Cystic fibrosis. In patients with cystic fibrosis (see p.166), the inflammatory response to chronic pulmonary infection with *Pseudomonas* organisms contributes to lung destruction. NSAIDs have been studied in patients with cystic fibrosis as an alternative to corticosteroids to reduce pulmonary inflammation. A systematic review[1] found evidence in support of using high-dose NSAIDs, most notably ibuprofen, to slow the progression of lung damage in patients with cystic fibrosis. However, there are limited data about the long-term safety of high doses[1] and some consider that this may have limited such use of NSAIDs;[2] others remain to be convinced that a benefit has been demonstrated.[3] The reviewers did consider that there were sufficient data to recommend that NSAIDs be temporarily stopped when intravenous aminoglycosides or other nephrotoxic drugs are used.[1]

1. Lands LC, Stanojevic S. Oral non-steroidal anti-inflammatory drug therapy for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 07/11/07).
2. Fennel PB, *et al*. Use of high-dose ibuprofen in a pediatric cystic fibrosis center. *J Cyst Fibros* 2007; **6:** 153–8.
3. Bush A, Davies J. Non! to non-steroidal anti-inflammatory therapy for inflammatory lung disease in cystic fibrosis (at least at the moment). *J Pediatr* 2007; **151:** 228–30.

Pain. Findings from a long-term study[1] in 585 patients (mean age of 64 years) with knee pain suggested that oral and topical ibuprofen had an equivalent analgesic effect although the former was associated with more minor adverse effects; there was no difference in the rate of major adverse effects.

1. Underwood M, *et al*. Topical or oral ibuprofen for chronic knee pain in older people: the TOIB study. *Health Technol Assess* 2008; **12:** 1–176.

Patent ductus arteriosus. Ibuprofen or its lysine salt may be given **parenterally** for the treatment of patent ductus arteriosus (p.68) in preterm infants of less than 34 weeks' gestation; doses are expressed in terms of ibuprofen. Three intravenous doses (infused over 15 minutes) are given at 24-hour intervals; the initial dose is equivalent to 10 mg/kg of ibuprofen followed by two further doses of 5 mg/kg. If, 48 hours after this course of therapy the ductus remains open, a second course may be given, but if this produces no response surgery may be necessary. Ibuprofen injection, *when given as the base*, should be used undiluted, but if necessary it may be reconstituted with sodium chloride 0.9% or glucose 5% for injection. *When given as the lysine salt*, it should be diluted with sodium chloride 0.9% or glucose 5%.

For a suggestion that ibuprofen might be a better choice than indometacin for the treatment of patent ductus arteriosus, see p.68.

