Nepafenac *(USAN, rINN)*

AHR-9434; AL-6515; Népafénac; Nepafenaco; Nepafenacum. 2-(2-Amino-3-benzoylphenyl)acetamide.

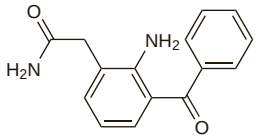
Непафенак

$C_{15}H_{14}N_2O_2$ = 254.3.

CAS — 78281-72-8.

ATC — S01BC10.

ATC Vet — QS01BC10.



Profile

Nepafenac, an NSAID (p.96), is a prodrug of amfenac. It is used in the treatment of pain and inflammation following cataract surgery. An ophthalmic suspension containing nepafenac 0.1% is instilled 3 times daily starting on the day before surgery and continuing for 2 weeks after surgery.

◊ References.

1. Colin J, Paquette B. Comparison of the analgesic efficacy and safety of nepafenac ophthalmic suspension compared with diclofenac ophthalmic solution for ocular pain and photophobia after excimer laser surgery: a phase II, randomized, double-masked trial. *Clin Ther* 2006; **28:** 527–36.
2. Lane SS. Nepafenac: a unique nonsteroidal prodrug. *Int Ophthalmol Clin* 2006; **46:** 13–20.
3. Lane SS, *et al.* Nepafenac ophthalmic suspension 0.1% for the prevention and treatment of ocular inflammation associated with cataract surgery. *J Cataract Refract Surg* 2007; **33:** 53–8. Correction. *ibid.*; 564.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Nevanac; ***Chile:*** Nevanac; ***Cz.:*** Nevanac; ***Port.:*** Nevanac; ***USA:*** Nevanac.

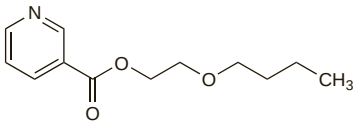
Nicoboxil *(rINN)*

Butoxyethyl Nicotinate; Nicoboxilo; Nicoboxilum. 2-Butoxyethyl nicotinate.

Никобоксил

$C_{12}H_{17}NO_3$ = 223.3.

CAS — 13912-80-6.



Profile

Nicoboxil is a nicotinate used in topical preparations as a rubefacient. It is also included in some topical preparations used for the treatment of acne vulgaris.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Finalgon; ***Austria:*** Finalgon; ***Canad.:*** Finalgon†; ***Ger.:*** Finalgon; ***Ital.:*** Anti-Acne; ***NZ:*** Finalgon†; ***Port.:*** Finalgon; ***Rus.:*** Betalgon (Беталгон); Betanicomylon (Бетаникомилон); Finalgon (Финалгон); ***Spain:*** Finalgon; ***UK:*** Actinac.

Nicomorphine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de nicomorfina; Nicomorphine, Chlorhydrate de; Nicomorphini Hydrochloridum. 3,6-Di-*O*-nicotinoylmorphine hydrochloride; (–)-(5*R*,6*S*)-4,5-Epoxy-9a-methylmorphin-7-en-3,6-diyl dinicotinate hydrochloride.

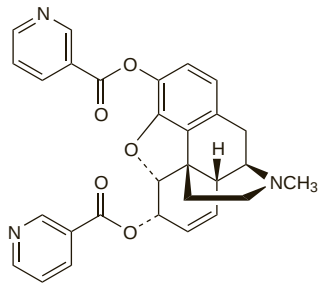
Никоморфина Гидрохлорид

$C_{29}H_{25}N_3O_5$,HCl = 532.0.

CAS — 639-48-5 (nicomorphine); 12040-41-4 (nicomorphine hydrochloride); 35055-78-8 (nicomorphine xHCl).

ATC — N02AA04.

ATC Vet — QN02AA04.



(nicomorphine)

Profile

Nicomorphine hydrochloride is an opioid analgesic (p.101) used in the treatment of moderate to severe pain. It is given in oral doses of 5 to 10 mg daily or by intramuscular, slow intravenous, or subcutaneous injection in doses of 10 to 20 mg; higher doses have also been used. It may also be given rectally in usual doses of 10 to 20 mg daily.

◊ References.

