Uses and Administration
Flufenamic acid, an anthranilic acid derivative related to mefenamic acid (p.80), is an NSAID (p.99). Flufenamic acid is mainly used topically in a concentration of 3 or 3.5% for the relief of pain and inflammation associated with musculoskeletal, joint, and soft-tissue disorders. Flufenamic acid and its aluminium salt have also been given orally.

Preparations
Proprietary Preparations (details are given in Part 3)
Ger.: Dignodolin†; ***Jpn:*** Opyrin.

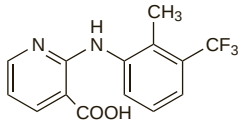
Multi-ingredient: ***Austria:*** Mobilisin; Mobilisin plus; Rheugesal; ***Belg.:*** Mobilisin; ***Braz.:*** Mobilisin Composto; ***Ger.:*** Algesalona†; ***Hung.:*** Mobilisin†; ***Ital.:*** Mobilisin; ***Port.:*** Latesil; Mobilisin; ***Spain:*** Movilisin; ***Switz.:*** Algesalona†; Assan; Assan thermo; Mobilisin.

Flunixin Meglumine *(BANM, USAN, rINNM)*
Fluniksiinimeglumiini; Flunixin megluminová sůl; Flunixine méglumine; Flunixini megluminum; Flunixinmeglumin; Flunixino meglumina; Flunixinum Megluminicum; Meglumini Flunixinum; Sch-14714 (flunixin). 2-{[2-Methyl-3-(trifluoromethyl)phenyl]amino}-3-pyridinecarboxylic acid compounded with 1-deoxy-1-(methylamino)-D-glucitol (1:1); 2-(α^3,α^3,α^3-Trifluoro-2,3,-xylidino)nicotinic acid compounded with 1-deoxy-1-(methylamino)-D-glucitol (1:1).

Меглумина Флуниксин

$C_{14}H_{11}F_3N_2O_2,C_7H_{17}NO_5$ = 491.5.

CAS — 38677-85-9 (flunixin); 42461-84-7 (flunixin meglumine).



(flunixin)

Pharmacopoeias. In *Eur.* (see p.vii) and *US* for veterinary use only.
Ph. Eur. 6.2 (Flunixin Meglumine for Veterinary Use; Flunixin Meglumine BP(Vet) 2008). A white to almost white crystalline powder. Freely soluble in water and in methyl alcohol; practically insoluble in acetone. A 5% solution in water has a pH of 7.0 to 9.0.
USP 31 (Flunixin Meglumine). A white to off-white crystalline powder. Soluble in water, in alcohol, and in methyl alcohol; practically insoluble in ethyl acetate. pH of a 5% solution in water is between 7.0 and 9.0. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Profile
Flunixin meglumine is an NSAID (p.96) used in veterinary medicine for the relief of pain and inflammation in acute and chronic disorders and as adjunctive therapy in the treatment of endotoxic or septic shock and mastitis.

Flupirtine Maleate *(BANM, USAN, rINNM)*
D-9998; Flupirtine, Maléate de; Flupirtini Maleas; Maleato de flupirtina; W-2964M. Ethyl 2-amino-6-(4-fluorobenzylamino)-3-pyridylcarbamate maleate.

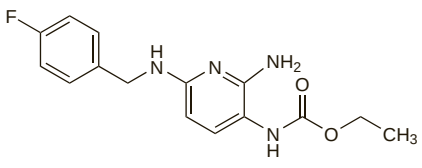
Флупиртина Малеат

$C_{15}H_{17}FN_4O_2,C_4H_4O_4$ = 420.4.

CAS — 56995-20-1 (flupirtine); 75507-68-5 (flupirtine maleate).

ATC — N02BG07.

ATC Vet — QN02BG07.



(flupirtine)

Profile
Flupirtine maleate is an analgesic that has been given for the relief of pain (see Choice of Analgesic, p.2) in usual doses of 100 mg three or four times daily by mouth, or 150 mg three or four times daily as a rectal suppository; daily doses of up to 600 mg by mouth or 900 mg rectally have been used where necessary. Flupirtine has also been given by intramuscular injection as the gluconate in the management of acute pain.

There has been some interest in the potential of flupirtine to treat prion diseases such as Creutzfeldt-Jakob disease (see below).

