Voltaren Ophtha; ***Chile:*** 3A Ofteno; Amofen; Artren; Autdol; Cataflam; Deflamat; Diclotaren; Dicogel; Dignofenac†; Elitiran; Exflam; Flector; Flotac; Lertus; Merpal; Noxiflex†; Oftic; Pirexyl; Piroflam; Pro Lertus; Sipirac; Turbogesic; Voltaren; ***Cz.:*** Almiral; Apo-Diclo; Arthrotec†; Diclofen; Dicloreum; DIKY; Dolmina; Dorosan; Feloran†; Flector; Inflamac†; Monoflam; Myogit; Naclof†; Naklofen; Olfen; Rewodina; Uniclophen; Uno; Veral; Voltaren; ***Denm.:*** Arthrotec; Diclodan; Diclogea†; Diclon; Difenet; Flector; Modifenac; Solaraze; Voltaren; Vostar; ***Fin.:*** Arthrotec; Diclometin; Diclomex; Eeze; Flector; Motifene; Solaraze; Trabona†; Voltaren; ***Fr.:*** Artotec; Flector; Solaraze; Voldal; Voltarendolo; Voltarene; Xenid; ***Ger.:*** Allvoran; Arthrotec; Benfofen†; Delphinac†; Diclac; Diclo; Diclo-Divido; Diclo-Gel; Diclo-Puren; Dicloxa-saar; Diclodoc; Diclofenbeta; Diclophlogont†; Difen; Dolgit-Diclo; duravolten†; Effekton; Jenafenac; Jutafenac; Lexobene†; Monoflam; Myogit; Rewodina; Sigafenac†; Solaraze; Voltaren; Voltaren Ophtha; ***Gr.:*** Anthraxiton; Arthrotec; Cataflam†; Clonac†; Declofon; Delimon; Denaclof; Diclofast; Diclophlogont†; Dicloplast; Difend†; Dinaclon†; Evinopon; Eyeclof; Fenoclof; Figrel†; Flefarmin; Optobet; Pengon†; Pennsaid; Relipain; Rheumavek; Ruvominox; Sfinac; Topalgon; Urigon; Vilacril†; Vilonit; Voltaren; Vurdon; ***Hong Kong:*** Almiral; Analpan; Apo-Diclo; Arthrotec; Cataflam; Clofec; Clofenac; Curinflam; Diclo-Denk; Diclofen; Diclogesic; Diclowal†; Difenac; Difenol; Erdon; Eurofenac; Flector; Flogofenac; Grofenac; Inflanac; Novo-Difenac†; Olfen; Remafen; Remethan; Ren; Rhemofenac; Uniren; Vartelon; Voltaren; Voltaren Ophtha; Votalen; Zolterol; ***Hung.:*** Cataflam; Diclac; Diclomel; Flamenil; Flector; Fortedol; Huma-Difenac†; Olfen†; Veral†; Voltaren; Voltaren Ophta; ***India:*** Cofenac; Diclomol; Diclonac; Dicloran†; Doflex; Dolocide K; Dolocide Plus; Esgipyrin DS; Fenlodac†; Fensaide†; I-Gesic; Jonac; K-Fenac; Nac; Nac Gel; Oxalgin; Oxalgin-D; Oxalgin-SR; Profenac; Reactine; Relaxyl; Solunac; Tromagesic; Tromax; Voveran; ***Indon.:*** Abdiflam; Alflam; Atranac; Berifen; Cataflam; Catanac; Deflamat; Dicloflam; Diclomec; Diflam; Divoltar; Eflagen; Exaflam; Fenaren; Fenavel; Flamar; Flamenac; Kadiflam; Kaflam; Kamaflam; Klotaren; Laflanac; Linac; Matsunaflam; Merflam; Nadifen; Neurofenac; Nichoflam; Nilaren; Potazen; Prostanac; Provoltar; Reclofen; Renadinac; Renvol; Scanaflam; Scantaren; Tirmaclo; Valto; Volmatik; Voltadex; Voltaren; Voltaren Ophtha; Voren; X-Flam; Xepathritis; Yariflam; Zegren; ***Irl.:*** Arthrotec; Cataflam; Diclac; Diclo; Diclomax; Diclomel; Difene; Solaraze; Vologen†; Voltarol; Voltarol Ophtha; ***Israel:*** Abitren; Arthrotec; Betaren; Cataflam; Dicloplast; Diclorengel; Olfen; Voltaren; Voltaren Ophtha; ***Ital.:*** Algosenac; Artrofenac†; Artrotec; Dealgic; Deflamat; Diclocular; Diclofan; Dicloftil; Dicloral; Dicloreum; Diclotears; Dolaut; Doroxan; Dropflam; Fenadol; Fender; Flector; Flogofenac; Forgenac; Itami; Leviogel; Lisiflen†; Misofenac; Molfenac; Novapirina; Pennsaid; Ribex Flu†; Solaraze; Topfans; Voltadol; Voltaren; Voltfast; Zeroflog; ***Jpn:*** Anavan; ***Malaysia:*** Almiral; Apo-Diclo†; Cataflam; Clofec; Clofenac; Difnal; Fenac; Fenadium†; Inflanac; Lesflam; Neo-Pyrazon; Olfen; Remafen†; Remethan; Rhewlin†; Taks†; Uniren; Voltaren; Voren; Wari-Diclowal†; Zolterol; ***Mex.:*** 3A Ofteno; Alsidexten; Ariflam; Artrenac; Artrenac Pro; Artrene; Artrotec; Atalak; Cataflam; Clo-Far; Clonodifen; Coral; Deflox; Dicfafena; Diclac; Dicloran; Diclosol; Dioxaflex; Dirret; Docril; Dofen; Dolaren; Dolflam; Dolofenac; Doltarac; Evadol; Fenagel; Fenalgin; Fervex; Flamydol; Flamygel; Flankol; Flogoken; Flotac; Fortical; Fustaren; Galedol; Hipo