1. Koopman-Kimenai PM, *et al.* Pharmacokinetics of intravenously administered nicomorphine and its metabolites in man. *Eur J Anaesthesiol* 1993; **10:** 125–32.
2. Koopman-Kimenai PM, *et al.* Rectal administration of nicomorphine in patients improves biological availability of morphine and its glucuronide conjugates. *Pharm World Sci* 1994; **16:** 248–53.
3. Koopman-Kimenai PM, *et al.* The bioavailability of intramuscularly administered nicomorphine (Vilan) with its metabolites and their glucuronide conjugates in surgical patients. *Int J Clin Pharmacol Ther* 1995; **33:** 442–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Vilan; ***Denm.:*** Vilan; ***Neth.:*** MorZet; Vilan†; ***Switz.:*** Vilan.

Niflumic Acid *(rINN)*

Acide niflumique; Ácido niflúmico; Acidum niflumicum; UP-83. 2-(ααα-Trifluoro-*m*-toluidino)nicotinic acid.

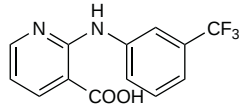
Нифлумовая Кислота

$C_{13}H_9F_3N_2O_2$ = 282.2.

CAS — 4394-00-7.

ATC — M01AX02; M02AA17.

ATC Vet — QM01AX02; QM02AA17.



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

Ph. Eur. 6.2 (Niflumic Acid). A pale yellow, crystalline powder. Practically insoluble in water; soluble in alcohol and in methyl alcohol; freely soluble in acetone.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Fluoride-associated osteosis has been reported with prolonged use. Niflumic acid should be stopped if hypersensitivity skin reactions appear.

Effects on the skin. From a case-control study[1] of children admitted to a hospital emergency department in Italy it was calculated that the odds-ratio of users of niflumic acid, or its derivative morniflumate, developing serious cutaneous reactions was 4.9. Given this figure and the fact that safer drugs were available the authors considered that there was no indication for which niflumic acid was required in children. However, a large cohort study[2] involving 193 727 children aged between 0 and 14 years found that niflumic acid was not associated with a higher risk of mucocutaneous reactions when compared with other NSAIDs or paracetamol. The authors of the later study suggested that the conclusions of the original study may have been confounded because there was no adjustment for age or indication.

1. Menniti-Ippolito F, *et al.* Niflumic acid and cutaneous reactions in children. *Arch Dis Child* 2001; **84:** 430–1.
2. Sturkenboom M, *et al.* Incidence of mucocutaneous reactions in children treated with niflumic acid, other nonsteroidal antiinflammatory drugs, or nonopioid analgesics. Abstract: *Pediatrics* 2005; **116:** 212. Full version: http://pediatrics.aappublications.org/cgi/content/full/116/1/e26 (accessed 08/11/07)

Uses and Administration

Niflumic acid, a nicotinic acid derivative, is an NSAID (p.99). It has been used in inflammatory and musculoskeletal and joint disorders in usual oral doses of about 250 mg three or four times daily; up to 1500 mg daily has been used in severe disorders. It has also been used topically as a 3% cream or ointment or 2.5% gel. The morpholinoethyl ester, morniflumate (p.86), has similar uses.

Niflumic acid glycinamide has been used topically in inflammatory mouth disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Flogovital; ***Belg.:*** Niflugel; Nifluril; ***Cz.:*** Niflugel; Nifluril; ***Fr.:*** Flunir†; Niflugel; Nifluril; ***Gr.:*** Niflamol; Novopone†; ***Hung.:*** Donalgin; ***Ital.:*** Niflam; ***Port.:*** Nifluril; ***Rus.:*** Donalgin (Доналгин); ***Spain:*** Niflactol.

Multi-ingredient: ***Arg.:*** Flogodisten.

Nimesulide *(BAN, rINN)*

Nimesulid; Nimesulida; Nimesulidas; Nimésulide; Nimesulidi; Nimesulidinum; Nimesulidum; Nimeszulid; R-805. 4′-Nitro-2′-phenoxymethanesulphonanilide.

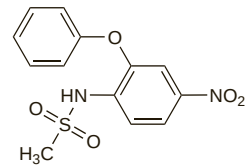
Нимесулид

$C_{13}H_{12}N_2O_5S$ = 308.3.

