; **297:** 921.
2. Andrews R, Russell N. Aplastic anaemia associated with a non-steroidal anti-inflammatory drug: relapse after exposure to another such drug. *BMJ* 1990; **301:** 38.

Effects on the lungs. In January 1989 the UK CSM reported that it had received 7 reports of a suspected association between rash and an allergic interstitial lung disorder in patients receiving fenbufen.[1] In 5 patients, the lung disorder was diagnosed as pulmonary eosinophilia; in the 2 other patients the pulmonary component of the reaction was described as allergic alveolitis. Several of these reactions have been reported in the literature.[2,3]

1. CSM. Fenbufen, rash and pulmonary eosinophilia. *Current Problems 24* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024431&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)
2. Swinburn CR. Alveolitis and haemolytic anaemia induced by azapropazone. *BMJ* 1987; **294:** 375.
3. Burton GH. Rash and pulmonary eosinophilia associated with fenbufen. *BMJ* 1990; **300:** 82–3.

Effects on the skin. In September 1988 the UK CSM reported[1] that it was still receiving large numbers of reports of adverse reactions to fenbufen when such reports were expected to have declined. Fenbufen was the most commonly reported suspect drug in 1986 and 1987. At the time of the report more than 6000 such reports had been received, 80% concerning mucocutaneous reactions and most involving a generalised florid erythematous rash, often with pruritus. There were 178 reports of erythema multiforme, 30 of Stevens-Johnson syndrome, and 2 fatalities.

1. CSM. Fenbufen and mucocutaneous reactions. *Current Problems 23* 1988. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024430&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)

Hypersensitivity. See under Effects on the Lungs (above).

Interactions

For interactions associated with NSAIDs, see p.99.

Use of fenbufen with aspirin may result in decreased serum concentrations of fenbufen and its metabolites.

Pharmacokinetics

Fenbufen is absorbed from the gastrointestinal tract after oral use and peak plasma concentrations are reached in about 70 minutes. Fenbufen is over 99% bound to plasma proteins. It is metabolised in the liver to the active metabolites, biphenylacetic acid and 4-hydroxy-biphenylbutyric acid. Fenbufen and its metabolites are reported to have plasma half-lives of about 10 to 17 hours and are mainly eliminated as conjugates in the urine. Metabolites of fenbufen have been detected in breast milk in small amounts.

Uses and Administration

Fenbufen, a propionic acid derivative, is an NSAID (p.99). It is given for the relief of pain and inflammation associated with musculoskeletal and joint disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis in oral doses of 900 mg daily; the dose may be either 450 mg in the morning and evening or 300 mg in the morning with 600 mg in the evening.

Preparations

BP 2008: Fenbufen Capsules; Fenbufen Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Lederfen†; ***Indon.:*** Cybufen; ***Irl.:*** Lederfen; ***Port.:*** Basifen; Reugast†; ***Thai.:*** Cepal; Cinopal†; ***Turk.:*** Cinopal; ***UK:*** Lederfen.

Fenoprofen Calcium *(BANM, USAN, rINNM)*

Calcii Fenoprofenum; Fénoprofène Calcique; Fenoprofeno cálcico; Lilly-69323; Lilly-53858 (fenoprofen); Lilly-61169 (fenoprofen sodium). Calcium (±)-2-(3-phenoxyphenyl)propionate dihydrate.

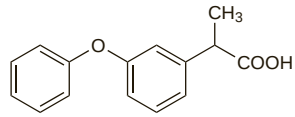
Кальций Фенопрофен

$(C_{15}H_{13}O_3)_2Ca,2H_2O$ = 558.6.

CAS — 31879-05-7 (fenoprofen); 34597-40-5 (anhydrous fenoprofen calcium); 53746-45-5 (fenoprofen calcium dihydrate).

ATC — M01AE04.

ATC Vet — QM01AE04.



(fenoprofen)

Pharmacopoeias. In *Br.*, *Chin.*, and *US.*
BP 2008 (Fenoprofen Calcium). A white or almost white odourless or almost odourless crystalline powder. Slightly soluble in water and in chloroform; soluble in alcohol.
USP 31 (Fenoprofen Calcium). A white crystalline powder. Slightly soluble in water, in methyl alcohol, and in n-hexanol; practically insoluble in chloroform. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Dysuria, cystitis, haematuria, interstitial nephritis, and acute renal insufficiency have been reported with fenoprofen. Nephrotic syndrome, which may be preceded by fever, rash, arthralgia, oliguria, azotaemia, and anuria, has also occurred. Upper respiratory-tract infection and nasopharyngitis have been reported. There have been reports of severe hepatic reactions, including jaundice and fatal hepatitis.

Breast feeding. Fenoprofen is distributed into breast milk although the amount is considered by the *BNF* to be too small to be harmful to a breast-fed infant. In contrast, licensed product information does not recommend its use since safety has not been established.

Effects on the blood. Haematological adverse effects including agranulocytosis,[1] aplastic anaemia,[2] and thrombocytopenia[3,4] have been reported in patients taking fenoprofen; licensed product information also reports haemolytic anaemia.

1. Simon SD, Kosmin M. Fenoprofen and agranulocytosis. *N Engl J Med* 1978; **299:** 490.
2. Ashraf M, *et al.* Aplastic anaemia associated with fenoprofen. *BMJ* 1982; 284: 1301–2.
3. Simpson RE, *et al.* Acute thrombocytopenia associated with fenoprofen. *N Engl J Med* 1978; **298:** 629–30.
4. Katz ME, Wang P. Fenoprofen-associated thrombocytopenia. *Ann Intern Med* 1980; **92:** 262.