Preparations

BP 2008: Ibuprofen Cream; Ibuprofen Gel; Ibuprofen Oral Suspension; Ibuprofen Tablets;
USP 31: Ibuprofen and Pseudoephedrine Hydrochloride Tablets; Ibuprofen Oral Suspension; Ibuprofen Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Actron; Acuilfem; Afebril; Algioprofen†; Atomo Desinflamante Ibu; Bistryl†; Brunal†; Butidiona; Causalon Ibu; Copiron; Dolocox†; Dolorsyn; Druisel; Fabogesic; Febratic; Fontol; Ibu; Ibu Evanol; Ibu-Lady†; Ibu-Novalgina; Ibubenitol; Ibucalmin; Ibucler; Ibufabra; Ibufix; Ibulam; Ibumar; Ibumultin; Ibup; Ibupirac; Ibupiretas; Ibuprofenix; Ibuprofex; Ibusi; Ibusol; Ibusumal; Ibutenk; Ibuxim; Ibuzidine; Kesan†; Matrix; Motrax†; Novo Geniol; Oxibut; Pakurat; Paraflex Crema†; Ponstil Mujer; Ponstin; Ponstinetas; Salivia; Sindol; Teprix; Tonal; Vefren; ***Austral.:*** ACT-3; Actiprofen; Advil; Brufen; Bugesic†; Dimetapp Pain & Fever Relief; Hexal Compufen†; Nurofen; Proven; Rafen; Tri-Profen; ***Austria:*** Advil; Aktren; Avallone; Brufen; Dismenol Neu; Dolgit; Dolibu; Dolofort; Duafen; Ibu; Ibudol; Ibufem; Ibugel; Ibumetin; Ibupron; Iburem†; Ibutop; Imbun; Kratalgin; Momento; Nurofen; ratioDolor; Tabcin; Urem†; ***Belg.:*** Adulfen Lysine; Advil Mono; Brufen; Buprophar; Dolofin; Epsilon; Extrapan; Ibu-Slow†; Ibumed; Ibutop; Junifen; Malafene; Nurofebryl; Nurofen; Optalidon Nieuwe Formule; Perdofemina; Perdophen; Perviam; Provenol; Siprofen†; Spidifen; ***Braz.:*** Actiprofen; Advil; Algiflex; Algy-Flanderil†; Alivium; Artril; Dalsy; Doraplax†; Doretrim†; Dorigren; Frenador†; Ib-Profeno†; Ibufran; Ibupril; Ibuprofan; Lombalgina; Motrin; Parartrin; Spidufen; Uniprofen; ***Canad.:*** Advil; Motrin; Novo-Profen; ***Chile:*** Actron; Advil†; Bediatil; Bladex†; Deucodol; Dolorub; Fenpic†; Fortapal; Ibu; Ibu-4†; Ibu-6†; Ibupirac; Ipson; Kin; Motrin; Niofen; Pediaprofen; Pironal; Pyriped; Tifen†; ***Cz.:*** Advil; Baroc; Brufen; Dolgit; Ibalgin; Ibumax; Irfen†; Nurofen; Nurofen Advance; Nurofen Stopgrip; Pabiprofen; Panafen; Pedea; Solpaflex; Tomaflex; Urgo; ***Denm.:*** Apain; Brufen; Ibumetin; Ibureumin; Ibutop; Ipren; Pedea; Solpaflex†; ***Fin.:*** Brufen; Burana; Ibumax; Ibumetin; Ibusal; Ibuxin; ***Fr.:*** Advil; Anadvil; Antarene; Brufen; Dolgit; Doltaque; Ergix; Expanfen; Gelufene; Hemagene Tailleur; Ibualgic†; Ibutop; Intralgis; Nureflex; Nurofen; Nurofentabs; Nuroflash; Pedea; Solufen; Spedifen; Spifen; Upfen; ***Ger.:*** Advel; Aktren; Contraneural; Dismenol N; Dolgit; Dolo Sanol; Dolo-Puren; Dolodoc; Dolormin; Esprenit; Eudorlin Extra; Eudorlin Migrane; Gyno-Neuralgin; Gynofug†; Ibu; Ibu Benuron; ibu-Attritin; Ibu-ratiopharm; Ibubeta; Ibudolor; Ibuflam; Ibuhexal; Ibumerck; Ibuphlogont†; Ibuprof†; Ibutad; Ibutop; Ilvico grippal†; Imbun; Jenaprofen; Kontagripp; Mensoton; Migranin Ibuprofen; Novogent†; Nurofen; Optalidon; Opturem; Parsal; Pedea; Pfeil†; Phamoprofen†; ratioDolor†; Schmerz-Dolgit; Spalt; Tabalon; Tempi†; Tispol Ibu-DD; Togal Akut Ibuprofen; Trauma-Dolgit; Urem; ***Gr.:*** Advil; Algofren; Brufen; Buscofem; Nurofen; Rozovin†; ***Hong Kong:*** Advil; Bifen; Brufen†; Bupogesic; Dolo-Spedifen†; Ibufac; Ibupen; Neutropain; Nurofen; Perofen; Profen; Rupan†; Schufen; Spedifen; ***Hung.:*** Advil; Algoflex; Dolgit; Huma-Profen; Ibulos†; Ibumax; Ibutop; Melfen; Nurofen; Solpaflex; Spedifen; ***India:*** Brufen; Butafen†; Cipgesic; Emflam; Ibugesic; Ibupal; ***Indon.:*** Anafen; Arthrifen; Bufect; Dofen; Dolofen-F; Febryn; Fenris; Iprox; Lexaprofen; Nofena; Ostarin; Prifen; Profen; Proris; Rhelafen; Ribunal; Shelrofen; Spedifen; Yariven; ***Irl.:*** Advil; Brufen; Bufigen; Fenopine; Ibugel; Melfen; Nurofen; Phorpain; Proflex; Solfen†; ***Israel:*** Adex; Advil; Artofen; Ibufen; Ibuleve; Nurofen; ***Ital.:*** Algofen; Antalfebal; Antalfort; Antalgil; Antalisin; Arfen; Benflogin; Brufen; Buscofen; Calmine; Cibalgina Due Fast; Dolocyl; Dolofast; Edenil; Faspic; Ganaprofene†; Gineflor; Ginenorm; Moment; Nureflex; Nurofast; Nurofen; Nurosolv; Pedea; Subitene; Zafen†; ***Malaysia:*** Bifen; Brugesic†; Ibufac; Ibufen†; Nurofen; Perofen; Rupan†; Spedifen; ***Mex.:*** ABKI; Actron; Adivon; Advil; Aflusil; Ainex; Aldofen; Algidol; Bestafen; Carone; Citalgan; Dadicil; Days; Dibufen; Dipofen; Diprodol; Dolprin; Dolprofen; Dolval; Dolver; Eufenil; Febratic; Fidoin-Q; Flexafen; Gelidol; Gobrosan; Ibuflam; Ibuflex; Ifentil; Inpained; Maxifen; Medifen; Mejorultra†; Motrin; Natiken†; Novartril†; Offeno†; Pro-XB; Proartinal; Probuxil; Quadrax; Realdrax; Ribufen; Tabalon; ***Neth.:*** Advil; Brufen; Femapirin; Ibosure; Ibulgan†; Nurofen; Pedea; Roco; Sarixell; Spidifen; Zafen; ***Norw.:*** Brufen; Ibumetin; Ibuprox; Ibux; ***NZ:*** ACT-3; Brufen; Fenapaed; Ibucare; Nurofen; Panafen; ***Philipp.:*** Advil; Brufen; Dolan; Idyl; Medicol; Midol; Skelan; ***Pol.:*** Bolinet; Deep Relief†; Dolgit; Ibufen; Ibum; Ibupar; Ibuprom; Nurofen; Pedea; ***Port.:*** Anadvil; Arfen; Baroc; Brufen; Calbrun; Dolocyl; Dolomate; Dolormin; Faspic; Frenidor; Ibupax†; Junifen; Moment; Motrin†; Norvectan; Nupriland†; Nurofen; Ozonol; Pedea; Plusofen; Seclodin; Solufen; Solvium; Spidifen; Sporfen; Trifene; Zafen; Zip-A-Dol; ***Rus.:*** Aldospray (Альдоспрей); Burana (Бурана); Dolgit (Долгит); Ibufen (Ибуфен); Nurofen (Нурофен); Solpaflex (Солпафлекс); ***S.Afr.:*** Advil; Antiflam†; Betagesic; Betaprofen; Brufen; Brugesic†; Iboflam; Ibugesic; Ibuleve; Ibumax; Ibumed; Inza; Lenafen†; Norflam Ti; Nurofen; Painil†; Ranfen; ***Singapore:*** Ampifen†; Bifen; Ibufen; Ibuloid†; Nurofen; ***Spain:*** Advil; Aldospray Analgesico; Algiasdin; Algidrin; Alogesia; Altior; Babypiril; Bexistar; Calmafher†; Dadosel; Dalsy; Diltix; Doctril; Dolbufen; Dolorac; Dorival; Espidifen; Factopan; Feminalin; Fiedosin; Frenatermin; Gelofeno; Ibubex; Ibufen; Ibumac; Ibuprox; Inadol†; Isdibudol†; Isdol†; Junifen; Narfen; Neobrufen; Nodolfen; Norvectan; Nurofen; Oberdol; Oltyl†; Optajun; Paidofebril; Pedea; Pirexin; Pocyl†; Ratiodol; Remidol†; Saetil; Solvium; Takigrip†; Tedifebrin; ***Swed.:*** Alindrin; Brufen; Ibumetin; Ipren; ***Switz.:*** Algifor; Artofen; Brufen; Dismenol; Dolo-Dismenol; Dolo-Spedifen; Dolocyl; Ecoprofen; Grefen; Ibufen-L; Ibusifar; Iproben; Iprogel†; Irfen; Melabon; Nurofen; Optifen; Perskindol Ibuprofen acute; Saridon N; Sinedol Ibuprofen; Spedifen; Treupel Dolo Ibuprofen; ***Thai.:*** Ambufen; Anbifen; Aprofen; Babefen Sus†; Borafen; Borakid; Brufen; Brumed†; Bruprin; Brusil; Bumed; Cefen; Cenbufen; Duran†; Faspic; G-Fen; Gesica; Greatofen; Heidi; Ibrofen; Ibu; Ibufac; Ibugan; Ibulan; Iburen†; Junifen†; Mano-Bruzone; Nurofen; Ostofen†; P-Fen; Perofen†; Pippen; Probue; Probufen; Profena†; Profeno; Rheumanox; Rumasian; Rumatifen; Rupan†; Schufen; Skelan IB; Tofen; Trofen; Umafen; ***Turk.:*** Advil; Artril; Bebol; Biophen; Brufen; Dolgit; Dolven; Gerofen; Ibu-600; Ibufen; Nurofen; Pedifen; Profen; Repozal; Rofen; Siyafen; Suprafen; Temsofen; Ultrafen; Upren; ***UAE:*** Profinal; ***UK:*** Advil; Anadin Ibuprofen; Anadin Joint Pain; Anadin Ultra; Arthrofen; Biatain-Ibu; Brufen; Calprofen; Cuprofen; Ebufac; Fenbid; Fenpaed; Feverfen; Galprofen; Hedex Ibuprofen; Ibrufhalal; Ibufem; Ibugel; Ibuleve; Ibumousse; Ibuspray; Ibutop Cuprofen; Ibutop Ralgex; Librofem; Mandafen; Manorfen; Mentholatum Ibuprofen; Migrafen; Motrin†; Novaprin; Nurofen; Nurofen Migraine; Obifen; Orbifen; Pacifene; Pedea; Phor Pain; Proflex; Radian-B Ibuprofen; Relcofen; Rimafen; ***USA:*** Advil; Anadar; Genpril†; Haltran†; Ibu; Ibu-Tab; Ibu-4, -6, -8; Ibutab; Menadol; Midol Cramp & Body Aches; Motrin; NeoProfen; Nuprin†; Saleto-200; ***Venez.:*** Advil; Brugesic; Bupriten†; Buprodol; Butilene†; Dologesic; Femicaps; Femmex Plus; Ibucaps; Ibufen; Ibufenac†; Iburin; Iburox†; Ibutan; Lumbax; Max; Maydol; Mestral; Motrin; Pedibu.