CAS — 51803-78-2.

ATC — M01AX17.

ATC Vet — QM01AX17.



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

Ph. Eur. 6.2 (Nimesulide). A yellowish crystalline powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in dehydrated alcohol; freely soluble in acetone.

Profile

Nimesulide is an NSAID (p.96) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It may be given in oral doses of up to 100 mg twice daily for inflammatory conditions, fever, pain, and dysmenorrhoea; use in the EU is limited to a maximum of 15 days due to reports of hepatotoxicity (see Adverse Effects, below). It has also been given rectally in a dose of 200 mg twice daily or applied topically as a 3% gel. Nimesulide betadex (nimesulide betacyclodextrin complex) has been used similarly.

◊ References.

1. Bennett A, *et al.* Nimesulide: a multifactorial therapeutic approach to the inflammatory process? a 7-year clinical experience. *Drugs* 1993; **46:** (suppl 1): 1–283.
2. Senna GE, *et al.* Nimesulide in the treatment of patients intolerant of aspirin and other NSAIDs. *Drug Safety* 1996; **14:** 94–103.
3. Vizzardi M, *et al.* Nimesulide beta cyclodextrin (nimesulide-betadex) versus nimesulide in the treatment of pain after arthroscopic surgery. *Curr Ther Res* 1998; **59:** 162–71.
4. Bernareggi A. Clinical pharmacokinetics of nimesulide. *Clin Pharmacokinet* 1998; **35:** 247–74.
5. Shah AA, *et al.* Selective inhibition of COX-2 in humans is associated with less gastrointestinal injury: a comparison of nimesulide and naproxen. *Gut* 2001; **48:** 339–46.
6. Nüing RM, *et al.* Pathogenetic role of cyclooxygenase-2 in hyperprostaglandin E syndrome/antenatal Bartter syndrome: therapeutic use of the cyclooxygenase-2 inhibitor nimesulide. *Clin Pharmacol Ther* 2001; **70:** 384–90.

Adverse effects. Although *thrombocytopenia* is a common feature in patients infected with HIV, a group of workers considered that thrombocytopenia in one of their patients was related to the use of nimesulide.[1]

There have been reports[2-4] of *hepatotoxicity* after treatment with nimesulide. Data from spontaneous reports has also suggested that nimesulide may be associated with a higher risk of hepatotoxicity than other NSAIDs.[4] A cohort study[5] involving about 400 000 users of NSAIDs in one region of Italy between 1997 and 2001 found that those taking nimesulide were 1.3 times more likely to develop hepatotoxicity than users of other NSAIDs and 1.9 times more likely to suffer severe liver injury. In May 2007 the Irish regulatory authority withdrew nimesulide from the Irish market after concerns about hepatotoxicity.[6] Since being licensed in 1995, nimesulide had generated 53 adverse reaction reports involving liver toxicity, including 9 cases of liver failure, 3 of which resulted in death and 6 in liver transplantation; there had also been 1 other liver-related fatality. The EMEA[7] subsequently recommended that treatment with nimesulide should be limited to 15 days.

There have been reports[8,9] of *toxic pustuloderma* (acute generalised exanthematous pustulosis) after receiving oral nimesulide. *Fixed drug eruptions* have also been seen.[10]

An infant developed hypotension and hypothermia after inadvertently taking an *overdose* of 8 times the recommended daily dose of nimesulide.[11] The patient recovered after gastric lavage with activated charcoal and supportive therapy.

1. Pasticci MB, *et al.* Nimesulide, thrombocytopenic purpura, and human immunodeficiency virus (HIV) infection. *Ann Intern Med* 1990; **112:** 233–4.