Sport; Lertus; Lifenac; Liroken; Lodyfen; Logesic†; Lonatec; Lufac-Z; Mafena; Manacon; Merxil; Metracin; Musol; Nediclon; Neo-Dolaren; Pharmaflam; Practiser; Precifenac; Selectofen; Solof; Still; Uni-Fenil†; Vicmafen; Volfenac; Voltaren; ***Neth.:*** Arthrotec; Artrotec; Cataflam; Itami; Misofenac; Naclof; Normulen; Otriflu; Voltaren; ***Norw.:*** Arthrotec; Cataflam; Modifenac; Otriflu; Solaraze; Voltaren; Voltaren Ophtha; ***NZ:*** Apo-Diclo; Cataflam; Diclax; Diclohexal; Flameril; Voltaren; Voltaren Ophtha; Voltfast; ***Philipp.:*** Acuflam; Cataflam; Clofenix; Clofil; Clonaren; Difenax; Diflapane; Doloflam; Dycon; Eslofen; Fenaspec; Lobafen; Lofenax; Neo-Pyrazon; Nepenthe; Parafortan; Rheuflam; Uniclonax; Volfenn; Voltaren; Voren; Zobid; ***Pol.:*** Apo-Diclo; Arthrotec; Cataflam; Diclac; Dicloberl; DicloDuo; Dicloratio; Dicloreum; Difadol; Diklonat P; Diklozijaja; Felogel; Majamil; Naclof; Naklofen; Olfen; Ratiogel; Rewodina; Veral; Voltaren; Voltenac; ***Port.:*** Arthrotec; Cataflam; Clofen; Dicloabak; Diclodent; Diclofital; Diclospray; Diclotec; Difnan; Dofene; Dolacen; Dorcalor; Fenac; Fenil-V; Flameril; Flector; Olfen; Otriflu; Painex; Pennsaid; Solaraze; Voltaren; ***Rus.:*** Almiral (Алмирал); Apo-Diclo (Апо-дикло); Arthrotec (Артротек)†; Diclac (Диклак); Diclo-F (Дикло-ф); Diclobene (Диклобене); Dicloberl (Диклоберл); Diclonat (Диклонат); Dicloran (Диклоран); Diclovit (Дикловит); Feloran (Фелоран)†; Naclof (Наклоф); Naklofen (Наклофен); Naklofen Duo (Наклофен Дуо); Rapten Rapid (Рапттен Рапид); Voltaren (Вольтарен); ***S.Afr.:*** Adco-Clofelam; Arcanafenac; Arthrotec; Arthru-Derm; Cataflam; Dicloflam; Diclohexal; Dynak; Flexagen; Fortfen; Infla-Ban; K-Fenak; Panamor; Pharmaflam†; Veltex; Voltaren; Voltaren Ophtha; ***Singapore:*** Almiral; Cataflam; Clofec; Clofenac; Diclo; Diclo-Denk†; Dicloran; Diclowal†; Difenac; Difnal; Inac; Inflanac; Lesflam; Neo-Pyrazon†; Olfen; Pritaren; Remafen; Remethan†; Rhewlin; Ultrafen; Uniren; Voltaren; Voltaren Ophtha; Voren; Zolterol; ***Spain:*** Artrotec; Di Retard; Dolo Nervobion; Dolo-Voltaren; Dolotren; Luase; Normulen; Sulexon; Voltaren; ***Swed.:*** Arthrotec; Flector; Modifenac†; Solaraze; Voltaren; Voltaren Ophtha; Voltaren T; ***Switz.:*** Agofenac†; Arthrotec; Athrofen; Deflamat†; Diclac; diclo-basan; Diclo†; Diclosifar; Ecofenac; Effigel; Flector; Fortenac; Grofenac; Inflamac; Olfen; Primofenac; Relova; Tonopan; Vifenac; Voltaren Dolo; Voltaren Emulgel; Voltaren Ophta; Voltarene; ***Thai.:*** Almiral†; Ammi-Votara; Ammimac; Arclonac; Arthrotec†; Cataflam; Catanac; Cencenag; Chinclonac; Clofec; Clofon; Demac; Diclofen†; Diclogel; Diclolan; Diclomol; Diclosian; Difelene†; Difen; Difenac; Difengesic; Difeno; Dinac; Dinefec†; Dosanac; Fenac; Fenagel; Flexy; Inflanac; Lesflam; Lofenac; Masaren; Medaren†; Myfenax; Myonac; N-Zen; Naclof; Olfen†; Ostaren; Posnac; Putaren†; Remethan; Rhumanol; Rumatab†; Sefnac; Silflam†; Subsyde; Taks; Tarjen†; Tarjena; Uniren; Vasalen; Veenac; Ventarone; Volfenac; Volnac; Volta; Voltanac; Voltaren; Volverac; Votamed; ***Turk.:*** Actinoma; Cataflam; Deflamat; Diclo-flam; Diclomec; Difenak; Dikloron; Dolorex; Inflased; Kalidren; Miyadren; Voltaren; Voltaren Ophta; ***UAE:*** Clofen; ***UK:*** Acoflam†; Arthrotec; Defanac; Defenac; Dexomon; Dicloflex; Diclomax; Diclovol; Diclozip; Dyloject; Econac; Fenactol; Flamatak; Flamrase; Lofensaid†; Motifene; Pennsaid; Rheumatac; Rhumalgan; Slofenac; Solaraze; Volraman; Volsaid; Voltarol; Voltarol Ophtha; ***USA:*** Arthrotec; Cataflam; Flector; Solaraze; Voltaren; ***Venez.:*** 3A Ofteno; Arthrotec; Artren; Campal; Cataflam; Clofen; Clofenac; Diagesic; Diclofen P; Diclosal; Diclostan†; Difenac; Diklason; Diralon; Dival; Doltren†; Flogaren; Flotac; Klafenac; Viavox; Voltaren; Volten; Votaxil.