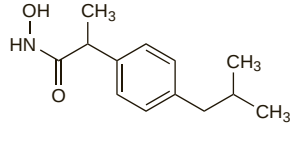
Multi-ingredient: ***Arg.:*** Aliviagrip; Bioneural B12†; Buscapina Fem; Butidiona†; Causalon Gesic†; Deep Relief†; Dexprofeno; Espasmo Ibupirac†; Espasmo Motrax†; Espasmofin; Ibu Evanol Plus; Ibu-Buscapina†; Ibu-Tetralgin; Ibudolofrix; Ibudristan; Ibumar Migra†; Ibunastizol; Ibupirac Fem; Ibupirac Flex; Ibupirac Migra; Mensalgin; Migral II; Novo Wilpan†; Roveril; Supragesic; ***Austral.:*** Dimetapp Headcold & Flu; Nurofen Cold & Flu; Nurofen Plus; Panafen Plus; Sudafed Sinus & Anti-inflammatory Pain Relief; Tri-Profen Cold & Flu†; ***Austria:*** Advil Cold; Ardinex; ***Belg.:*** Adulfen Codeine; ***Braz.:*** Algi-Itamanil†; Algi-Reumatril; Algifen†; Fymnal†; Reuplex; ***Canad.:*** Advil Cold & Sinus; Advil Cold & Sinus Plus; Childrens Advil Cold; Dristan Sinus†; Robax Platinum; Sudafed Sinus Advance; Vicks DayQuil Sinus & Pain Relief; ***Chile:*** Adona; Artritapsin; Butartrol; Deucodol Plus; Dioran†; Dolnix; Dolo Winasorb; Dolo-Niofen; Dolo-Octirona; Dolonase; Gedol†; Ibupirac Compuesto; Ibupirac Flu; Ipson-D; Midol†; Neo Butartrol; Niofen Flu; Predual DI†; Silartrin†; Termo-Niofen; ***Cz.:*** Advil Cold; Ardinex†; Ibu-Hepa; Ibufein†; Modafen; ***Fin.:*** Ardinex; Burana-C; ***Fr.:*** Anadvil Rhume; Cliptol; Nurofen Rhume; Rhinadvil; Rhinathiol Rhume†; Rhinureflex; Vicks Rhume†; ***Gr.:*** Nurofen CF; Vicks; ***Hung.:*** Advil Cold; Algoflex-M; Deep Relief; Nurofen Cold & Flu; Rhinathiol Cold; ***India:*** Acks; Anaflam; Answell; Bruace; Cipgesic Plus; Combiflam; Duoflam; Duoflam Plus; Emflam Plus; Flexon; Flexon-MR; Ibu-Proxyvon; Ibuflamar-P; Ibugesic Plus; Ibugesic-M; Reactine Forte; Reducin-A†; Robiflam; Somaflam; ***Indon.:*** Aknil; Axalan; Iremax; Limasip; Neo Rheumacyl; Neuralgin; Shelrod-Plus; ***Irl.:*** Advil Cold & Flu; Codafen Continus†; Nurofen Cold & Flu; Nurofen Plus; ***Israel:*** Nurofen Cold & Flu; ***Ital.:*** Solviflu; Vicks Flu-Action; ***Jpn:*** Colgen Kowa IB Toumei; ***Mex.:*** Algitrin; Bipasmin Compuesto NF†; Carbager-Plus; Dualgos; Sinutab Advance; ***NZ:*** Nurofen Cold & Flu; Nurofen Plus; ***Philipp.:*** Alaxan; Anoflam; Brustan; Flexigesic; Muskelax; Restolax; Selxan; ***Pol.:*** Ardinex; Dip Rilif; Ibalgin Sport; Ibuprom Zatoki; Metafen; Modafen; Nurofen Antigrip; Nurofen Plus; ***Rus.:*** Brustan (Брустан); Ibuclin (Ибуклин); Novigan (Новиган); Nurofen Plus (Нурофен Плюс); ***S.Afr.:*** Advil CS; Dentopain; Gen-Payne; Ibucod; Ibumol; Ibupain; Ibupain Forte; Lotem; Mybucod; Mybulen; Mypaid; Myprodol; Nurofen Cold & Flu; Sinumax IB; ***Spain:*** Nurofen Complex; Salvarina; ***Swed.:*** Ardinex; ***Switz.:*** Ibufen-L; ***Thai.:*** Alaxan Pl; Brustan; Cetan; Dologen; Kintal†; Rumatifen-Plus; Skelan; ***Turk.:*** Nurofen Cold & Flu; ***UAE:*** Profinal Cold & Sinus; Profinal FM; Profinal XP; ***UK:*** Codafen Continus†; Cuprofen Plus; Deep Relief; Lemsip Flu 12Hr; Lemsip Pharmacy Powercaps; Non-Drowsy Sudafed Dual Relief Max; Nurofen Cold & Flu; Nurofen Plus; Nurofen Sinus; Orbifen Cold & Flu; Solpadeine Migraine; Solpaflex; ***USA:*** Advil Allergy Sinus; Advil Cold & Sinus; Advil PM; Anadar Cold & Flu; Childrens Advil Cold; Childrens Ibuprofen Cold; Childrens Motrin Cold; Combunox; Dimetapp Childrens Cold & Fever; Dimetapp Sinus; Dristan Sinus; Ibudone; Motrin IB Sinus; Reprexain; Sine-Aid IB; Vicoprofen; ***Venez.:*** Brudol; Brugesina; Colfene; Femmexultra; Ibucoden.

Ibuproxam *(rINN)*

Ibuproxamum. 4-Isobutylhydratropohydroxamic acid.

Ибупроксам

$C_{13}H_{19}NO_2$ = 221.3.
CAS — 53648-05-8.
ATC — M01AE13.
ATC Vet — QM01AE13.



Profile

Ibuproxam is an NSAID (p.96) that has been used topically as a 5% ointment in musculoskeletal, joint, and soft-tissue disorders.

Preparations

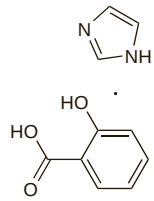
Proprietary Preparations (details are given in Part 3)
Ital.: Ibudros†; ***Spain:*** Nialen.

Imidazole Salicylate *(rINN)*

Imidazole, Salicylate d'; Imidazoli Salicylas; Salicilato de imidazol. Imidazole compounded with salicylic acid.

Имидазола Салицилат

$C_{10}H_{10}N_2O_3$ = 206.2.
CAS — 36364-49-5.
ATC — N02BA16.
ATC Vet — QN02BA16.



Profile

Imidazole salicylate is a salicylic acid derivative (see Aspirin, p.20) that has been used in the treatment of fever and inflammatory respiratory-tract and otorhinolaryngeal disorders. Imidazole salicylate has been given in oral doses of up to 2.25 g daily in divided doses. It has also been given as a rectal suppository and has been applied topically as a 5% gel for the relief of muscular and rheumatic pain.

Preparations

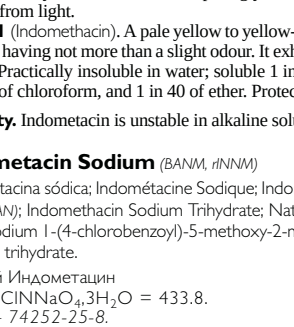
Proprietary Preparations (details are given in Part 3)
Ital.: Selezen.

Indometacin *(BAN, rINN)*

Indometacina; Indometacinas; Indométacine; Indometacinum; Indometacyna; Indometasiini; Indometasin; Indomethacin *(USAN)*. [1-(4-Chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid.

Индометацин

$C_{19}H_{16}ClNO_4$ = 357.8.
CAS — 53-86-1.
ATC — C01EB03; M01AB01; M02AA23; S01BC01.
ATC Vet — QC01EB03; QM01AB01; QM02AA23; QS01BC01.



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

Ph. Eur. 6.2 (Indometacin). A white or yellow, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol. Protect from light.

USP 31 (Indomethacin). A pale yellow to yellow-tan, crystalline powder having not more than a slight odour. It exhibits polymorphism. Practically insoluble in water; soluble 1 in 50 of alcohol, 1 in 30 of chloroform, and 1 in 40 of ether. Protect from light.

Stability. Indometacin is unstable in alkaline solution.

Indometacin Sodium *(BANM, rINNM)*

Indometacina sódica; Indométacine Sodique; Indomethacin Sodium *(USAN)*; Indomethacin Sodium Trihydrate; Natrii Indometacinum. Sodium 1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate, trihydrate.

Натрий Индометацин

$C_{19}H_{15}ClNNaO_4,3H_2O$ = 433.8.
CAS — 74252-25-8.

Pharmacopoeias. In *US*.

USP 31 (Indomethacin Sodium). Protect from light.

Incompatibility. Indometacin sodium injection is reconstituted with preservative-free sodium chloride for injection 0.9% or preservative-free water for injection. Preparations containing glucose should not be used; reconstitution at a pH below 6 may

cause precipitation of indometacin. Visual incompatibility has been reported between indometacin sodium injection and tolazoline hydrochloride,[1] 7.5 and 10% glucose injection, calcium gluconate, dobutamine, dopamine, cimetidine,[2] gentamicin sulfate, levofloxacin,[3] and tobramycin sulfate.[4] A pH below 6 may account for the visual incompatibility of indometacin sodium and several of these drugs.

1. Marquardt ED. Visual compatibility of tolazoline hydrochloride with various medications during simulated Y-site injection. *Am J Hosp Pharm* 1990; **47:** 1802–3.
2. Ishisaka DY, *et al.* Visual compatibility of indomethacin sodium trihydrate with drugs given to neonates by continuous infusion. *Am J Hosp Pharm* 1991; **48:** 2442–3.
3. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; **56:** 1458–90.
4. Thompson DF, Heflin NR. Incompatibility of injectable indomethacin with gentamicin sulfate or tobramycin sulfate. *Am J Hosp Pharm* 1992; **49:** 836–8.

