

Volaren Ophtha; **Chile:** 3A Ofteno; Amofen; Artren; Autdol; Cataflam; Deflamat; Diclofenac; Dicogel; Dignofenac†; Ekliran; Exflam; Flectam; Flotac; Lertus; Merial; Noflex†; Ofir; Pirexy; Profam; Pro Lertus; Spirac; Turbogesis; Voltaren; **Cz:** Almiral; Apo-Diclo; Arthroctec†; Diclofen; Dilorcum; DIKY; Dolmina; Doras; Feloran†; Flector; Inflamac†; Monoflam; Myogit; Naclofl†; Naklofen; Olfen; Rewodina; Unidophen; Uno; Veral; Voltaren; **Denn:** Arthroctec; Diclofan; Diclodge†; Diclone; Difenet; Flector; Modifenac; Solaraze; Voltaren; Vostar; **Fin:** Arthroctec; Diclofenat; Diclomex; Ezeer; Flector; Motifene; Solaraze; Trabona†; Voltaren; **Fr:** Artrotec; Flector; Solaraze; Voldal; Voltarendolo; Voltarene; Xenid; **Ger:** Alivoran; Arthotec; Benfopen†; Delphinac†; Diclac; Diclod; Diclodo-Diclo; Diclod; Diclod-Puren; Diclodo-saar; Diclodoc; Diclodenbeta; Diclodophogon†; Diflen; Doltig-Diclo; duravolent†; Effeikon; Jenafenac; Jufatenac; Lexobene†; Monoflam; Myogit; Rewodina; Sigafenac†; Solaraze; Voltaren; Voltaren Ophtha; **Gr:** Anthraxiton; Arthroctec; Cataflam†; Clonac†; Dedeofen; Delimon; Denadof; Diclodast; Diclodophogon†; Diclodipast; Difend†; Dinaclo†; Eviponon; Eyedof; Fenoclof; Fignel†; Fieflamin; Optobest; Pengon†; Pennsaid; Relpain; Rheumace; Ruvinomox; Sinaac; Topalgon; Urgon; Vlacril†; Vilonit; Voltaren; Vurdon; **Hong Kong:** Almiral; Analpain; Apo-Diclo; Arthroctec; Cataflam; Clodex; Clodenac; Cuniflam; Diclodo-Denk; Dicloden; Diclodiges; Diclowl†; Difenan; Difenal; Erdon; Eurofenac; Flector; Flogofenac; Grofenac; Inflana; Novo-Difenac†; Olfen; Remafen; Remethan; Ren; Rheumofenac; Uniren; Vartelon; Voltaren; Voltaren Ophtha; Votalen; Zolterol; **Hung:** Cataflam; Diclac; Diclomel; Flameril; Flector; Fortedol; Huma-Difenac†; Olfen†; Veralf†; Voltaren; Voltaren Ophtha; **India:** Cofenac; Diclomel; Diclodon; Diclodon†; Doflex; Dolocide K; Dolocide Plus; Esgipyrin DS; Fenlodac†; Fensaider†; I-Gesic; Jonac; K-Fenac; Nac; Nac Gel; Oxalgin; Oxalgin-D; Oxalgin-SR; Profenac; Reactine; Relaxyl; Solunac; Tromagesic; Tromax; Voveran; **In-don:** Abdiflam; Ailflam; Atranan; Berifen; Cataflam; Catanan; Deflamat; Diclowlam; Diclomex; Dillam; Divoltar; Eflagen; Exaflam; Fenaren; Fenavel; Flamar; Flamenac; Kadiflam; Kaflam; Kamaflam; Klotaren; Laflana; Linac; Matsunaflam; Merflam; Nadifen; Neurofenac; Nichoflam; Nilaren; Potazen; Pratanac; Provoltar; Reclofen; Renadinac; Renvol; Scanaflam; Scantaren; Tirmaclo; Valtol; Voltamit; Voltadex; Voltaren; Voltaren Ophtha; Voren; X-Flam; Xepathritis; Yaniflam; Zegren; **Irl:** Arthroctec; Cataflam; Diclac; Diclod; Diclomax; Diclomel; Difene; Solaraze; Vologen†; Voltarol; Voltarol Ophtha; **Israel:** Abitren; Arthroctec; Betaren; Cataflam; Diclodipast; Diclodengel; Olfen; Voltaren; Voltaren Ophtha; **Ital:** Algosenac; Artrofenac†; Arthroctec; Dealgic; Deflamat; Dicloular; Diclolan; Diclodifil; Diclodal; Diclodeum; Diclodears; Dolaut; Doroxan; Droplam; Fenadol; Fender; Flector; Flogofenac; Forgenac; Itami; Levigol; Lisifen†; Misofenac; Monofenac; Novapirina; Pennsaid; Ribex Flu†; Solaraze; Topflam; Voltadol; Voltaren; Voltfast; Zero-flog; **Jpn:** Anavan; **Malaysia:** Almiral; Apo-Diclo†; Cataflam; Clodex; Clodenac; Difinal; Fenac; Fenadium†; Inflana; Lesflam; Neo-Pyrazon; Olfen; Remafen†; Remethan; Rhewin†; Takst†; Uniren; Voltaren; Voren; Wan-Diclowl†; Zolterol; **Mex:** 3A Ofteno; Alsidexten; Ariflam; Artrenac; Artrenac N; Artrenac; Arthroctec; Atalak; Cataflam; Clo-Far; Clonodifen; Coral; Deflox; Diclafena; Diclac; Diclolan; Diclodos; Dioxaflex; Dirret; Docril; Dofen; Dolaren; Doflaml; Dolo-fenac; Doltarac; Evadol; Fenagel; Fenalgin; Fervex; Flamydol; Flamygel; Flankol; Flogoken; Flotac; Fortical; Fustaren; Gal-edol; Hilo Sport; Lertus; Lifenan; Liroken; Lodyfen; Logesic†; Lonatec; Lu-fac-Z; Mafena; Manacox; Merxil; Metracin; Musok; Nedidon; Neo-Dolaren; Phamaflam; Pratiser; Precifenac; Selectofen; Stofil; Uni-Fenil†; Vicma-fen; Voltaren; Voltaren; **Neth:** Arthroctec; Arthroctec; Cataflam; Itami; Mis-ofenac; Naclofl; Normulen; Otrifur; Voltaren; **Norw:** Arthroctec; Cataflam; Modifenac; Otrifur; Solaraze; Voltaren; Voltaren