Multi-ingredient: ***Arg.:*** Albesine Biotic; Algicler; Algio Nervomax; Algio Nervomax Fuerte; Amixen Plus; Befol Plus; Belmalen; Blokium B12; Blokium Flex; Blokium Gesic; Corteroid Gesic; Curinflam Plus; Delta Tomanil B12; Desinflam Biotic†; Diclogesic Forte; Diclogesic Plus B12; Diclogesic Relax; Diclomar Flex; Diclonex Relax; Dioxaflex B12; Dioxaflex Forte; Dioxaflex Gesic; Dioxaflex Plus; Dolo Nervobion; Dolo Nervobion 10000; Dolvan Flex; Doxtran B12; Doxtran Flex; Doxtran Gesic; Flaval; Glifapen; Hyanac†; Iglodine Flex; Ingebrax; Lertus Biotic†; Metaflex Gesic; Metaflex Plus NF; Meticil; Mio Aldoron NF; Mio-Virobron NF; Nalgiflex Relax; Oxa B12; Oxa Forte; Oxa Sport; Oxadisten; Oxafem; Oxagesic; Pancloflex; Panclogesic; Rodinac B12; Rodinac Biotic; Rodinac Flex; Rodinac Gesic; Silfox Flex; Tafirol Artro; Tobradiclo; Tobratlas; Tomanil Flex; Vesalion B12; Vesalion Flex; Vesalion Gesic; Viartril Flex; Virobron B12 NF; Voltaren Flex; Voltaren Forte; Xedenol B12; Xedenol Flex; Xedenol Gesic; ***Austria:*** Diclovit; Dolo-Neurobion; Neodolpasse; Neurofenac; Voltamicin; ***Belg.:*** Ocubrax; ***Braz.:*** Algi-Butazolon†; Algi-Tanderil†; Beserol; Cedrilax†; Codaten; Diclofetamol; Flexalgin; Mioflex A; Sedilax; Tandene; Tanderalgin; Tandriflan; Tandrilax; Torsilax; Trilax†; ***Cz.:*** Neodolpasse; Voltamicin†; ***Ger.:*** Combaren; Voltaren Plus; ***Gr.:*** Tobrafen; ***Hong Kong:*** Neurofenac†; Vartelon-B; Vidaclofen-Plus; ***Hung.:*** Neodolpasse; Ocubrax†; Voltamicin†; ***India:*** Actimol; Buta-Proxyvon; Cip-Zox; Cipzen D; Cofenac; Diclogenta; Diclomol; Dicloran MS; Dicloran-A†; Diclospa; Diser; Doflex Plus; Dolocide KP; Dolocide MR; DP Gesic; Duoflam Gel; Esgipyrin; Fenaplus; Fenaplus-MR; Fensaide-P†; Flamar-MX; Flanzen-D; Inflazone; Myospaz Forte; New Panazox; Nicip D; Omnigel; Osteoflam-MR; Oxalgin-DP; Pacizox; Paracip Plus; Parvon Forte; Reactine Forte; Reactine Plus; Relaxyl Plus; Spasmo-Proxyvon Forte; Systaflam; ***Indon.:*** Dolofenac; ***Ital.:*** Voltamicin†; ***Malaysia:*** Voren Plus; ***Mex.:*** Ariflam Forte; Diclovith-B; Dolaren; Dolo-Neurobion; Dolo-Pangavit; Duciclon; Duoflex; Empatil; Lertus CD; Ortocol; Tafirol AC; Trazinac; Tribedoce Compuesto; Uni-Dox; Voltaren Forte; ***Pol.:*** Venozel; ***Rus.:*** Diclofenacol (Диклофенакол); Dicloran Plus (Диклоран Плюс); ***Singapore:*** Voltamicin†; ***Spain:*** Ocubrax; ***Switz.:*** Tobrafen; Voltamicin; ***Turk.:*** Ocubrax; ***Venez.:*** Combaren; Painfort; Todenac; Trazinac.