Stability. A reconstituted solution of indometacin sodium 500 micrograms/mL was stable for 14 days when stored at 2° to 6° in either the manufacturer's original glass vial or in a polypropylene syringe.[1]

1. Walker SE, *et al.* Stability of reconstituted indomethacin sodium trihydrate in original vials and polypropylene syringes. *Am J Health-Syst Pharm* 1998; **55:** 154–8.

Adverse Effects and Treatment

As for NSAIDs in general, p.96.

Adverse effects are more frequent with indometacin than with many other NSAIDs, the most common being gastrointestinal disturbances, headache, vertigo, dizziness, and lightheadedness. Gastrointestinal perforation, ulceration, and bleeding may also occur; rarely, intestinal strictures have been reported. Other adverse effects include depression, drowsiness, tinnitus, confusion, insomnia, psychiatric disturbances, syncope, convulsions, coma, peripheral neuropathy, blurred vision, corneal deposits and other ocular effects, oedema and weight gain, hypertension, haematuria, skin rashes, pruritus, urticaria, stomatitis, alopecia, and hypersensitivity reactions. Leucopenia, purpura, thrombocytopenia, aplastic anaemia, haemolytic anaemia, agranulocytosis, epistaxis, hyperglycaemia, hypoaldosteronism and hyperkalaemia, and vaginal bleeding have been reported. There have also been reports of hepatitis, jaundice, and renal failure. Hypersensitivity reactions may also occur in aspirin-sensitive patients. Rectal irritation and bleeding has been reported occasionally in patients who have received indometacin suppositories.

Adverse effects associated with the use of indometacin injection in premature **neonates** may also include haemorrhagic, renal, gastrointestinal, metabolic, and coagulation disorders; pulmonary hypertension, intracranial bleeding, fluid retention, and exacerbation of infection may also occur.

Effects on the blood. There were 1261 reports of adverse reactions to indometacin reported to the UK CSM between June 1964 and January 1973. These included 157 reports of blood disorders (25 fatal) including thrombocytopenia (35; 5 fatal), aplastic anaemia (17; no fatalities), and agranulocytosis or leucopenia (21; 3 fatal).[1] Subsequently, the First Report from the International Agranulocytosis and Aplastic Anemia Study confirmed a significant relationship between the use of indometacin and agranulocytosis and aplastic anaemia.[2] Neutropenia has also been noted in a premature infant with patent ductus arteriosus after use of indometacin.[3]

Although use of indometacin in 20 women being treated for premature labour did not affect maternal prothrombin or activated partial thromboplastin time, maternal bleeding time during therapy was increased.[4] However, no cases of neonatal intraventricular haemorrhage or maternal postpartum haemorrhage were seen.

1. Cuthbert MF. Adverse reactions to non-steroidal antirheumatic drugs. *Curr Med Res Opin* 1974; **2:** 600–10.
2. The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anemia: a first report of their relation to drug use with special reference to analgesics. *JAMA* 1986; **256:** 1749–57.
3. Bengtsson B-OS, *et al.* Indomethacin-associated neutropenia with subsequent Gram-negative sepsis in a preterm infant: cause or coincidence? *J Perinatol* 2006; **26:** 381–3.
4. Lunt CC, *et al.* The effect of indomethacin tocolysis on maternal coagulation status. *Obstet Gynecol* 1994; **84:** 820–2.

Effects on cerebral blood flow. See Patent Ductus Arteriosus under Uses and Administration, below.

Effects on the eyes. Severe and irreversible retinopathy, presumably due to long-term ingestion of high doses of indometacin occurred in a 33-year-old man.[1] A summary of previous literature reports of indometacin-induced ocular effects indicated that indometacin was retinotoxic, although to what degree was uncertain. For reference to effects on the optic nerve associated with indometacin, see p.97.

1. Graham CM, Blach RK. Indomethacin retinopathy: case report and review. *Br J Ophthalmol* 1988; **72:** 434–8.

Effects on the gastrointestinal tract. Nausea, vomiting, dyspepsia, gastrointestinal lesions, and serious reactions including gastrointestinal bleeding, ulceration, and perforation have occurred in patients receiving indometacin. Although it is well established that NSAIDs can produce adverse effects on the upper gastrointestinal tract, indometacin and other NSAIDs can also affect the large intestines.[1] Giving indometacin to preterm neonates increases the risk of small bowel perforation and necrotising enterocolitis.[2-4] Risk seems to be increased in very-low-birth-weight or extremely premature infants.

1. Oren R, Ligumsky M. Indomethacin-induced colonic ulceration and bleeding. *Ann Pharmacother* 1994; **28:** 883–5.
2. Grosfeld JL, *et al.* Increased risk of necrotizing enterocolitis in premature infants with patent ductus arteriosus treated with indomethacin. *Ann Surg* 1996; **224:** 350–7.
3. Shorter NA, *et al.* Indomethacin-associated bowel perforations: a study of possible risk factors. *J Pediatr Surg* 1999; **34:** 442–4.
4. Fujii AM. Neonatal necrotizing enterocolitis with intestinal perforation in extremely premature infants receiving early indomethacin treatment for patent ductus arteriosus. *J Perinatol* 2002; **22:** 535–40.

Effects on the joints. For references to concern that NSAIDs such as indometacin may accelerate the rate of cartilage destruction in patients with osteoarthritis, see Effects on Bone, under NSAIDs, p.96.

Effects on the kidneys. Acute renal failure,[1] nephrotic syndrome,[2] and renal papillary necrosis[3] have been reported in patients given indometacin. There have been suggestions that misoprostol might reduce the risk of indometacin-induced renal toxicity.[4,5]

Renal impairment has also occurred in **neonates** given indometacin intravenously for patent ductus arteriosus. Although rare, and usually reversible, the effect may be serious in neonates with pre-existing renal disorders.[6] Serious or fatal renal toxicity has been reported in neonates exposed to indometacin due to maternal ingestion.[7] The renal effects of prenatal indometacin may be prolonged.[8]

1. Chan X. Fatal renal failure due to indomethacin. *Lancet* 1987; **ii:** 340.
2. Boiskin I, *et al.* Indomethacin and the nephrotic syndrome. *Ann Intern Med* 1987; **106:** 776–7.
3. Mitchell H, *et al.* Indomethacin-induced renal papillary necrosis in juvenile chronic arthritis. *Lancet* 1982; **ii:** 558–9.
4. Weir MR, *et al.* Minimization of indomethacin-induced reduction in renal function by misoprostol. *J Clin Pharmacol* 1991; **31:** 729–35.
5. Wong F, *et al.* The effect of misoprostol on indomethacin-induced renal dysfunction in well-compensated cirrhosis. *J Hepatol* 1995; **23:** 1–7.
6. Cuzzolin L, *et al.* NSAID-induced nephrotoxicity from the fetus to the child. *Drug Safety* 2001; **24:** 9–18.
7. van der Heijden BJ, *et al.* Persistent anuria, neonatal death, and renal microcystic lesions after prenatal exposure to indomethacin. *Am J Obstet Gynecol* 1994; **171:** 617–23.
8. Butler-O'Hara M, D'Angio CT. Risk of persistent renal insufficiency in premature infants following the prenatal use of indomethacin for suppression of preterm labor. *J Perinatol* 2002; **22:** 541–6.

Effects on the liver. Cholestasis occurred in a 52-year-old woman several days after starting indometacin;[1] liver function values returned to normal once indometacin was stopped.

1. Cappell MS, *et al.* Indomethacin-associated cholestasis. *J Clin Gastroenterol* 1988; **10:** 445–7.

Hypersensitivity. Hypersensitivity reactions including acute asthma have been reported after use of indometacin suppositories,[1] eye drops,[2] or capsules[3] by patients who were aspirin-sensitive or had a history of asthma.

1. Timperman J. A fatal asthmatic attack following administration of an indomethacin suppository. *J Forensic Med* 1971; **18:** 30–2.
2. Sheehan GJ, *et al.* Acute asthma attack due to ophthalmic indomethacin. *Ann Intern Med* 1989; **111:** 337–8.
3. Johnson NM, *et al.* Indomethacin-induced asthma in aspirin-sensitive patients. *BMJ* 1977; **2:** 1291.

Precautions

As for NSAIDs in general, p.98.