Effects on the liver. Cholestatic jaundice and hepatitis developed in a 68-year-old woman after receiving fenoprofen 600 mg four times daily for 7 weeks. Subsequent use of naproxen and indometacin did not result in hepatotoxicity.[1] However, there has been a report of cross-hepatotoxicity between fenoprofen and naproxen.[2]

1. Stennett DJ, *et al.* Fenoprofen-induced hepatotoxicity. *Am J Hosp Pharm* 1978; **35:** 901.
2. Andrejak M, *et al.* Cross hepatotoxicity between non-steroidal anti-inflammatory drugs. *BMJ* 1987; **295:** 180–1.

Effects on the skin. Toxic epidermal necrolysis was associated with fenoprofen in 2 patients.[1]

1. Stotts JS, *et al.* Fenoprofen-induced toxic epidermal necrolysis. *J Am Acad Dermatol* 1988; **18:** 755–7.

Overdosage. A report of coma, respiratory depression, hypotension, and metabolic acidosis in a patient who had ingested between 24 and 36 g of fenoprofen.[1] The patient responded to gastric lavage and activated charcoal and intensive supportive care.

1. Kolodzik JM, *et al.* Nonsteroidal anti-inflammatory drugs and coma: a case report of fenoprofen overdose. *Ann Emerg Med* 1990; **19:** 378–81.

Interactions

For interactions associated with NSAIDs, see p.99.

Aspirin is reported to reduce plasma concentrations of fenoprofen.

Antiepileptics. *Phenobarbital* might increase the rate of metabolism of fenoprofen.[1] US licensed product information suggests that dosage adjustment of fenoprofen may be required when given with phenobarbital.

1. Helleberg L, *et al.* A pharmacokinetic interaction in man between phenobarbitone and fenoprofen, a new anti-inflammatory agent. *Br J Clin Pharmacol* 1974; **1:** 371–4.

Pharmacokinetics

Fenoprofen is readily absorbed from the gastrointestinal tract; bioavailability is about 85% but food and milk may reduce the rate and extent of absorption. Peak plasma concentrations occur 1 to 2 hours after a dose. The plasma half-life is about 3 hours. Fenoprofen is 99% bound to plasma proteins. About 90% of a dose is excreted in the urine in 24 hours, chiefly as the glucuronide and the glucuronide of hydroxylated fenoprofen. Fenoprofen is distributed into breast milk.

Uses and Administration

Fenoprofen, a propionic acid derivative, is an NSAID (p.99) used in the management of mild to moderate pain and for the relief of pain and inflammation associated with disorders such as osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. It is given as the calcium salt although doses are expressed in terms of the base; fenoprofen calcium (dihydrate) 1.2 g is equivalent to about 1 g of fenoprofen. A usual oral dose is the equivalent of 300 to 600 mg of fenoprofen three or four times daily, adjusted thereafter according to response. In the USA, lower doses of 200 mg every 4 to 6 hours are recommended for mild to moderate pain. It has been recommended that the total daily dose should not exceed 3 g (UK) or 3.2 g (USA).

Preparations

BP 2008: Fenoprofen Tablets;
USP 31: Fenoprofen Calcium Capsules; Fenoprofen Calcium Tablets.

Proprietary Preparations (details are given in Part 3)
Braz.: Trandor†; ***Canad.:*** Nalfon†; ***Denm.:*** Nalfon†; ***Fr.:*** Nalgesic; ***Gr.:*** Expron†; ***Mex.:*** Nalfon†; ***S.Afr.:*** Fenopron†; ***UK:*** Fenopron; ***USA:*** Nalfon; ***Venez.:*** Fenopron†.

Fentanyl *(BAN, rINN)* ⊗

Fentanil; Fentanilis; Fentanilo; Fentanylum; Fentanyyli. *N*-(1-Phenethyl-4-piperidyl) propionanilide.

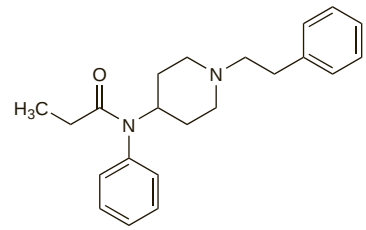
Фентанил

$C_{22}H_{28}N_2O$ = 336.5.

CAS — 437-38-7.

ATC — N01AH01; N02AB03.

ATC Vet — QN01AH01; QN02AB03.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of fentanyl:
Apache; China girl; China town; China white; Dance fever; Fentanest; Friend; Goodfellas; Great bear; He-man; Jackpot; King ivory; Murder 8; Poison; Tango & Cash; TNT; T.N.T.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Fentanyl). A white or almost white polymorphic powder. Practically insoluble in water; freely soluble in alcohol and in methyl alcohol. Protect from light.

Fentanyl Citrate *(BANM, USAN, rINNM)* ⊗

Citrato de fentanilo; Fentanil-citrát; Fentanilio citratas; Fentanyl, citrate de; Fentanylcitrat; Fentanyl-citrát; Fentanyli citras; Fentanylu cytrynian; Fentanyylisitraatti; McN-JR-4263-49; Phentanyl Citrate; R-4263. *N*-(1-Phenethyl-4-piperidyl)propionanilide dihydrogen citrate.

Фентанила Цитрат

$C_{22}H_{28}N_2O,C_6H_8O_7$ = 528.6.

CAS — 990-73-8.