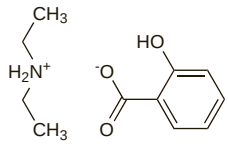
Diethylamine Salicylate

Diaethylamini Salicylas; Dietylaminsalicylat; Dietyyliamiinisalisylaatti; Salicilato de dietilamina; Salisilat Dietilamin.

Диэтиламин Салицилат; Салицилат Диэтиламина

$C_{11}H_{17}NO_3$ = 211.3.

CAS — 4419-92-5.



Pharmacopoeias. In *Br.* and *Chin.*

BP 2008 (Diethylamine Salicylate). White or almost white, odourless or almost odourless crystals. Very soluble in water; freely soluble in alcohol and in chloroform. Protect from light. Avoid contact with iron or iron salts.

Profile

Diethylamine salicylate is a salicylic acid derivative used topically in rubefacient preparations similarly to methyl salicylate (p.85) for rheumatic and muscular pain.

Preparations

BP 2008: Diethylamine Salicylate Cream.

Proprietary Preparations (details are given in Part 3)

Belg.: Algesal; ***Canad.:*** Physiogesic; ***Fin.:*** Algesal; ***Hung.:*** Aciphen; ***India:*** Multigesic†; ***Ital.:*** Algesal†; ***Neth.:*** Algesal; ***Norw.:*** Algesal; ***Pol.:*** Saldiam; ***Port.:*** Algicum; Algiderma; Massagim; ***Swed.:*** Algesal; ***Turk.:*** Algesal; Reparil N; ***UK:*** Algesal; Lloyd's Cream; ***Venez.:*** Alesal.

Multi-ingredient: ***Arg.:*** Algesal; Cartiflex; Crema Antiinflamatoria; Feparil†; Rati Salil Flex; Salicrem; ***Austral.:*** Rubesal; ***Austria:*** Algesal; Derivon; Dolo-Menthoneurin; Dolorex†; Igitur-antirheumatische; Igitur-Rheumafluid; Latesyl; Pasta rubra salicylata; Reparil; Rheugesal; Thermal; ***Belg.:*** Reparil; ***Braz.:*** Reparil; ***Chile:*** Repariven; ***Cz.:*** Algesal; Reparil-Gel N; ***Fr.:*** Algesal Suractive; Reparil; Traumalgyl; ***Ger.:*** Algesal; Algesalona†; Dolo-Menthoneurin†; Doloneuro†; Reparil-Gel N; ***Gr.:*** Algesal Suractive; Ponostop; ***Hong Kong:*** Reparil; Rubesal; ***Hung.:*** Algesal; Reparil N; ***Indon.:*** Algesal Superactive; ***Ital.:*** Edeven; Reparil; Sedalpan; Via Mal Traumagel; ***Mex.:*** Algesal†; ***Neth.:*** Algesal Forte; ***Norw.:*** Thermal†; ***Pol.:*** Reparil N; ***Port.:*** Algesal; Latesil; Medalginan; Venoparil; ***S.Afr.:*** Reparil; ***Spain:*** Algesal; Contusin; Doctomitil†; Dolmitin; Feparil; Radio Salil; ***Switz.:*** Algesal†; Algesalona†; Mavena Proctal-Gen; Reparil; ***Thai.:*** Reparil; Veno Gel; ***Turk.:*** Algesal Suractive; Prepagel; ***UAE:*** Rubicalm; ***UK:*** Fiery Jack; Transvasin Heat Spray; ***Venez.:*** Lemazol.