Indometacin should be used with caution in patients with epilepsy, parkinsonism, or psychiatric disorders. Dizziness may affect the performance of skilled tasks such as driving. Patients on long-term indometacin therapy should be examined regularly for adverse effects, and the *BNF* particularly recommends periodic blood and ophthalmic examinations. Rectal use should be avoided in patients with proctitis and haemorrhoids.

In addition indometacin should not be given to **neonates** with untreated infection, with significant renal impairment, or with necrotising enterocolitis. Infants who are bleeding (especially gastrointestinal bleeding or intracranial haemorrhage) or who have thrombocytopenia or coagulation defects should not be given indometacin and those receiving indometacin should be monitored during treatment for signs of bleeding. Electrolytes and renal function should also be monitored and if anuria or marked oliguria is evident at the time of a scheduled second or third dose, it should be delayed until renal function has returned to normal.

False-negative results in the dexamethasone suppression test have been reported in patients taking indometacin.

Breast feeding. Convulsions in a one-week old breast-fed infant appeared to be associated with maternal ingestion of indometacin;[1] the child had normal motor and mental development at the age of 1 year and seizures had not recurred.

Indometacin has been detected in breast milk, but some workers[2,3] and the *BNF* consider that the amount is so small that it should not constitute a contra-indication to breast feeding. The American Academy of Pediatrics[4] also states that indometacin is usually compatible with breast feeding despite acknowledging the above case report of convulsions. However, licensed product information recommends that indometacin should not be used in nursing mothers.

1. Eeg-Olofsson O, *et al.* Convulsions in a breast-fed infant after maternal indomethacin. *Lancet* 1978; **ii:** 215.
2. Beaulac-Baillargeon L, Allard G. Distribution of indomethacin in human milk and estimation of its milk to plasma ratio in vitro. *Br J Clin Pharmacol* 1993; **36:** 413–16.
3. Lebedevs TH, *et al.* Excretion of indomethacin in breast milk. *Br J Clin Pharmacol* 1991; **32:** 751–4.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/11/07)

The elderly. After a study[1] of the pharmacokinetics of indometacin in the elderly it was suggested that the maintenance dose of indometacin in elderly patients should be reduced by 25%. The total clearance of indometacin in elderly subjects had been reduced when compared with that in young subjects; this was thought to be due to reduced hepatic metabolism in the elderly.

1. Oberbauer R, *et al.* Pharmacokinetics of indomethacin in the elderly. *Clin Pharmacokinet* 1993; **24:** 428–34.

Pregnancy. See Premature Labour under Uses and Administration, below.

Interactions

For interactions associated with NSAIDs, see p.99.

Anti-inflammatory doses of aspirin decrease indometacin blood concentrations by about 20%. Diflunisal decreases the renal clearance and increases plasma concentrations of indometacin. Use of diflunisal with indometacin has also resulted in fatal gastrointestinal haemorrhage, and the two should not be used together. Plasma concentrations of indometacin are likely to be increased in patients receiving probenecid.

Antibacterials. Indometacin has been reported to increase plasma concentrations of *aminoglycosides*.

Antipsychotics. Severe drowsiness and confusion have been reported in patients given *haloperidol* with indometacin.[1]

1. Bird HA, *et al.* Drowsiness due to haloperidol/indomethacin in combination. *Lancet* 1983; **i:** 830–1.

Bone modulating drugs. Indometacin has been reported to increase the bioavailability of *tiludronate*, see p.1106.

Desmopressin. The effect of desmopressin may be enhanced by indometacin.

Digoxin. In addition to increasing digoxin serum concentrations (see p.1263), combination of digoxin with indometacin has been reported to reduce the half-life of the latter in premature neonates (see Half-life under Pharmacokinetics, below).

Parasympathomimetics. The manufacturer of acetylcholine chloride ophthalmic preparations has stated that there have been reports that *acetylcholine* and *carbachol* have been ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Pharmacokinetics

Indometacin is readily absorbed from the gastrointestinal tract in adults; peak plasma concentrations are reached about 2 hours after a dose. Absorption may be slowed by food or by aluminium- or magnesium-containing antacids. In premature neonates, absorption of oral indometacin is poor and incomplete. The bioavailability of rectal suppositories in adults has been reported to be comparable with or slightly less than the bioavailability with oral dosage forms.

Indometacin is about 99% bound to plasma proteins. It is distributed into synovial fluid, the CNS, and placen-

ta. Low concentrations have been distributed into breast milk. The terminal plasma half-life has been reported to range from 2.6 to 11.2 hours in adults. The terminal half-life in neonates has been reported to be between 12 and 28 hours (see also below). Indometacin is metabolised in the liver to its glucuronide conjugate and to desmethylindomethacin, desbenzoylindomethacin, desmethyl-desbenzoylindomethacin, and to their glucuronides. Some indometacin undergoes N-deacylation. Indometacin and its conjugates undergo enterohepatic circulation. Excretion of indometacin and its metabolites is mainly in the urine with lesser amounts appearing in the faeces.

◊ References.

1. Moise KJ, *et al.* Placental transfer of indomethacin in the human pregnancy. *Am J Obstet Gynecol* 1990; **162:** 549–54.
2. Mannila A, *et al.* Plasma and cerebrospinal fluid concentrations of indomethacin in children after intravenous administration. *J Clin Pharmacol* 2007; **47:** 94–100.

Half-life. The plasma half-life of indometacin in premature infants can be variable but appears to be inversely proportional to post-natal age and weight.[1,2] One population model suggests that for an infant of 1.17 kg, half-life would be 22.3 hours at a post-natal age of 8 days, but 16.1 hours at 25 days (and only 11.2 hours if also receiving digoxin).[2]

1. Wiest DB, *et al.* Population pharmacokinetics of intravenous indomethacin in neonates with symptomatic patent ductus arteriosus. *Clin Pharmacol Ther* 1991; **49:** 550–7.
2. Smyth JM, *et al.* Intravenous indometacin in preterm infants with symptomatic patent ductus arteriosus: a population pharmacokinetic study. *Br J Clin Pharmacol* 2004; **58:** 249–58.

Uses and Administration

Indometacin, an indole acetic acid derivative, is an NSAID (p.99). It is used in musculoskeletal and joint disorders including ankylosing spondylitis, osteoarthritis, rheumatoid arthritis, and acute gout, and in periarticular disorders such as bursitis and tendinitis. It may also be used in inflammation, pain, and oedema following orthopaedic procedures, in mild to moderate pain in conditions such as dysmenorrhoea, and it has been used in the management of postoperative pain as an adjunct to opioids, and in the treatment of fever. Indometacin is also used as the sodium salt to close patent ductus arteriosus in premature infants (see below).

The usual initial oral dose in **chronic musculoskeletal and joint disorders** is 25 mg two or three times daily increased, if required, by 25 to 50 mg at weekly intervals to 150 to 200 mg daily. To alleviate night pain and morning stiffness, up to 100 mg of the total daily dose may be given orally, or rectally as a suppository, on retiring. Alternatively, the total daily dose may be given rectally as 100 mg in the morning and at night. The total daily combined oral and rectal dose should not exceed 200 mg. In acute gout the daily dose is 150 to 200 mg in divided doses until all symptoms and signs subside; in dysmenorrhoea up to 75 mg daily has been suggested. Modified-release preparations of indometacin are available for use once or twice daily. For doses in children, see below.

Indometacin has been used as eye drops, usually of 0.1 or 0.5%, to **prevent miosis during cataract surgery**; the usual dose is 2 drops, repeated after 2 hours, on the day before surgery, then 2 drops 3 hours before and 2 drops 1 hour before surgery. The eye drops may then be instilled up to 6 times daily postoperatively to prevent **cystoid macular oedema**; treatment should be continued until inflammatory signs have disappeared. Indometacin eye drops have also been used in other inflammatory eye disorders in doses similar to those used to prevent oedema.

Meglumine indometacin and indometacin farnesil, a lipid soluble ester of indometacin ($C_{34}H_{40}ClNO_4$ = 562.1), have also been given for painful and inflammatory conditions. A complex of indometacin and L-arginine, known as indoarginine, has also been used.

Administration in children. Although indometacin is not licensed in the UK for the treatment of **rheumatic diseases** such as juvenile idiopathic arthritis in children, the *BNFC* suggests an oral dose of 0.5 to 1 mg/kg twice daily in those aged 1 month to 18 years; higher doses may sometimes be required.

Indometacin is also used in the treatment of **patent ductus arteriosus** in premature infants; see below for further details including doses.

