is being investigated in the management of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.

◊ References.

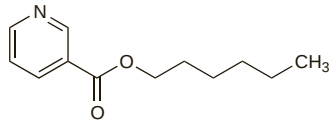
1. Zhou H, *et al.* Pharmacokinetics and safety of golimumab, a fully human anti-TNF-α monoclonal antibody, in subjects with rheumatoid arthritis. *J Clin Pharmacol* 2007; **47:** 383–96.
2. Kay J, *et al.* Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum* 2008; **58:** 964–75.

Hexyl Nicotinate

Heksyylinikotinaatti; Hexylnicotinatum; Hexylnikotinat; Nicotinato de hexilo. *n*-Hexyl nicotinate.

$C_{12}H_{17}NO_2$ = 207.3.

CAS — 23597-82-2.



Profile

Hexyl nicotinate is used in topical preparations as a rubefacient.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Transvane; ***Irl.:*** Transvasin; ***Port.:*** Hipodor†; ***UK:*** Transvasin Heat Rub.

Hydrocodone Hydrochloride *(BANM, rINNM)*

Hidrocloruro de hidrocodona; Hydrocodone, Chlorhydrate d'; Hydrocodoni Hydrochloridum.

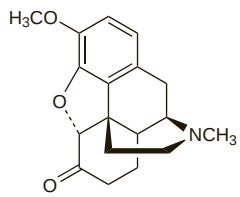
Гидрокодона Гидрохлорид

$C_{18}H_{21}NO_3$,HCl,2 / H_2O = 380.9.

CAS — 25968-91-6 (anhydrous hydrocodone hydrochloride).

ATC — R05DA03.

ATC Vet — QR05DA03.



(hydrocodone)

Hydrocodone Tartrate *(BANM, rINNM)*

Dihydrocodeinone Acid Tartrate; Hydrocodone Acid Tartrate; Hydrocodone Bitartrate *(USAN)*; Hydrocodone, Tartrate d'; Hydrocodoni Bitartras; Hydrocodoni Tartras; Hydrocone Bitartrate; Tartrato de dihidrocodeinona; Tartrato de hidrocodona. 6-Deoxy-3-*O*-methyl-6-oxomorphine hydrogen tartrate hemipentahydrate; (–)-(5*R*)-4,5-Epoxy-3-methoxy-9a-methylmorphinan-6-one hydrogen tartrate hemipentahydrate.

Гидрокодона Тартрат

$C_{18}H_{21}NO_3$,$C_4H_6O_6$,2 / H_2O = 494.5.

CAS — 125-29-1 (hydrocodone); 143-71-5 (anhydrous hydrocodone tartrate); 34195-34-1 (hydrocodone tartrate hemipentahydrate).

ATC — R05DA03.

ATC Vet — QR05DA03.

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

- Co-hycodAPAP (*PEN*)—hydrocodone tartrate and paracetamol.
  The following terms have been used as 'street names' (see p.vi) or slang names for various forms of hydrocodone tartrate:
  Cough Syrup; Vikes.

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

Ph. Eur. 6.2 (Hydrocodone Hydrogen Tartrate 2.5-Hydrate). White or almost white, hygroscopic, crystalline powder. Freely soluble or soluble in water; sparingly soluble in alcohol; practically insoluble in cyclohexane. A 2% solution in water has a pH of 3.2 to 3.8. Store in airtight containers. Protect from light.

USP 31 (Hydrocodone Bitartrate). Fine, white crystals or crystalline powder. Soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 2% solution in water is between 3.2 and 3.8. Store in airtight containers. Protect from light.

Profile

Hydrocodone, a phenanthrene derivative, is an opioid analgesic (p.101) related to codeine (p.37) and has similar actions, but is more potent on a weight-for-weight basis. Hydromorphone (below) is one of the metabolites of hydrocodone.

Hydrocodone is used mainly as the tartrate in combination preparations for the relief of irritant cough, though it has no particular advantage over codeine. Hydrocodone tannate has been used similarly. Hydrocodone tartrate is also used for the relief of moderate to moderately severe pain, usually with paracetamol. The usual oral dose of hydrocodone tartrate in such combination preparations is 5 to 10 mg every 4 to 6 hours.

For details of doses in children, see below.