Diflunisal *(BAN, USAN, rINN)*

Diflunisaali; Diflunisalis; Diflunisalum; Difluniszal; MK-647. 5-(2,4-Difluorophenyl)salicylic acid.

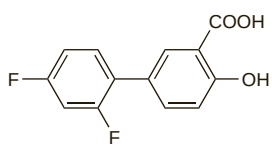
Дифлунисал

$C_{13}H_8F_2O_3$ = 250.2.

CAS — 22494-42-4.

ATC — N02BA11.

ATC Vet — QN02BA11.



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

Ph. Eur. 6.2 (Diflunisal). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Diflunisal). A white to off-white, practically odourless, powder. Insoluble in water and in hexane; freely soluble in alcohol and in methyl alcohol; soluble in acetone and in ethyl acetate; slightly soluble in carbon tetrachloride, in chloroform, and in dichloromethane.

Adverse Effects and Treatment

As for NSAIDs in general, p.96. The commonest adverse effects occurring with diflunisal are gastrointestinal disturbances, headache, and rash. Peptic ulceration and gastrointestinal bleeding have been reported. Dizziness, drowsiness, insomnia, and tinnitus may also occur.

Effects on the blood. Haematological adverse effects associated with diflunisal appear to be infrequent. Thrombocytopenia associated with diflunisal-induced peripheral platelet destruction has been reported in a patient with rheumatoid arthritis.[1] Heinz-body haemolytic anaemia has also been reported, see Hypersensitivity, below.

1. Bobrove AM. Diflunisal-associated thrombocytopenia in a patient with rheumatoid arthritis. *Arthritis Rheum* 1988; **31:** 148–9.

Effects on the kidneys. Acute interstitial nephritis, presenting as acute oliguric renal failure, erythroderma, and eosinophilia has followed the use of diflunisal.[1]

1. Chan LK, *et al.* Acute interstitial nephritis and erythroderma associated with diflunisal. *BMJ* 1980; **280:** 84–5.

Effects on the lungs. For reference to pneumonitis associated with diflunisal therapy, see Hypersensitivity, below.

Effects on the skin. Reports of Stevens-Johnson syndrome associated with diflunisal.[1,2] See also Hypersensitivity, below.

1. Hunter JA, *et al.* Diflunisal and Stevens-Johnson syndrome. *BMJ* 1978; **2:** 1088.
2. Grom JA, *et al.* Diflunisal-induced erythema multiforme major. *Hosp Formul* 1986; **21:** 353–4.

Hypersensitivity. Three cases of hypersensitivity to diflunisal in which the main clinical features were fever, elevated liver enzyme values, erythroderma, and eosinophilia, have been reported.[1] Heinz-body haemolytic anaemia occurred in one of the patients. Other hypersensitivity reactions associated with diflunisal therapy have included pneumonitis[2] and fulminant necrotising fasciitis.[3]

1. Cook DJ, *et al.* Three cases of diflunisal hypersensitivity. *Can Med Assoc J* 1988; **138:** 1029–30.
2. Rich MW, Thomas RA. A case of eosinophilic pneumonia and vasculitis induced by diflunisal. *Chest* 1997; **111:** 1767–9.
3. Krige JEJ, *et al.* Necrotising fasciitis after diflunisal for minor injury. *Lancet* 1985; **ii:** 1432–3.

Overdosage. Diflunisal poisoning has sometimes been fatal.[1,2] A dose of 15 g has been reported to have caused death when no other drugs were involved but a dose of 7.5 g has also been fatal when taken with other drugs.

1. Court H, Volans GN. Poisoning after overdose with non-steroidal anti-inflammatory drugs. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 1–21.
2. Levine B, *et al.* Diflunisal related fatality: a case report. *Forensic Sci Int* 1987; **35:** 45–50.

Precautions

As for NSAIDs in general, p.98. Diflunisal may need to be given in reduced dosage in patients with significant renal impairment and should not be given when renal impairment is severe. Aspirin and other acetylated salicylates are not recommended for use in children unless specifically indicated, because of the risk of Reye's syndrome. Although this precaution has not been specifically extended to diflunisal it is not generally licensed for use in children.

Interactions

For interactions associated with NSAIDs, see p.99.

Aspirin may produce a small decrease in the plasma concentration of diflunisal. Diflunisal has been reported to increase the plasma concentrations of indometacin and paracetamol; diflunisal with indometacin has been associated with fatal gastrointestinal haemorrhage and therefore the combination should not be used. Regular use of antacids may reduce the absorption of diflunisal.

Benzodiazepines. For the effect of diflunisal on plasma concentrations of *oxazepam*, see p.989.