◊ References.
1. Friedel HA, Fitton A. Flupirtine: a review of its pharmacological properties, and therapeutic efficacy in pain states. *Drugs* 1993; **45:** 548–69.

Creutzfeldt-Jakob disease. A double-blind placebo-controlled study[1] in 28 patients with Creutzfeldt-Jakob disease (CJD) found flupirtine to have beneficial effects on cognitive function. However, further studies are needed to establish any place in therapy.
1. Otto M, *et al.* Efficacy of flupirtine on cognitive function in patients with CJD: a double-blind study. *Neurology* 2004; **62:** 714–18.

Preparations
Proprietary Preparations (details are given in Part 3)
Braz.: Katadolon; ***Ger.:*** Katadolon; Trancopal Dolo; ***Port.:*** Metanor; Novocebrin; ***Rus.:*** Katadolon (Катадолон).

Flurbiprofen *(BAN, USAN, rINN)*
BTS-18322; Flurbiprofeeni; Flurbiprofén; Flurbiprofenas; Flurbiprofène; Flurbiprofeno; Flurbiprofenum; U-27182. 2-(2-Fluorobiphenyl-4-yl)propionic acid.

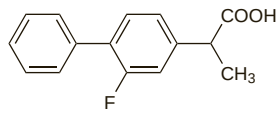
Флурбипрофен

$C_{15}H_{13}FO_2$ = 244.3.

CAS — 5104-49-4.

ATC — M01AE09; M02AA19; S01BC04.

ATC Vet — QM01AE09; QM02AA19; QS01BC04.



Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Flurbiprofen). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol and in dichloromethane; dissolves in aqueous solutions of alkali hydroxides and carbonates.
USP 31 (Flurbiprofen). A white crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, in ether, and in methyl alcohol; soluble in acetonitrile. Store in airtight containers.

Flurbiprofen Sodium *(BANM, rINNM)*
Flurbiprofène Sodique; Flurbiprofeno sódico; Natrii Flurbiprofenum. Sodium (±)-2-(2-fluoro-4-biphenylyl)propionate dihydrate.

Натрий Флурбипрофен

$C_{15}H_{12}FNaO_2,2H_2O$ = 302.3.

CAS — 56767-76-1.

Pharmacopoeias. In *Br.* and *US*.
BP 2008 (Flurbiprofen Sodium). A white to creamy-white, crystalline powder. Sparingly soluble in water; soluble in alcohol; practically insoluble in dichloromethane.

Adverse Effects and Treatment
As for NSAIDs in general, p.96.

Minor symptoms of ocular irritation including transient burning and stinging have been reported on instillation of flurbiprofen sodium eye drops; there may be increased bleeding from ocular surgery and wound healing may be delayed. Local irritation has also followed rectal use, and local effects including a sensation of warming or burning in the mouth may be seen after using flurbiprofen lozenges.

Incidence of adverse effects. Reports from the manufacturers on the range and incidence of the adverse effects of flurbiprofen.[1,2]
1. Sheldrake FE, *et al.* A long-term assessment of flurbiprofen. *Curr Med Res Opin* 1977; **5:** 106–16.
2. Brooks CD, *et al.* Clinical safety of flurbiprofen. *J Clin Pharmacol* 1990; **30:** 342–51.

Effects on the CNS. A severe symmetrical parkinsonian syndrome developed in a 52-year-old man who had taken flurbiprofen for 7 days.[1]
1. Enevoldson TP, *et al.* Acute parkinsonism associated with flurbiprofen. *BMJ* 1990; **300:** 540–1.

Effects on the kidneys. Renal papillary necrosis has been described in a patient who had used flurbiprofen for many years.[1] Acute flank pain and reversible renal dysfunction has been reported in 2 patients treated with flurbiprofen.[2,3] Membranous nephropathy also developed in a patient who took flurbiprofen daily for 12 to 18 months.[4]
1. Nafría EC, *et al.* Renal papillary necrosis induced by flurbiprofen. *DICP Ann Pharmacother* 1991; **25:** 870–1.
2. Kaufhold J, *et al.* Flurbiprofen-associated tubulointerstitial nephritis. *Am J Nephrol* 1991; **11:** 144–6.
3. McIntire SC, *et al.* Acute flank pain and reversible renal dysfunction associated with nonsteroidal anti-inflammatory drug use. *Pediatrics* 1993; **92:** 459–60.
4. MacKay K. Membranous nephropathy associated with the use of flurbiprofen. *Clin Nephrol* 1997; **47:** 279–80.