Hydrocodone hydrochloride is given orally and also by injection. The polistirex derivative (a hydrocodone and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) is used in modified-release preparations.

Hydrocodone has also been used in the treatment of dyspnoea.

Abuse. The abuse or overuse of preparations containing hydrocodone and paracetamol has been associated with *sensorineural hearing loss.*[1,2] Cochlear implants improved the hearing loss in some of the patients.

A case of *palatal perforation* associated with intranasal abuse of a crushed preparation of hydrocodone and paracetamol has also been reported.[3]

1. Friedman RA, *et al.* Profound hearing loss associated with hydrocodone/acetaminophen abuse. *Am J Otol* 2000; **21:** 188–91.
2. Ho T, *et al.* Hydrocodone use and sensorineural hearing loss. *Pain Physician* 2007; **10:** 467–72.
3. Jewers WM, *et al.* Palatal perforation associated with intranasal prescription narcotic abuse. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **99:** 594–7.

Administration in children. Hydrocodone tartrate may be given as part of a combination preparation for the relief of irritant cough in children aged from 6 to 12 years in usual oral doses of 2.5 mg every 4 to 6 hours. Older children may be given the usual adult dose (see above).

Pharmacokinetics. References.

1. Hutchinson MR, *et al.* CYP2D6 and CYP3A4 involvement in the primary oxidative metabolism of hydrocodone by human liver microsomes. *Br J Clin Pharmacol* 2004; **57:** 287–97.

Preparations

USP 31: Hydrocodone Bitartrate and Acetaminophen Tablets; Hydrocodone Bitartrate and Homatropine Methylbromide Tablets; Hydrocodone Bitartrate Tablets.

Proprietary Preparations (details are given in Part 3)

Belg.: Biocodone; ***Canad.:*** Hycodan; ***Ger.:*** Dicodid; ***Switz.:*** Dicodid†; Hydrocodeinon.

Multi-ingredient: ***Arg.:*** Hidronovag Complex; ***Canad.:*** Coristine-DH†; Dalmacol; Dimetane Expectorant DC; Hycomine; Novahistex DH; Novahistine DH; ratio-Calmydone; ratio-Coristex-DH; Tussionex; Vasofrinic DH; ***India:*** Cardiazol-Dicodid†; ***USA:*** Alor; Anaplex HD; Anexsia; Atuss EX†; Atuss G; Atuss HC; Atuss HD; Atuss HS; Atuss HX; Bancap HC; Ceta Plus; Co-Gesic; Co-Tuss V; Codal-DH; Codiclear DH; Codimal DH; Cophene XP; Cordron-HC; Cyndal HD†; Cytuss HC; Cytuss-HC NR; Damason-P; De-Chlor G; De-Chlor HC; De-Chlor HD†; De-Chlor MR; De-Chlor NX; Deconamine CX; Dolacet; Donatussin DC; Drocon-CS; Duocet; Duratuss HD; Dytan-HC; ED Tuss HC; ED-TLC; Endagen-HD; Endal-HD; Endal-HD Plus; Entex HC; Entuss Expectorant; Entuss-D; Entuss-D Jr; H-Tuss-D†; Histex HC; Histinex D; Histinex HC; Histinex PV; Histussin D†; Histussin HC; Hy-KXP; Hy-Phen; Hycet; HycoClear Tuss; Hycodan; Hycomine Compound; Hycotuss; Hydex PD; Hydro DP; Hydro PC†; Hydro-GP; Hydro-Tussin HD; Hydro-Tussin HG; Hydrocet; Hydrocodone CP; Hydrocodone GF; Hydrocodone HD; Hydrogesic; Hydromet; Hydron CP; Hydron EX; Hydron KGS; Hydron PSC; Hydropane; Hyphed; HyTan; Ibudone; Iodal; Iotussin HC; Kwelcof; Levall 5.0; Liquicet; Lorcet 10/650; Lorcet Plus; Lorcet-HD; Lortab; Lortab ASA; Lortuss HC; Marcof; Margesic H; Maxi-Tuss HCG; Maxi-Tuss HCX; Maxidone; Nalex DH; Nalex Expectorant; Narcof; Nariz HC; Neo HC; Norco; Notuss PD; Notuss-Forte; Oncet; P-V-Tussin; Pancof XP; Pancof-HC; Pancof-XL; Para-Hist HD; Pneumotussin; Poly-Tussin; Pro-Red; Protuss-D†; Protuss†; Relacon-HC; Relasin-HCX; Reprexain; S-T Forte 2; SRC Expectorant; Stagesic; Su-Tuss HD; T-Gesic; Tusana-D; Tusdec-HC; Tusnel-HC; Tussafed HC†; Tussafed-HCG; Tussafin Expectorant; Tussanil DH; Tussend; Tussigon; Tussionex Pennkinetic; Tusso-DF; Tusso-HC; Tussplex; Tyrodone; Unituss HC; Vanex Expectorant; Vanex-HD; Vazotuss HC; Vicodin; Vicodin Tuss; Vicoprofen; Vitussin; Xodol; Z-Cof HC; Zamicet; Zydone; Zymine HC.