2. McCormick PA, *et al.* COX 2 inhibitor and fulminant hepatic failure. *Lancet* 1999; **353:** 40–1.
3. Sbeit W, *et al.* Nimesulide-induced acute hepatitis. *Ann Pharmacother* 2001; **35:** 1049–52.
4. Maciá MA, *et al.* Hepatotoxicity associated with nimesulide: data from the Spanish pharmacovigilance system. *Clin Pharmacol Ther* 2002; **72:** 596–7.
5. Traversa G, *et al.* Cohort study of hepatotoxicity associated with nimesulide and other non-steroidal anti-inflammatory drugs. *BMJ* 2003; **327:** 18–22.
6. Irish Medicines Board. Immediate suspension of the marketing of medicines containing nimesulide (issued 15th May, 2007). Available at: http://www.imb.ie/EN/Safety--Quality/Advisory-Warning--Recall-Notices/Human-Medicines/Nimesulide-Suspension.aspx?page=1&noticetypeid=-1&year=2007 (accessed 08/11/07)
7. EMEA. Questions and answers on the CHMP recommendation on nimesulide-containing medicines (issued 21st September, 2007). Available at: http://www.emea.europa.eu/pdfs/human/opinion/43098807en.pdf (accessed 08/11/07)
8. Lateo S, Boffa MJ. Localized toxic pustuloderma associated with nimesulide therapy confirmed by patch testing. *Br J Dermatol* 2002; **147:** 624–5.
9. Teixeira M, *et al.* Acute generalized exanthematous pustulosis induced by nimesulide. *Dermatol Online J* 2006; **12:** 20. Available at: http://dermatology.cdlib.org/126/case_presentations/agep/teixeira.html (accessed 08/11/07)
10. Malheiro D, *et al.* Nimesulide-induced fixed drug eruption. *Allergol Immunopathol (Madr)* 2005; **33:** 285–7.
11. Yapakci E, *et al.* Hypoglycaemia and hypothermia due to nimesulide overdose. *Arch Dis Child* 2001; **85:** 510.

Pregnancy. Irreversible *end-stage renal failure* has been reported in a neonate born to a mother who received nimesulide as a tocolytic from the 26th to the 32nd week of pregnancy.[1] Others have reported neonatal renal failure associated with nimesulide.[2] *Premature closure of the ductus arteriosus* leading, in some cases, to *persistent pulmonary hypertension* has also been seen in 10 neonates whose mothers self-medicated with nimesulide during the third trimester of pregnancy.[3]

1. Peruzzi L, *et al.* Neonatal end-stage renal failure associated with maternal ingestion of cyclo-oxygenase-type-2 selective inhibitor nimesulide as tocolytic. *Lancet* 1999; **354:** 1615. Correction. *ibid*. 2000; **355:** 238.
2. Balasubramaniam J. Nimesulide and neonatal renal failure. *Lancet* 1999; **355:** 575.
3. Paladini D, *et al.* Severe ductal constriction in the third-trimester fetus following maternal self-medication with nimesulide. *Ultrasound Obstet Gynecol* 2005; **25:** 357–61.

Premature labour. Nimesulide has been tried as an alternative to indometacin to delay labour in patients with a history of preterm delivery (p.2003). Nimesulide was given from 16 to 34 weeks of gestation and a successful delivery started 6 days after withdrawal.[1] There appeared to be no adverse effect on fetal renal function or the ductus arteriosus. The authors suggested that fetal prostaglandin synthesis might be mainly mediated through cyclo-oxygenase-1 (COX-1) and that a relatively selective COX-2 inhibitor such as nimesulide might produce fewer adverse effects on the fetus than other non-selective NSAIDs. However, in a small study short-term effects on the fetus were similar for nimesulide, indometacin, and sulindac.[2]

Adverse effects have been reported in some neonates whose mothers received nimesulide during their pregnancies, see above.