Bartter's syndrome. The treatment of Bartter's syndrome can often be difficult (see p.1670). Blocking the kinin-prostaglandin axis with a cyclo-oxygenase inhibitor such as indometacin improves hypokalaemia and other clinical features (including growth retardation) in children with the syndrome.[1-5]

1. Littlewood JM, *et al.* Treatment of childhood Bartter's syndrome with indomethacin. *Lancet* 1976; **ii:** 795.
2. Seidel C, *et al.* Pre-pubertal growth in the hyperprostaglandin E syndrome. *Pediatr Nephrol* 1995; **9:** 723–8.
3. Craig JC, Falk MC. Indomethacin for renal impairment in neonatal Bartter's syndrome. *Lancet* 1996; **347:** 550.
4. Mourani CC, *et al.* Bartter syndrome in a neonate: early treatment with indomethacin. *Pediatr Nephrol* 2000; **14:** 143–5.
5. Vaisbich MH, *et al.* Bartter syndrome: benefits and side effects of long-term treatment. *Pediatr Nephrol* 2004; **19:** 858–63.

Diabetes insipidus. Indometacin and other prostaglandin synthetase inhibitors have been reported to decrease urine volume in all types of nephrogenic diabetes insipidus (p.2179).

References.

1. Rosen GH, *et al.* Indomethacin for nephrogenic diabetes insipidus in a four-week-old infant. *Clin Pharm* 1986; **5:** 254–6.
2. Libber S, *et al.* Treatment of nephrogenic diabetes insipidus with prostaglandin synthesis inhibitors. *J Pediatr* 1986; **108:** 305–11.
3. Allen HM, *et al.* Indomethacin in the treatment of lithium-induced nephrogenic diabetes insipidus. *Arch Intern Med* 1989; **149:** 1123–6.
4. Martinez EJ, *et al.* Lithium-induced nephrogenic diabetes insipidus treated with indomethacin. *South Med J* 1993; **86:** 971–3.
5. Hohler T, *et al.* Indomethacin treatment in amphotericin B induced nephrogenic diabetes insipidus. *Clin Investig* 1994; **72:** 769–71.
6. Lam SS, Kjellstrand C. Emergency treatment of lithium-induced diabetes insipidus with nonsteroidal anti-inflammatory drugs. *Ren Fail* 1997; **19:** 183–8.

Malignant neoplasms. In common with some other NSAIDs (see p.100) it has been suggested that indometacin might possess some antineoplastic activity.[1] Some NSAIDs such as indometacin may also be of value for the differential diagnosis and the management of neoplastic fever, as they appear to be more effective in reducing this type of fever than against fever associated with infections.[2] Indometacin has also been tried for the treatment of fever and flu-like symptoms associated with interleukin-2 therapy although there has been concern over exacerbation of renal toxicity (see NSAIDs, under Interactions, p.736).

1. Mertens WC, *et al.* Effect of indomethacin plus ranitidine in advanced melanoma patients on high-dose interleukin-2. *Lancet* 1992; **340:** 397–8.
2. Engervall P, *et al.* Antipyretic effect of indomethacin in malignant lymphoma. *Acta Med Scand* 1986; **219:** 501–5.

Neonatal intraventricular haemorrhage. Indometacin has been tried prophylactically to prevent the development of intraventricular haemorrhage in neonates at risk (see p.1050). Several mechanisms have been proposed for its possible action including reduction of cerebral flow as a result of vasoconstriction, reduction of oxygen free-radical damage, and accelerated maturation of blood vessels around the ventricles. Early studies[1-3] of the use of indometacin for prevention of intraventricular haemorrhage produced conflicting results. A subsequent large multicentre study[4] (the Indomethacin Intraventricular Haemorrhage Prevention Trial, IIHP) suggested that indometacin could reduce the incidence and severity of intraventricular haemorrhage, especially for the more severe forms. Neonates with a birth-weight of 600 to 1250 g were given indometacin in a dose of 100 micrograms/kg intravenously at 6 to 12 hours after delivery and then every 24 hours for 2 additional doses. There was, however, concern[5] that an unusually large number of neonates with severe intraventricular haemorrhage in the control group might have biased the findings.

A concern with the use of indometacin is the possibility that it may produce cerebral ischaemia due to its vasoconstrictor action and therefore increase the risk of developmental handicaps. Follow-up at 3 years,[6] at 4½ years,[7] and at 8 years of age[8] in the infants included in the IIHP study reported no adverse effects on cognitive or motor development. However, another large multicentre study[9] (the Trial of Indomethacin Prophylaxis in Preterms, TIPP) in extremely-low-birth-weight infants (less than 1000 g) found that although indometacin reduced the incidence of severe haemorrhage, it did not improve survival without neurosensory impairment at 18 months. A subsequent systematic review[10] also concluded that indometacin prophylaxis did not improve survival free of neurosensory disability although, again, the incidence of severe intraventricular haemorrhage was reduced.

Further analysis of the data from the IIHP study has suggested that indometacin might reduce intraventricular haemorrhage in boys but have little effect in girls;[11] verbal scores at ages 3 to 8 years were also higher in those boys treated with indometacin when compared to a control group of boys treated with saline; no differences in scores were noted in indometacin-treated girls and their control group. Re-analysis of data from the TIPP study[12] in extremely-low-birth-weight neonates suggested a weak gender difference in the effect of indometacin treatment when all primary outcomes such as death, cerebral palsy, cognitive delay, and severe intraventricular haemorrhage were considered; however, when outcomes were considered individually, there was a significant reduction in intraventricular haemorrhage in boys when compared with girls. The authors considered the results to be a consequence of an unfavourable effect of indometacin in girls rather than any positive effects in boys. Any true difference in effect between the sexes remains to be confirmed.

Indometacin does not appear to prevent the progression of existing haemorrhage.[13]

1. Ment LR, *et al.* Randomized indomethacin trial for prevention of intraventricular hemorrhage in very low birth weight infants. *J Pediatr* 1985; **107:** 937–43.
2. Rennie JM, *et al.* Early administration of indomethacin to preterm infants. *Arch Dis Child* 1986; **61:** 233–8.
3. Bada HS, *et al.* Indomethacin reduces the risks of severe intraventricular hemorrhage. *J Pediatr* 1989; **115:** 631–7.
4. Ment LR, *et al.* Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. *Pediatrics* 1994; **93:** 543–50.
5. Volpe JJ. Brain injury caused by intraventricular hemorrhage: is indomethacin the silver bullet for prevention? *Pediatrics* 1994; **93:** 673–7.
6. Ment LR, *et al.* Neurodevelopmental outcome at 36 months' corrected age of preterm infants in the multicenter indomethacin intraventricular hemorrhage prevention trial. *Pediatrics* 1996; **98:** 714–18.
7. Ment LR, *et al.* Outcome of children in the indomethacin intraventricular hemorrhage prevention trial. *Pediatrics* 2000; **105:** 485–91.
8. Vohr BR, *et al.* School-age outcomes of very low birth weight infants in the indomethacin intraventricular hemorrhage prevention trial. Abstract: *Pediatrics* 2003; **111:** 874. Full version: http://pediatrics.aappublications.org/cgi/content/full/111/4/e340 (accessed 07/11/07)
9. Schmidt B, *et al.* Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *N Engl J Med* 2001; **344:** 1966–72.
10. Fowlie PW, Davis PG. Prophylactic indomethacin for preterm infants: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F464–F466.
11. Ment LR, *et al.* Prevention of intraventricular hemorrhage by indomethacin in male preterm infants. *J Pediatr* 2004; **145:** 832–4.
12. Ohlsson A, *et al.* Male/female differences in indomethacin effects in preterm infants. *J Pediatr* 2005; **147:** 860–2.
13. Ment LR, *et al.* Low-dose indomethacin therapy and extension of intraventricular hemorrhage: a multicenter randomized trial. *J Pediatr* 1994; **124:** 951–5.

Patent ductus arteriosus. In the fetal circulation the ductus arteriosus connects the pulmonary artery and the descending aorta. After birth, various mechanisms, including a fall in prostaglandin concentration, trigger its closure but in some infants the ductus arteriosus fails to close, a condition known as persistent patent ductus arteriosus. This condition may be found in infants with congenital heart defects but is more commonly seen in premature neonates, especially those with respiratory distress syndrome.