Ophtha; **NZ:** Apo-Diclo; Cataflam; Diclac; Diclodhexal; Flameril; Voltaren; Voltaren Ophtha; Voltfast; **Philipp:** Aculflam; Cataflam; Clodex; Clodif; Clonaren; Difenan; Dillapan; Diclolan; Dycon; Eslofen; Fenaspex; Lobafen; Lofenac; Neo-Pyrazon; Nephente; Parafortan; Rheuflam; Unidolac; Voltaren; Voltaren; Voren; Zo-bid†; **Pol:** Apo-Diclo; Arthroctec; Cataflam; Diclac; Diclodober; DiclodoDuo; Diclodon†; Diclodeum; Diclodo; Diclodon†; P. Diclodozaj; Felogel; Majami; Naclofl; Naklofen; Olfen; Ratiogel; Rewodina; Veral; Voltaren; Voltarenac; **Port:** Arthroctec; Cataflam; Cloden; Diclodabac; Diclodent; Diclodifal; Diclodispray; Diclodex; Diclone; Dofene; Dolacox; Dorcalor; Fenac; Fenil-V; Flameril; Flector; Olfen; Otrifur; Painex; Pennsaid; Solaraze; Voltaren; **Rus:** Almiral (Аммирал); Apo-Diclo (Апо-дикло); Arthroctec (Артротек); Diclac (Диклак); Diclod-F (Дикло-Ф); Diclodene (Диклобене); Diclodier (Диклобер); Diclodonat (Диклонат); Diclolan (Диклолан); Diclovit (Дикловит); Feloran (Фелоран); Naclof (Наклоф); Naklofen (Наклофен); Naklofen Duo (Наклофен Дью); Rapten Rapid (Раттен Рэпид); Voltaren (Вольтарен); **S.Afr:** Adco-Clodiflam; Arcanafenac; Arthroctec; Arthru-Derm; Cataflam; Diclowlam; Diclodhexal; Dynac; Flexagen; Fortifen; Infla-Bar; K-Fenac; Panamor; Phamaflam†; Veltex; Voltaren; Voltaren Ophtha; **Singapore:** Almiral; Cataflam; Clodex; Clodenac; Diclod; Diclodo-Denk†; Diclolan; Diclowl†; Difenan; Difinal; Inac; Inflana; Lesflam; Neo-Pyrazon†; Olfen; Pritaren; Remafen; Remethan†; Rhewin; Ultrafen; Uniren; Voltaren; Voltaren Ophtha; Voren; Zolterol; **Spain:** Arthroctec; Di Retard; Dolo Nervobion; Dolo-Voltaren; Doltoren; Luase; Normulen; Sulexon; Voltaren; **Swed:** Arthroctec; Flector; Modifenac†; Solaraze; Voltaren; Voltaren Ophtha; Voltaren T; **Switz:** Agofenac†; Arthroctec; Athrofen; Deflamat†; Diclac; diclodo-basan; Diclod†; Diclodifal; Ecofenac; Efligel; Flector; Fortenac; Grofenac; Inflamac; Olfen; Primofenac; Relova; Tonopon; Vifenac; Voltaren Dolo; Voltaren Emulgel; Voltaren Ophtha; Voltarene; **Thai:** Almiral†; Ammi-Votara; Ammi-nac; Arclonan; Arthroctec†; Cataflam; Catanan; Cencenac; Chinclonac; Clodex; Clodex; Demac; Dicloden†; Diclodgel; Diclolan; Diclomel; Diclodian; Dicloden†; Diflen; Difenan; Difengiesic; Difeno; Dinac; Dinefec†; Dosanac; Fenac; Fenagel; Flexy; Inflana; Lesflam; Lofenac; Masaren; Medaren†; My-fenac; Myonac; N-Zen; Naclof; Olfen†; Ostaren; Posnac; Putaren†; Remethan; Rhumalon†; Rumatab†; Sefnac; Sillam†; Subsyde; Taks; Tarjen†; Tarjena; Uniren; Vasalen; Veenac; Ventarone; Voltarenac; Volnac; Volta; Voltanac; Voltaren; Voltarenac; **Turk:** Actinoma; Cataflam; Deflamat; Diclodiflam; Diclomex; Difenan; Diclolan; Dolorex; Inflased; Kalidren; Miyadren; Voltaren; Voltaren Ophtha; **UAE:** Cloden; **UK:** Acoflam†; Arthroctec; Defanac; Defenan; Dexomxon; Diclodex; Diclomax; Diclowl†; Diclodip; Dyloject; Econac; Fenactol; Flamatka; Flamrase; Lofensaid†; Motifene; Pennsaid; Rheumatac; Rhumalgol; Slofenac; Solaraze; Voltarenac; Voltaren; Voltarol; Voltarol Ophtha; **USA:** Arthroctec; Cataflam; Flector; Solaraze; Voltaren; **Venez:** 3A Ofteno; Arthroctec; Artren; Campal; Cataflam; Cloden; Clodenac; Diagesic; Dicloden P; Diclodal; Diclodant†; Difenan; Diclodon; Diclolan; 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 Gestic; Corteroid Gestic; Cuniflam Plus; Delta Tomanil B12; Desiniflam Biotic†; Diclodigesic Forte; Diclodigesic Plus B12; Diclodigesic Relax; Diclodon Flex; Diclodon Relax; Dioxaflex B12; Dioxaflex Forte; Dioxaflex Gestic; Dioxaflex Plus; Dolo Nervobion; Dolo Nervobion 10000; Dolvan Flex; Doxtran B12; Doxtran Flex; Doxtran Gestic; Flaval; Glifapen; Hyancat; Igloodine Flex; Ingebrax; Lertus Biotic†; Metaflex Gestic; Metaflex Plus NF; Metilic; Mio Aldoron NF; Mio-Virobion NF; Naligflex Relax; Oxa B12; Oxa Forte; Oxa Sport; Oxadisten; Oxafem; Oxagesic; Pandoflex; Pandogesic; Rodinac B12; Rodinac Biotic; Rodinac Flex; Rodinac Gestic; Silfox Flex; Tafilol Artro; Tobradiclo; Tobratlas; Tomanil Flex; Vesalion B12; Vesalion Flex; Vesalion Gestic; Viartil Flex; Virobion B12 NF; Voltaren Flex; Voltaren Forte; Xedenol B12; Xedenol Flex; Xedenol Gestic; **Austria:** Diclowl; Dolo-Neu-