1. Sawdy R, *et al.* Use of a cyclo-oxygenase type-2-selective non-steroidal anti-inflammatory agent to prevent preterm delivery. *Lancet* 1997; **350:** 265–6.
2. Sawdy RJ, *et al.* A double-blind randomized study of fetal side effects during and after the short-term maternal administration of indomethacin, sulindac, and nimesulide for the treatment of preterm labor. *Am J Obstet Gynecol* 2003; **188:** 1046–51.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Aldoron; Aulin†; Doloctaprin†; Flogovital NF; Metaflex†; Virobron; ***Austria:*** Aulin; Mesulid; ***Belg.:*** Mesulid; ***Braz.:*** Antiflogil†; Cimelide; Deflogen; Deltaflan; Fasulide; Flogilid†; Inflalid; Maxsulid; Neosulida; Nimalgex†; Nimedalin†; Nimeflan†; Nimesilam; Nimesubal; Nimesulin; Nimesulix; Nimesulon; Nisalgen†; Nisoflan; Nisuflex; Nisulid; Optaflan†; Scaflam; Scalid; Sintalgin; ***Chile:*** Áinex; Aulin†; Doloc; Nimepast; Nimesyl; Nimex†; Nisulid; Nisural; ***Cz.:*** Aulin; Coxtral; Mesulid; Nimed; Nimesil; ***Fin.:*** Nimed†; ***Fr.:*** Nexen; ***Gr.:*** Aflogen; Alencast; Algosulid; Algover; Amocetin; Aulin; Auromelid; Chemisulide†; Cliovyl; Discorid; Dolostop; Edrigyl; Elinap; Erlecit; Fladalgin; Flogostop; G-Revm; Kartal; Lalide; Lasazin; Lemesil; Lizepat; Londopon†; Lovirem; Melicate; Melimont; Mesulid; Mesupon; Min-A-Pon; Mosuolit; Multiformil; Myxina; Naofid; Niberan; Nimegel; Nimelide; Nimesul; Omnibus; Rhemid; Ristolzit; Ritamine; Rolaket; Scaflam†; Specilid; Sudinet; Tranzicalm; Ventor; Volonten; ***Hong Kong:*** Mesulid; Nidol; Nimm; ***Hung.:*** Mesulid; Nidol; Nimelid; Xilox; ***India:*** Beta Nicip; Mesulid; Nicip; Nilide; Nimcet; Nimfast; Nimica; Nimodol; Nimulid; Nimusyp; Nimutab; Nimvista; Nise; Willgo†; ***Indon.:*** Arnid; Aulin; Nicox; Nimed; Nimost; Sohoflam; Ximede; ***Irl.:*** Aulin†; Mesine†; Mesulid†; ***Israel:*** Mesulid; ***Ital.:*** Algimesil; Algolider; Antalgo; Areuma; Aulin; Biosal†; Delfos; Dimesul; Doleside†; Doloxtren†; Domes; Edemax†; Efridol; Erreflog; Eudolene; Fansidol†; Fansulide; Flolid; Idealid; Isodol; Laidor†; Ledolid†; Ledoren; Lidenix†; Mesulid; Migraless; Nerelid; Nide†; Nimedex; Nimenol; Nimesil; Nimesulene; Nimexan†; Nims; Noalgos; Noxalide; Pantames; Remov; Resulin; Solving; Sulidamor; Sulide; ***Malaysia:*** Nidol†; ***Mex.:*** Apolide; Cargespril; Defam; Degorflan; Dexlin; Eskaflam; Fenoxil; Flamide; Flamozin; Inim; Lesiden; Lusemin; Meliden; Mesulid; Minus†; Nimepis; Nizurin; Quidofril; Redaflam; Severin; Sidel; Sindel; Sulidek; Sundir; Ul-Flam; ***Philipp.:*** Aulin; Flamesul; Mesulid; Nidolid; Sorini; ***Pol.:*** Aulin; Minesulin; Nimesil; ***Port.:*** Aulin; Donulide; Gerilide; Jabasulide; Nimalge; Nimartin; Nimed; Nimesulene; Reumolide; Sulidor; Sulimed; Vitolide; ***Rus.:*** Actasulid (Актасулид); Aponil (Апонил); Coxtral (Кокстрал); Nimesil (Нимесил); Nimica (Нимика); Nise (Найз); ***Singapore:*** Nidol†; Nise†; ***Switz.:*** Aulin; Nisulid; ***Thai.:*** Neptide; Nidol; Nilide; Nimes†; Nimind; Nimulid; ***Turk.:*** Mesulid; Motival; Nimes; Sulidin; ***Venez.:*** Ainex; Aulin; Drexel; Nimecox; Nimelid; Nimepirex†; Niprolide†; Nise†; Normosilen†; Reduben; Scaflan.