- Some infants may be asymptomatic or have only slight clinical symptoms and no immediate intervention is required. In many cases spontaneous closure will occur after several months, or else surgical ligation may be performed if clinical symptoms persist.
- In some infants a patent ductus arteriosus is necessary for maintaining some oxygenation of the blood, for example in pulmonary artery atresia or transposition of the great arteries. These infants require treatment with a prostaglandin such as *alprostadil* or *dinoprostone* to maintain patency of the ductus arteriosus until surgery can be performed to correct the malformation.
- Infants with haemodynamically significant ductus arteriosus, signs of heart failure, and who require ventilation should undergo treatment to close the patent ductus arteriosus.

Initial **management** involves fluid restriction, diuretics, correction of anaemia, and support of respiration. *Chlorothiazide* and *furosemide* are diuretics commonly used. There has been concern that furosemide might delay closure in infants with respiratory distress syndrome.[1,2] A systematic review[3] concluded that this did not seem to be the case, and that the diuretic might reduce adverse renal effects of indometacin; however, the evidence for this was limited and it was felt that there was not enough evidence to support the use of furosemide in infants treated with indometacin.

If initial treatment fails to control symptoms after 24 to 48 hours then *indometacin* is generally given to promote closure of the ductus.[1,4-6] The benefits of treatment with indometacin as soon as symptoms become apparent, rather than delaying treatment until signs of congestive failure develop, have been debated.[7,8] Early treatment may significantly reduce the morbidities arising from a persistent patent ductus arteriosus.[7] However, delaying treatment until the end of the first week of life can allow for spontaneous closure and avoid the need of exposing infants to the toxic effects of indometacin.[8]

Indometacin probably leads to closure of the ductus through inhibition of prostaglandin synthesis. It is given as the sodium salt in three intravenous doses at 12- to 24-hour intervals; each dose should be infused over 20 to 30 minutes. Indometacin sodium injection is reconstituted with preservative-free sodium chloride 0.9% for injection or water for injection; glucose solutions should not be used (see Incompatibility, above). The dose of indometacin sodium (expressed as indometacin) depends upon the

age of the neonate and the following doses have been suggested based upon the age at the first dose:

- less than 48 hours old: 200 micrograms/kg initially followed by two further doses of 100 micrograms/kg each
- 2 to 7 days old: three doses of 200 micrograms/kg each
- over 7 days old: 200 micrograms/kg initially followed by two further doses of 250 micrograms/kg each

If, 48 hours after this course of therapy the ductus remains open or re-opens, a second course may be used, but if this produces no response (which may be the case in 25% of infants treated[4,9]) surgery may be necessary.

Indometacin has been given orally where the injection is unavailable, but absorption of oral indometacin is poor and incomplete in premature neonates.

A decreased need for surgical closure and reduced recurrences were seen in neonates in whom standard intravenous indometacin therapy was then followed by maintenance therapy (intravenous indometacin 200 micrograms/kg daily for an additional 5 days).[10] Prolonged therapy using high doses of up to 1 mg/kg as a single dose every 12 hours has also been used with some success in a few infants who have not responded to standard regimens.[11] Similar beneficial findings were reported[12] in infants given prolonged low-dose indometacin therapy (100 micrograms/kg daily for 6 days). An additional benefit was a lower incidence of adverse effects; fewer infants had a rise in serum creatinine or urea concentrations. However, a systematic review[13] has suggested that such regimens are no more effective than the shorter standard regimens, and found an increased rather than decreased incidence of adverse effects (including a trend towards increased risk of necrotising enterocolitis[1,6]). Prolonged treatment with indometacin could not be recommended.[13] Prophylactic treatment or treatment of asymptomatic ductus with indometacin has been tried in premature infants, and there is good evidence to suggest that this is effective in reducing the risk of symptomatic patent ductus arteriosus and intraventricular haemorrhage (see above) in such patients;[7,14,15] however, prophylactic treatment has not been shown to significantly reduce the risk of short-term pulmonary complications such as bronchopulmonary dysplasia. Systematic reviews[14,15] have also found no evidence of either benefit or harm in neurological development or other longer term outcomes.

Some other NSAIDs have also been tried in the treatment of patent ductus arteriosus. Ibuprofen appears to be effective in closing a patent ductus arteriosus,[16] and it has been suggested that ibuprofen might be a better choice than indometacin as, unlike indometacin, it does not have adverse effects on renal, mesenteric, and cerebral haemodynamics. However, a recent systematic review[16] found no significant difference in the effectiveness of ibuprofen compared to indometacin and, although the risk of oliguria was reduced with ibuprofen, the risk for chronic lung disease may be increased. Ibuprofen is also effective when used prophylactically; however, there have been reports of pulmonary hypertension with such use and ibuprofen is not recommended.[17]

Oral therapy with ibuprofen has also been tried.[18]

1. Bhatt V, Nahata MC. Pharmacologic management of patent ductus arteriosus. *Clin Pharm* 1989; **8:** 17–33.
2. Anonymous. Delayed closure of the ductus. *Lancet* 1983; **ii:** 436.
3. Brion LP, Campbell DE. Furosemide for prevention of morbidity in indomethacin-treated infants with patent ductus arteriosus. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 07/11/07).
4. Silove ED. Pharmacological manipulation of the ductus arteriosus. *Arch Dis Child* 1986; **61:** 827–9.
5. Barst RJ, Gersony WM. The pharmacological treatment of patent ductus arteriosus: a review of the evidence. *Drugs* 1989; **38:** 249–66.
6. Archer N. Patent ductus arteriosus in the newborn. *Arch Dis Child* 1993; **69:** 529–32.
7. Clyman RI. Recommendations for the postnatal use of indomethacin: an analysis of four separate treatment strategies. *J Pediatr* 1996; **128:** 601–7.
8. Van Overmeire B, *et al.* Early versus late indomethacin treatment for patent ductus arteriosus in premature infants with respiratory distress syndrome. *J Pediatr* 2001; **138:** 205–11.
9. Gersony WM, *et al.* Effects of indomethacin in premature infants with patent ductus arteriosus: results of a national collaborative study. *J Pediatr* 1983; **102:** 895–906.
10. Hammerman C, Aramburo MJ. Prolonged indomethacin therapy for the prevention of recurrences of patent ductus arteriosus. *J Pediatr* 1990; **117:** 771–6.
11. Sperandio M, *et al.* Effectiveness and side effects of an escalating, stepwise approach to indomethacin treatment for symptomatic patent ductus arteriosus in premature infants below 33 weeks of gestation. *Pediatrics* 2005; **116:** 1361–6.
12. Rennie JM, Cooke RWI. Prolonged low dose indomethacin for persistent ductus arteriosus of prematurity. *Arch Dis Child* 1991; **66:** 55–8.
13. Herrera C, *et al.* Prolonged versus short course of indomethacin for the treatment of patent ductus arteriosus in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 07/11/07).
14. Fowlie PW, Davis PG. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 07/11/07).
15. Cooke L, *et al.* Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 07/11/07).
16. Ohlsson A, *et al.* Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 16/07/08).
17. Shah SS, Ohlsson A. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 07/11/07).
18. Heyman E, *et al.* Closure of patent ductus arteriosus with oral ibuprofen suspension in premature newborns: a pilot study. *Pediatrics* 2003; **112:** 1170. Full version: http://pediatrics.aappublications.org/cgi/reprint/112/5/e354.pdf (accessed 07/11/07)

Polyhydramnios. Reports[1-3] of the beneficial effects of indometacin in the management of polyhydramnios (an excessive accumulation of amniotic fluid). Polyhydramnios is a feature of the neonatal variant of Bartter's syndrome (see also above).

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Premature labour. The most common approach to postponing premature labour (p.2003) with drugs has historically been with a selective $beta_2$ agonist. However, as prostaglandins have a role in uterine contraction and cervical ripening and dilatation, prostaglandin synthetase inhibitors such as indometacin have also been used. Comparative studies[1,2] have shown that indometacin and ritodrine are equally effective in inhibiting uterine contractions and delaying delivery in patients in preterm labour who have intact membranes and in whom the gestational age is less than or equal to 34 weeks. In one study[2] an initial oral loading dose of indometacin 50 mg was given, followed by 25 to 50 mg orally every 4 hours until contractions stopped and then by a maintenance dose of 25 mg every 4 to 6 hours. In the other comparative study[1] indometacin was given as a 100-mg rectal suppository followed by 25 mg orally every 4 hours for 48 hours; if regular uterine contractions persisted 1 to 2 hours after the initial suppository, an additional 100-mg suppository was given before beginning oral therapy. Terbutaline was given for maintenance therapy.