Effects on the liver. A case of cholestatic jaundice probably due to flurbiprofen has been reported.[1]
1. Kotowski KE, Grayson MF. Side effects of non-steroidal anti-inflammatory drugs. *BMJ* 1982; **285:** 377.

Effects on the skin. Cutaneous vasculitis apparently due to flurbiprofen occurred in a 59-year-old woman with long-standing rheumatoid arthritis.[1] Contact dermatitis has also been seen in a 22-year-old woman who applied a poultice containing flurbiprofen to her wrist.[2]
1. Wei N. Flurbiprofen and cutaneous vasculitis. *Ann Intern Med* 1990; **112:** 550–1.
2. Kawada A, *et al.* Contact dermatitis due to flurbiprofen. *Contact Dermatitis* 2000; **42:** 167–8.

Hypersensitivity. A diffuse, pruritic, maculopapular rash developed in a patient 48 hours after taking a second dose of flurbiprofen.[1] Two days later, the rash had become urticarial, and angioedema and hypotension were also noted. Patch testing with flurbiprofen powder was positive.

See also Effects on the Skin, above.
1. Romano A, Pietrantonio F. Delayed hypersensitivity to flurbiprofen. *J Intern Med* 1997; **241:** 81–3.

Precautions
As for NSAIDs in general, p.98.

Breast feeding. Flurbiprofen is distributed into breast milk; however, the *BNF* and licensed product information consider the amount to be too small to be harmful to a breast-fed infant.

Herpes simplex keratitis. Whether flurbiprofen can exacerbate infection when used to treat ocular herpes simplex is unclear from *animal* studies,[1,2] but licensed product information for flurbiprofen sodium eye drops recommends that they should not be used in patients with active epithelial herpes simplex keratitis. Patients with a history of herpes simplex keratitis should also be monitored closely when undergoing treatment with these eye drops.
1. Trousdale MD, *et al.* Effect of flurbiprofen on herpes simplex keratitis in rabbits. *Invest Ophthalmol Vis Sci* 1980; **19:** 267–70.
2. Hendricks RL, *et al.* The effect of flurbiprofen on herpes simplex virus type 1 stromal keratitis in mice. *Invest Ophthalmol Vis Sci* 1990; **31:** 1503–11.

Interactions
For interactions associated with NSAIDs, see p.99.

Parasympathomimetics. Licensed product information for acetylcholine chloride ophthalmic preparations and for flurbiprofen sodium eye drops states that there have been reports that *acetylcholine* and *carbachol* have been ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Pharmacokinetics
Flurbiprofen is readily absorbed from the gastrointestinal tract after oral doses with peak plasma concentrations occurring about 1 to 2 hours after ingestion. Absorption after rectal doses may be more rapid. It is about 99% bound to plasma proteins and has a plasma half-life of about 3 to 6 hours. It is metabolised mainly by hydroxylation (via the cytochrome P450 isoenzyme CYP2C9) and conjugation in the liver and excreted in urine. Flurbiprofen is distributed into breast milk.

Flurbiprofen is a chiral compound given as the racemate and the above pharmacokinetic characteristics refer to the racemic mixture. Allowance may have to be made for the different activities of the enantiomers.

◊ References.
1. Aarons L, *et al.* Plasma and synovial fluid kinetics of flurbiprofen in rheumatoid arthritis. *Br J Clin Pharmacol* 1986; **21:** 155–63.
2. Smith IJ, *et al.* Flurbiprofen in post-partum women: plasma and breast milk disposition. *J Clin Pharmacol* 1989; **29:** 174–84.
3. Kean WF, *et al.* The pharmacokinetics of flurbiprofen in younger and elderly patients with rheumatoid arthritis. *J Clin Pharmacol* 1992; **32:** 41–8.
4. Davies NM. Clinical pharmacokinetics of flurbiprofen and its enantiomers. *Clin Pharmacokinet* 1995; **28:** 100–14.

Uses and Administration
Flurbiprofen, a propionic acid derivative, is an NSAID (p.99). It is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, in soft-tissue disorders such as sprains and strains, for postoperative pain, and in mild to moderate pain including dysmenorrhoea and migraine. Flurbiprofen is also used as lozenges in the