Probenecid. Average steady-state plasma concentrations of diflunisal were increased by 65% when it was given with probenecid.[1] This was due mainly to reduced formation of the phenolic and acyl glucuronides. However, plasma concentrations of these glucuronides and the sulfate conjugate were also increased even more because probenecid also reduced their renal clearance.

1. Macdonald JI, *et al.* Effect of probenecid on the formation and elimination kinetics of the sulphate and glucuronide conjugates of diflunisal. *Eur J Clin Pharmacol* 1995; **47:** 519–23.

Pharmacokinetics

Diflunisal is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 2 to 3 hours after ingestion of a single dose. It is more than 99% bound to plasma protein and has a plasma half-life of about 8 to 12 hours. Diflunisal exhibits non-linear pharmacokinetics so that doubling the dose more than doubles drug accumulation. Due to the long half-life and non-linear kinetics, several days are required to reach steady-state plasma concentrations after multiple dosing. The time to steady-state concentrations can be reduced by giving an initial loading dose. Concentrations of diflunisal in synovial fluid reach about 70% of those in plasma. Diflunisal is excreted in the urine mainly as glucuronide conjugates. Some biliary recycling may

also occur. Diflunisal is distributed into breast milk with concentrations reported to be about 2 to 7% of those in plasma.

◊ References.

1. Loewen GR, *et al.* Effect of dose on the glucuronidation and sulphation kinetics of diflunisal in man: single dose studies. *Br J Clin Pharmacol* 1988; **26:** 31–9.
2. Eriksson L-O, *et al.* Influence of renal failure, rheumatoid arthritis and old age on the pharmacokinetics of diflunisal. *Eur J Clin Pharmacol* 1989; **36:** 165–74.
3. Verbeeck RK, *et al.* The effect of multiple dosage on the kinetics of glucuronidation and sulphation of diflunisal in man. *Br J Clin Pharmacol* 1990; **29:** 381–9.
4. Macdonald JI, *et al.* Sex-difference and the effects of smoking and oral contraceptive steroids on the kinetics of diflunisal. *Eur J Clin Pharmacol* 1990; **38:** 175–9.
5. Nuernberg B, *et al.* Pharmacokinetics of diflunisal in patients. *Clin Pharmacokinet* 1991; **20:** 81–9.

Uses and Administration

Diflunisal is a salicylic acid derivative (see Aspirin, p.23) but it is not hydrolysed to salicylate and its clinical effects resemble more closely those of propionic acid derivative NSAIDs such as ibuprofen (p.65). Diflunisal is given in the acute or long-term management of mild to moderate pain, and pain and inflammation associated with osteoarthritis and rheumatoid arthritis. The usual initial oral dose for pain relief is 1 g followed by a maintenance dose of 500 mg every 12 hours. In some patients 250 mg every 8 to 12 hours may be sufficient but others may require 500 mg every 8 hours. Maintenance doses greater than 1.5 g daily are not recommended. The usual oral dose for arthritis is 500 mg to 1 g daily in 2 divided doses. Doses may need to be reduced in patients with renal impairment, see below.

Diflunisal arginine has been used similarly given by mouth or by intramuscular or intravenous injection.

Administration in renal impairment. Diflunisal may need to be given in reduced dosage in patients with significant renal impairment and should not be given when renal impairment is severe.

Preparations

BP 2008: Diflunisal Tablets;
USP 31: Diflunisal Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Dolobid†; ***Austria:*** Fluniget; ***Belg.:*** Biartac†; Diflusal; ***Denm.:*** Donobid†; ***Fin.:*** Donobid†; ***Fr.:*** Dolobis†; ***Gr.:*** Analeric; ***Irl.:*** Dolobid†; ***Israel:*** Dolobid†; ***Ital.:*** Artrodol; Dolobid†; ***Mex.:*** Dolobid†; ***Neth.:*** Dolobid; Dolocid; ***Norw.:*** Donobid; ***Port.:*** Dolobid†; Flunidor†; ***Spain:*** Dolobid; ***Swed.:*** Donobid; ***Switz.:*** Unisalt†; ***Thai.:*** Dolobid; ***Turk.:*** Dolphin; ***UK:*** Dolobid†; ***USA:*** Dolobid†; ***Venez.:*** Dolobid†.

Dihydrocodeine Phosphate

(BANM, rINNM)

Dihydrocodéine, Phosphate de; Dihydrocodeini Phosphas; Fosfato de dihidrocodeína; Hydrocodeine Phosphate.

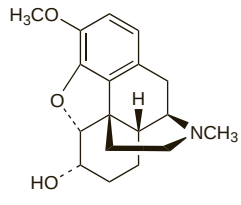
Дигидрокодеина Фосфат

$C_{18}H_{23}NO_3,H_3PO_4$ = 399.4.