Multi-ingredient: ***Arg.:*** Doloctaprin Plus†; Metaflex Plus†; Mio Aldoron; Mio-Virobron; ***India:*** Cipzen N; Niciflex-T; Nicip Cold; Nicip D; Nicip MR; Nicip Plus; Nicip Super; Nicip T; Nicispas; Nimica Plus; Nimulid MR; Nimulid Nugel; Nimulid SP; Nimvista Plus; Nizer; ***Mex.:*** Amoxiclide; Zithroflam.

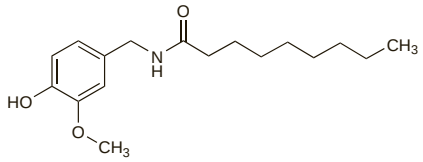
Nonivamide *(rINN)*

Nonivamida; Nonivamidum; Noniwamid; Nonylvanillamide; PAVA; Pelargonyl Vanillylamide; Pseudocapsaicin. *N*-Vanillylnonamide; *N*-[(4-Hydroxy-3-methoxyphenyl)methyl]nonanamide.

Нонивамид

$C_{17}H_{27}NO_3$ = 293.4.

CAS — 2444-46-4.



NOTE. Use of the term 'synthetic capsaicin' to describe nonivamide has arisen from the use of nonivamide as an adulterant for capsaicin and capsicum oleoresin.

Profile

Nonivamide is a synthetic analogue of capsaicin (p.32) that is used in topical preparations for the relief of muscular and rheumatic pain.

Nonivamide has also been used as a food flavour and in 'pepper sprays' for law enforcement and self defence.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: ABC Hydrogel-Warmepflaster; ***Ger.:*** ABC Warme-Pflaster Sensitive†; Gothaplast Capsicum-Warmepflaster; Hansaplast ABC Warme-Pflaster Sensitive†.

Multi-ingredient: ***Austral.:*** Finalgon; ***Austria:*** Finalgon; Rubriment; ***Canad.:*** Finalgon†; ***Cz.:*** Pain Expeller†; ***Ger.:*** Finalgon; Infrotto Ultra†; Lomazell forte N†; Ostochont†; Rheumasalbe†; Rubriment; Vertebralon N†; ***NZ:*** Finalgon†; ***Port.:*** Finalgon; ***Rus.:*** Betalgon (Беталгон); Betanicomylon (Бетаникомилон); Capsicam (Капсикам); Finalgon (Финалгон); ***Spain:*** Finalgon; ***Switz.:*** Forapin†; Histalgane; Radalgin; Thermocutan†; ***Thai.:*** Ammeltz.

Nonsteroidal Anti-inflammatory Drugs

AINE; AINS; Fármacos antiinflamatorios no esteroideos; NSAIDs; NSAİİ'ler.

НПВП; НПВС; НСПВП; Нестероидные Противовоспалительные Препараты

Adverse Effects and Treatment

The commonest adverse effects of NSAIDs are generally gastrointestinal disturbances, such as gastrointestinal discomfort, nausea, and diarrhoea; these are usually mild and reversible but in some patients peptic ulceration and severe gastrointestinal bleeding may occur. It is generally agreed that inhibition of cyclo-oxygenase-1 (COX-1) plays an important role in the gastrointestinal effects of NSAIDs; the selective inhibition of COX-2 improves gastrointestinal tolerance.

CNS-related adverse effects include headache, vertigo, dizziness, nervousness, tinnitus, depression, drowsiness, and insomnia. Hypersensitivity reactions may occur occasionally and include fever, angioedema, bronchospasm, and rashes. Hepatotoxicity and aseptic meningitis, which occur rarely, may also be hypersensitivity reactions. Some patients may experience visual disturbances.

Haematological adverse effects of NSAIDs include anaemias, thrombocytopenia, neutropenia, eosinophilia, and agranulocytosis. Unlike aspirin, inhibition of platelet aggregation is reversible with other NSAIDs.

Some NSAIDs have been associated with nephrotoxicity such as interstitial nephritis and nephrotic syndrome; renal failure may be provoked by NSAIDs especially in patients with pre-existing renal impairment. Haematuria has also occurred. Long-term use or abuse of analgesics, including NSAIDs, has been associated with nephropathy.