Unfortunately indometacin can constrict the ductus arteriosus,[3-5] which may lead to pulmonary hypertension,[2] and has also been associated with bronchopulmonary dysplasia,[6] reduced volume of amniotic fluid (oligohydramnios)[2,4] and possible renal damage (see Effects on the Kidneys, above) in the fetus. Another complication is that prenatal indometacin exposure may increase both the incidence and severity of patent ductus arteriosus in premature infants,[7,8] as shown by the increased need for post-natal indometacin therapy and surgical ligation in such infants. However, there is evidence to suggest that there is no significant increase in the risk of neonatal complications in infants exposed to indometacin tocolysis when compared with control groups of infants who received either no treatment or tocolysis with drugs other than indometacin.[9,10]

The evidence for any overall benefit of indometacin in delaying labour is equivocal,[11-13] and it is generally reserved as a second-line tocolytic or for use with an intravenous tocolytic when an additive effect is required.

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Preparations

BP 2008: Indometacin Capsules; Indometacin Suppositories;
USP 31: Indomethacin Capsules; Indomethacin Extended-release Capsules; Indomethacin for Injection; Indomethacin Oral Suspension; Indomethacin Suppositories; Indomethacin Topical Gel.

Proprietary Preparations (details are given in Part 3)
Arg.: Agilex; IM 75; Indotex; Klonametacina; ***Austral.:*** Arthrexin; Indocid; Indocid PDA; ***Austria:*** Flexidin; Indo; Indobene; Indocid; Indocollyre; Indohexal; Indomelan; Indoptol; Liometacen; Luiflex; Ralicid; ***Belg.:*** Dolcidium; Indocid; Indocollyre; Luiflex; ***Braz.:*** Agilisin; Indocid; Indocid Colirio†; Metacidil†; ***Canad.:*** Indocid PDA; Indocid†; Indotec†; Novo-Methacin; Nu-Indo; Rhodacine; ***Chile:*** Flexono; Moviflex; ***Cz.:*** Bonidon†; Elmetacin; Indobene; Indocollyre; Vonum Cutan; ***Denm.:*** Confortid; Indocid†; ***Fin.:*** Confortid; Indocid; Indometin; ***Fr.:*** Chrono-Indocid; Indocid; Indocollyre; ***Ger.:*** Confortid; Elmetacin; Indo; Indo Top; Indo-paed; Indo-Phlogont†; Indocolir; Indocontin†; Indomet-ratiopharm; Indomet-ratiopharm m†; Indomet†; Indomisal†; Inflam; Mobilat Akut Indo; Rheubalmin Indo; Sigadoc†; ***Gr.:*** Begincalm†; Dolcispray; Fortathrine; Hastel; Indocid; Indomethol; Itapredin; Reumacid; Reumadolor; ***Hong Kong:*** Indocid; Indocin PDA; Indocollyre; Indogesic†; Indomet†; ***Hung.:*** Elmetacin; Indobene; Indocollyre; ***India:*** Idicin†; Indocap; Indocid; ***Indon.:*** Dialon; ***Irl.:*** Cidomel†; Flexin Continus; Indocid PDA; Indocid†; ***Israel:*** Indocollyre; Indomed; Indoptic†; Indotard; Indovis; ***Ital.:*** Imet†; Indocid; Indocollirio; Indom; Indoxen; Liometacen; Metacen; ***Jpn:*** Catlep; Idomethine; Infree; ***Malaysia:*** Arthrexin†; Domicap†; Indo; Indocid†; Indomen; ***Mex.:*** Antalgin; Artaxol; Biometacin; Draxil; Grindocin†; Indaflex; Indocarsil; Indocid; Indoman; Indotrin; Italon; Labymetacyn†; Malival; Mefazil; Soltacina; Stratasin; ***Neth.:*** Dometin†; Indocid; Indocid PDA; Indocollyre; Indoptol†; ***Norw.:*** Confortid; Indocid; ***NZ:*** Arthrexin; Elmetacin†; Indocid PDA; Rheumacin; ***Philipp.:*** Infree; Vi-Gel; ***Pol.:*** Elmetacin; Indocollyre; Metindol; ***Port.:*** Autritis; Dolovin; Elmetacin; Indocid; Indocollyre; Indogel; Indospray; Reumacide; ***Rus.:*** Indomin (Индомин); Indotard (Индотард)†; Indovis (Индовис)†; Metindol (Метиндол); ***S.Afr.:*** Acuflex; Adco-Indogel; Aflamin; Arthrexin; Betacin; Elmetacin; Flamaret; Flamecid; Indocid; Mediflex†; Methocaps; Nisaid; Restameth-SR†; ***Singapore:*** Indo; Indocollyre; Indomen; ***Spain:*** Aliviosin; Artrinovo; Flogoter; Inacid; Indocaf; Indolgina; Indonilo; Mederreumol†; Neo Decabutin; Reumo†; Reusin; ***Swed.:*** Confortid; Indomee; ***Switz.:*** Bonidon; Elmetacin; Indo-Mepha†; Indocid; Indophtal; ***Thai.:*** Ammi-Indocin; Bucin†; Docin; Elmego; Elmetacin; Idc; Indocid; Indocin; Indocollyre; Indomed; Indono; Inflamate; Inthacine; Liometacen; Metindo; Satogesic; ***Turk.:*** Endol; Endosetin; Indocolir; Inomet; ***UAE:*** Rothacin; ***UK:*** Flexin Continus†; Indocid PDA; Indocid†; Indolar SR; Indomax†; Indomod†; Pardelprin; Rimacid; Slo-Indo; ***USA:*** Indocin; ***Venez.:*** Cevimin; Elmetacin; Indocid; Melior†; Romazulan†.

Multi-ingredient: ***Austria:*** Vonum; ***Fin.:*** Indalgin; ***Fr.:*** Indobiotic; ***Ger.:*** Inflam†; ***Ital.:*** Difmetre; ***Jpn:*** Vantelin; ***Mex.:*** Artindol; Malival Compuesto; Morlan; Reupat; ***Port.:*** Indobiotic; ***Rus.:*** Indovasin (Индовазин); ***Spain:*** Artri; Fiacin; ***Switz.:*** Indobiotic†; Ralur†; ***Turk.:*** Indobiotic.

Infliximab *(BAN, rINN)*

cA2; CenTNF; Infliksimab; Infliksimabi; Infliximabum. Immunoglobulin G (human-mouse monoclonal cA2 heavy chain anti-human tumor necrosis factor), disulfide with human-mouse monoclonal cA2 light chain, dimer.

Инфликсимаб
CAS — 170277-31-3.
ATC — L04AB02.
ATC Vet — QL04AB02.

Adverse Effects, Treatment, and Precautions

Acute infusion reactions during or within 1 to 2 hours of infusion are common with infliximab, and other TNF inhibitors, particularly with the first or second dose. Symptoms include fever, chills, pruritus, urticaria, dyspnoea, chest pain, and hypertension or hypotension. Mild reactions may respond to a reduced rate of infusion or a temporary interruption. If reactions are more severe, therapy should be stopped. Pretreatment with paracetamol, corticosteroids, and antihistamines may be considered. TNF inhibitors should only be given where facilities for resuscitation are available. Delayed reactions have occurred 3 to 12 days after infliximab treatment; symptoms include myalgia, arthralgia, fever, and rash. Similar delayed reactions may also be seen when infliximab has been restarted after an extended period without treatment (see below).

Other, common, adverse effects include nausea and vomiting, abdominal pain, diarrhoea, fatigue, dizziness, headache, and back pain. Antibodies to infliximab (human antichimeric antibodies) may develop, and are associated with an increased incidence of hypersensitivity reactions. Antinuclear antibodies and anti-double-stranded-DNA antibodies have also developed with TNF inhibitor therapy. A lupus-like syndrome has occurred rarely; treatment should be stopped if it develops.

Infections are common in patients treated with infliximab or other drugs that inhibit TNF, and most often affect the upper respiratory tract and the urinary tract. TNF inhibitors have also been associated rarely with the development of serious opportunistic infections, sepsis, pneumonia, and onset or reactivation of tuber-