CAS — 24204-13-5.

ATC — N02AA08.

ATC Vet — QN02AA08.



(dihydrocodeine)

Pharmacopoeias. In *Jpn.*

Dihydrocodeine Tartrate *(BANM, rINNM)*

Dihidrokodein-hidrogén-tartrát; Dihidrokodeino-vandenilio tartratas; Dihydrocodeine Acid Tartrate; Dihydrocodeine Bitartrate; Dihydrocodeine Hydrogen Tartrate; Dihydrocodéine, hydrogénotartrate de; Dihydrocodéine, Tartrate de; Dihydrocodeini Bitartras; Dihydrocodeini hydrogenotartras; Dihydrocodeini Tartras; Dihydrokodeiinivetytartratti; Dihydrokodein-tartarát; Dihydrokodeinvätetartrat; Dihydrokodeiny wodorowinian; Drocode Bitartrate; Hydrocodeine Bitartrate; Tartrato de dihidrocodeína. 4,5-Epoxy-3-methoxy-17-methylmorphinan-6-ol hydrogen tartrate.

Дигидрокодеина Тартрат

$C_{18}H_{23}NO_3,C_4H_6O_6$ = 451.5.

CAS — 125-28-0 (dihydrocodeine); 5965-13-9 (dihydrocodeine tartrate).

NOTE. Compounded preparations of dihydrocodeine tartrate may be represented by the following names:

- Co-dydramol (*BAN*)—dihydrocodeine tartrate 1 part and paracetamol 50 parts (w/w).

The following terms have been used as 'street names' (see p.vi) or slang names for various forms of dihydrocodeine tartrate:
DFs; Diffs; Duncan Flockharts.

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

Ph. Eur. 6.2 (Dihydrocodeine Hydrogen Tartrate; Dihydrocodeine Tartrate BP 2008). A white or almost white crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in cyclohexane. A 10% solution in water has a pH of 3.2 to 4.2. Protect from light.

USP 31 (Dihydrocodeine Bitartrate). pH of a 10% solution in water is between 3.2 and 4.2. Store in airtight containers.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Dihydrocodeine has been subject to abuse (see under Precautions, below).

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102; adverse effects of dihydrocodeine are less pronounced than those of morphine.

Overdosage. A 29-year-old man who had taken 2.1 g of dihydrocodeine had biochemical evidence of acute renal and hepatic impairment when admitted 13 hours after the overdose.[1] Severe life-threatening respiratory depression subsequently developed 36 hours after the overdose and only responded to treatment with naloxone after large doses (a total of 46.6 mg of naloxone) over a long period (106 hours). Commenting on this report some questioned the evidence for hepatic impairment and considered that the raised liver enzyme values were of muscular origin as a result of rhabdomyolysis.[2-4] Rhabdomyolysis may also have contributed to renal failure.

An anaphylactoid reaction after an overdose with an unspecified number of dihydrocodeine tablets[5] appeared to respond to intravenous naloxone.

1. Redfern N. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287:** 751–2.
2. Buckley BM, Vale JA. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287:** 1547.
3. Blain PG, Lane RJM. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287:** 1547.
4. Wen P. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287:** 1548.
5. Panos MZ, *et al.* Use of naloxone in opioid-induced anaphylactoid reaction. *Br J Anaesth* 1988; **61:** 371.

Pain. For reference to increased postoperative pain associated with the use of dihydrocodeine, see under Uses and Administration, below.

Precautions

As for Opioid Analgesics in general, p.103.

Abuse. Dihydrocodeine has been reported to be widely abused by opiate addicts.[1-4]

1. Swadi H, *et al.* Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. *BMJ* 1990; **300:** 1313.
2. Robertson JR, *et al.* Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. *BMJ* 1990; **301:** 119.
3. Strang J, *et al.* Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. *BMJ* 1990; **301:** 119.
4. Seymour A, *et al.* The role of dihydrocodeine in causing death among drug users in the west of Scotland. *Scott Med J* 2001; **46:** 143–6.

The elderly. Despite some renal impairment an elderly group of patients[1] appeared to handle dihydrocodeine similarly to healthy young subjects. There was marked variability in all measurements and on the basis of this study no clear conclusions on guidelines for dosage in elderly patients could be drawn. However, the recommendation that small doses be given initially with subsequent doses according to response was endorsed.

1. Davies KN, *et al.* The effect of ageing on the pharmacokinetics of dihydrocodeine. *Eur J Clin Pharmacol* 1989; **37:** 375–9.

Renal impairment. Caution is necessary when giving dihydrocodeine to patients with severe renal impairment. Severe narcosis occurred in a patient with anuria and on maintenance haemodialysis after she had received dihydrocodeine orally for 4 days.[1] She responded to treatment with naloxone.

See also under Pharmacokinetics, below.