Fluid retention may occur, rarely precipitating heart failure in susceptible patients. Other cardiovascular adverse effects of NSAIDs, including those selective for COX-2 inhibition, are discussed in detail below.

Other adverse effects include photosensitivity. Alveolitis, pulmonary eosinophilia, pancreatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis are other rare adverse effects. Induction or exacerbation of colitis has also been reported.

Further details concerning the adverse effects of the individual NSAIDs may be found under their respective monographs.

Incidence of adverse effects. The relative toxicity of NSAIDs is a subject of debate.[1] Attempts have been made to rank these drugs according to their toxicity on various body systems.[2] The toxicity of selective cyclo-oxygenase-2 (COX-2) inhibitors has also been reviewed.[3] For further details see below under individual headings.

1. Skeith KJ, *et al.* Differences in NSAID tolerability profiles: fact or fiction? *Drug Safety* 1994; **10:** 183–95.
2. CSM/MCA. Relative safety of oral non-aspirin NSAIDs. *Current Problems* 1994; **20:** 9–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
3. Chaiamnuay S, *et al.* Risks versus benefits of cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs. *Am J Health-Syst Pharm* 2006; **63:** 1837–51.

Effects on the blood. The UK CSM has provided data on the reports it had received between July 1963 and January 1993 on agranulocytosis and neutropenia.[1] Several groups of drugs were commonly implicated, among them NSAIDs for which there were 133 reports of agranulocytosis (45 fatal) and 187 of neutropenia (15 fatal). The most frequently implicated NSAID was phenylbutazone with 74 reports of agranulocytosis (39 fatal) and 40 of neutropenia (4 fatal).

1. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)

Effects on bone. Prostaglandins have been shown to play an important role in the bone-healing process and, consequently, the decrease in prostaglandin levels produced by NSAID use may impair the healing process.[1] Under experimental conditions, many NSAIDs including the cyclo-oxygenase-2 (COX-2) inhibitors have been shown to reduce healing.[1] However, clinical evidence of such an effect is rare.[2] There is also concern that some NSAIDs such as indometacin may accelerate the rate of cartilage destruction in patients with osteoarthritis.[3,4]

1. Harder AT, An YH. The mechanisms of the inhibitory effects of nonsteroidal anti-inflammatory drugs on bone healing: a concise review. *J Clin Pharmacol* 2003; **43:** 807–15.
2. Glassman SD. *et al.* The effect of postoperative nonsteroidal anti-inflammatory drug administration on spinal fusion. *Spine* 1998; **23:** 834–8.
3. Rashad S, *et al.* Effect of non-steroidal anti-inflammatory drugs on the course of osteoarthritis. *Lancet* 1989; **ii:** 519–22.
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Effects on the cardiovascular system. ***BLOOD PRESSURE.*** A meta-analysis[1] of 50 randomised studies of the effects of NSAIDs on blood pressure in a total of 771 patients found that NSAIDs had elevated mean supine blood pressure by 5 mmHg. Piroxicam, indometacin, and ibuprofen had produced the greatest increase but the effect was only found to be statistically significant for piroxicam. Aspirin, sulindac, and flurbiprofen produced the smallest elevation in blood pressure while the effect of tiaprofenic acid, diclofenac, and naproxen was intermediate. The increase was more marked in studies in which patients had received antihypertensive therapy than in those where such treatment had not been used. NSAIDs had antagonised all antihypertensive therapy but the effect had been greater against beta blockers and vasodilators than against diuretics. An earlier meta-analysis of intervention studies had produced similar results.[2] Of the 1324 patients who had received NSAIDs, increases in mean arterial pressure were greatest in hypertensive patients who had taken either indometacin, naproxen, or piroxicam, although results were only significant for indometacin and naproxen. Sulindac and aspirin had minimal effects on mean arterial pressure.

It has been suggested that the use of NSAIDs in the elderly may increase the risk of the need for antihypertensive therapy.[3] A study[3] of 9411 patients aged 65 years or older who had just started treatment with antihypertensives found that 41% had used NSAIDs in the previous year compared with 26% of 9629 control patients not being treated with antihypertensives.

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2. Pope JE, *et al.* A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med* 1993; **153:** 477–84.
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