robin; Neodolpasce; Neurofenac; Voltamicin; **Belg:** Ocubrax; **Braz:** Algi-Butazonol†; Algi-Tanden†; Beseol; Cedrilax†; Codaten; Diclodetamol; Flex-algin; Mioflex X; Sedilax; Tandene; Tanderalgin; Tandrilan; Tandrilax; Torsilac; Triax†; **Cz:** Neurofenac; Voltamicin†; **Ger:** Combaren; Voltaren Plus; **Gr:** Tobrafen; **Hong Kong:** Neurofenac†; Vartelon-B; Viciadofen-Plus; **Hung:** Neodolpasce; Ocubrax†; Voltamicin†; **India:** Actimol; Buta-Proxylon; Cip-Zox; Cipzen D; Cofenac; Diclodenta; Diclomel; Diclolan M5; Diclolan-A†; Diclodisa; Diser; Doflex Plus; Dolocide KP; Dolocide MR; DP Gesic; Duoflam Gel; Esgipyrin; Fenapil; Fenapil-MR; Fensaider†; Flamar-MX; Flazen-D; Inflazon; Mysopaz Forte; New Panazon; Nicip D; Omnigel; Osteoflam-MR; Oxalgin-DP; Pacizox; Paracip Plus; Parvon Forte; Reactine Forte; Reactine Plus; Relaxyl Plus; Spasmo-Proxylon Forte; Systafam; **In-don:** Dolo-fenac; **Ital:** Voltamicin†; **Malaysia:** Voren Plus; **Mex:** Ariflam Forte; Diclodiv-B; Dolaren; Dolo-Neurobion; Dolo-Pangavit; Ducidol; Duoflex; Empatil; Lertus CD; Ortolcol; Tafilol AC; Trazinac; Tribedoce Compuesto; Uni-Dox; Voltaren Forte; **Pol:** Venozel; **Rus:** Diclodenal (Диклоденал); Diclolan Plus (Диклолан Плюс); **Singapore:** Voltamicin†; **Spain:** Ocubrax; **Switz:** Tobrafen; Voltamicin; **Turk:** Ocubrax; **Venez:** Combaren; Painfort; Todenac; Trazinac.