1. Barnes JN, Goodwin FJ. Dihydrocodeine narcosis in renal failure. *BMJ* 1983; **286:** 438–9.

Interactions

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

Quinidine. Dihydrocodeine is metabolised via the cytochrome P450 isoenzyme CYP2D6 to active metabolites, which may perhaps play a role in its analgesic activity in extensive metabolisers; quinidine impairs this metabolism, but a study in 11 healthy subjects did not find any reduced analgesic activity when dihydrocodeine was given with quinidine, despite a three- to fourfold reduction in plasma concentrations of the metabolite dihydromorphine.[1]

1. Wilder-Smith CH, *et al.* The visceral and somatic antinociceptive effects of dihydrocodeine and its metabolite, dihydromorphine: a cross-over study with extensive and quinidine-induced poor metabolizers. *Br J Clin Pharmacol* 1998; **45:** 575–81.

Pharmacokinetics

After oral doses peak concentrations of dihydrocodeine occur after about 1.2 to 1.8 hours; oral bioavailability is only about 20%, probably because of substantial first-pass metabolism in the gut wall or liver. Dihydrocodeine is metabolised in the liver via the cytochrome P450 isoenzyme CYP2D6, to dihydromorphine, which has potent analgesic activity, although the analgesic effect of dihydrocodeine appears to be primarily due to the parent compound; some is also converted via CYP3A4 to nordihydrocodeine. Dihydrocodeine is excreted in urine as unchanged drug and metabolites, including glucuronide conjugates. Elimination half-life is reported to range from about 3.5 to 5 hours.

◊ References.

1. Rowell FJ, *et al.* Pharmacokinetics of intravenous and oral dihydrocodeine and its acid metabolites. *Eur J Clin Pharmacol* 1983; **25:** 419–24.
2. Fromm MF, *et al.* Dihydrocodeine: a new opioid substrate for the polymorphic CYP2D6 in humans. *Clin Pharmacol Ther* 1995; **58:** 374–82.
3. Ammon S, *et al.* Pharmacokinetics of dihydrocodeine and its active metabolite after single and multiple dosing. *Br J Clin Pharmacol* 1999; **48:** 317–22.
4. Webb JA, *et al.* Contribution of dihydrocodeine and dihydromorphine to analgesia following dihydrocodeine administration in man: a PK-PD modelling analysis. *Br J Clin Pharmacol* 2001; **52:** 35–43.

Renal impairment. The pharmacokinetics of dihydrocodeine tartrate, given as a single oral 60-mg dose, were affected in 9 patients with chronic renal failure treated with haemodialysis when compared with 9 healthy subjects.[1] Time to peak plasma concentration in those with renal failure was 3 hours compared with 1 hour in healthy subjects; the area under the plasma concentration-time curve was greater in those with renal failure; and after 24 hours dihydrocodeine was still detectable in the plasma of all renal failure patients, but in only 3 of the healthy subjects.

1. Barnes JN, *et al.* Dihydrocodeine in renal failure: further evidence for an important role of the kidney in the handling of opioid drugs. *BMJ* 1985; **290:** 740–2.

Uses and Administration

Dihydrocodeine is an opioid analgesic (p.104). It is related to codeine (p.38) and has similar analgesic activity. Dihydrocodeine is used for the relief of moderate to severe pain, often in combination preparations with paracetamol. It has also been used as a cough suppressant.

For **analgesia** the usual oral dose of dihydrocodeine tartrate is 30 mg after food every 4 to 6 hours; up to 240 mg daily may be given for severe pain. Modified-release preparations are available for twice daily dosage in patients with chronic severe pain.

Dihydrocodeine tartrate may also be given by deep subcutaneous or intramuscular injection in doses of up to 50 mg every 4 to 6 hours.

For details of doses in children, see below.

As a **cough suppressant** dihydrocodeine tartrate may be given in oral doses of 10 to 30 mg up to three times daily.

Dihydrocodeine phosphate has also been used. Other salts of dihydrocodeine used, mainly for their antitussive effects, include the hydrochloride, the polistirex, and the thiocyanate. Dihydrocodeine polistirex has also been used in modified-release preparations.

Administration in children. In the UK, dihydrocodeine tartrate may be given orally, or by deep subcutaneous or intramuscular injection, for analgesia in children aged from 4 to 12 years in usual doses of 0.5 to 1 mg/kg (to a maximum of 30 mg) every 4 to 6 hours; older children may be given the usual adult dose (see above). Although unlicensed in children under 4 years, the *BNFC* suggests giving those aged 1 to 4 years 500 micrograms/kg every 4 to 6 hours.

Dyspnoea. Dihydrocodeine has been reported[1] to have produced benefit in normocapnic patients severely disabled by breathlessness due to chronic airflow obstruction. A dose of