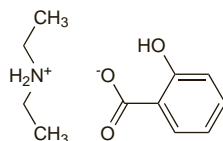
## Diethylamine Salicylate

Diaethylamini Salicylas; Diethylaminsalicylat; Dietyliamiinisalicylaatti; Salicilato de dietilamina; Salsilat Dietilamin.

Диэтиламин Салицилат; Салицилат Диэтиламина

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

CAS — 4419-92-5.



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

**Multi-ingredient:** **Arg:** Algesal; Cartiflex; Crema Antinfiammatoria; Fepar-ii†; Rati Sali Flex; Salicrem; **Austral:** Rubesal; **Austria:** Algesal; Derivon; Dolo-Menthoneurin; Dolorex†; Igitur-antirheumatische; Igitur-Rheumalfluid; Latesyl; Pasta rubra salicylata; Repari; Rheugesal; Thermal; **Belg:** Repari; **Braz:** Repari; **Chile:** Repari; **Cz:** Algesal; Repari-Gel N; **Fr:** Algesal Suractive; Repari; Traumalgyl; **Ger:** Algesal; Algesalona†; Dolo-Menthoneurin; Doloneuro†; Repari-Gel N; **Gr:** Algesal Suractive; Ponostop; **Hong Kong:** Repari; Rubesal; **Hung:** Algesal; Repari N; **Indon:** Algesal Super-active; **Ital:** Edeven; Repari; Sedaplan; Via Mal Traumagel; **Mex:** Algesal†; **Neth:** Algesal Forte; **Norw:** Thermal†; **Pol:** Repari N; **Port:** Algesal; Latesil; Medalgina; Venopari; **S.Afr:** Repari; **Spain:** Algesal; Contusin; Docomitil†; Dolmitin; Feparil; Radio Sali; **Switz:** Algesal†; Algesalona†; Mavena Proctol-Gem; Repari†; **Thai:** Repari; Veral; Gel; **Turk:** Algesal Suractive; Prepagel; **UAE:** Rubicalm; **UK:** Fiery Jack; Transvasin Heat Spray; **Venez:** Lemazol.

## Diflunisal (BAN, USAN, rINN)

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

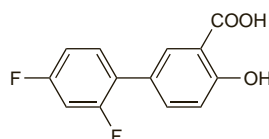
Дифлунисал

$C_{13}H_8F_2O_3 = 250.2$ .

CAS — 22494-42-4.

ATC — N02BA11.

ATC Vet — QN02BA11.



**Pharmacopeias.** 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.<sup>1</sup> 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.<sup>1</sup>

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.<sup>1,2</sup> 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.<sup>1</sup> Heinz-body haemolytic anaemia occurred in one of the patients. Other hypersensitivity reactions associated with diflunisal therapy have included pneumonitis<sup>2</sup> and fulminant necrotising fasciitis.<sup>3</sup>

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 JE, et al. Necrotising fasciitis after diflunisal for minor injury. *Lancet* 1985; **ii**: 1432–3.

**Overdose.** Diflunisal poisoning has sometimes been fatal.<sup>1,2</sup> 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.<sup>1</sup> 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 JJ, 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