Hydromorphone Hydrochloride

(BANM, rINNM) ⊗

Dihydromorphinone Hydrochloride; Hidrocloruro de dihidromorfinona; Hidrocloruro de hidromorfona; Hidromorfono hidrochloridas; Hydromorfon-hydrochlorid; Hydromorfonhydroklorid; Hydromorfonihydrokloridi; Hydromorphone, chlorhydrate d'; Hydromorphoni hydrochloridum. 6-Deoxy-7,8-dihydro-6-oxomorphine hydrochloride; (–)-(5*R*)-4,5-Epoxy-3-hydroxy-9a-methylmorphinan-6-one hydrochloride.

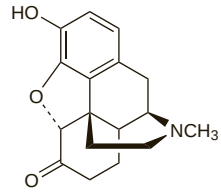
Гидроморфона Гидрохлорид

$C_{17}H_{19}NO_3$,HCl = 321.8.

CAS — 466-99-9 (hydromorphone); 71-68-1 (hydromorphone hydrochloride).

ATC — N02AA03.

ATC Vet — QN02AA03.



(hydromorphone)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of hydromorphone:
Dillies; HillBilly Heroin; Hospital heroin.

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

Ph. Eur. 6.2 (Hydromorphone Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. Protect from light.

USP 31 (Hydromorphone Hydrochloride). A fine white, or practically white, odourless, crystalline powder. Soluble 1 in 3 of water; sparingly soluble in alcohol; practically insoluble in ether. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Colour change from pale yellow to light green occurred when solutions of minocycline hydrochloride or tetracycline hydrochloride were mixed with hydromorphone hydrochloride in 5% glucose injection.[1] Mixtures of hydromorphone hydrochloride and dexamethasone sodium phosphate exhibited concentration-dependent incompatibility.[2] White cloudiness, haziness, or precipitation developed 4 hours after mixing thiopental sodium and hydromorphone hydrochloride.[3]

Stability of mixtures of fluorouracil and hydromorphone hydrochloride in 0.9% sodium chloride or 5% glucose depended on the concentration of fluorouracil present.[4] Hydromorphone hydrochloride 0.5 mg/mL with fluorouracil 1 mg/mL was stable for at least 7 days at 32° and for at least 35 days at 23°, 4°, or –20°. When the concentration of fluorouracil was increased to 16 mg/mL, hydromorphone was noted to decompose incurring unacceptable losses after 3 days at 32° or after 7 days at 23°, but was stable for at least 35 days at 4° or –20°.

1. Nieves-Cordero AL, *et al.* Compatibility of narcotic analgesic solutions with various antibiotics during simulated Y-site injection. *Am J Hosp Pharm* 1985; **42:** 1108–9.
2. Walker SE, *et al.* Compatibility of dexamethasone sodium phosphate with hydromorphone hydrochloride or diphenhydramine hydrochloride. *Am J Hosp Pharm* 1991; **48:** 2161–6.
3. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
4. Xu QA, *et al.* Stability and compatibility of fluorouracil with morphine sulfate and hydromorphone hydrochloride. *Ann Pharmacother* 1996; **30:** 756–61.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p.102.

UK licensed product information contra-indicates the use of hydromorphone hydrochloride in patients with hepatic impairment; however, product information in the USA permits its cautious use although doses may need to be reduced. It should also be used with caution and given in reduced doses to those with renal impairment.

Effects on the nervous system. Myoclonus has been reported[1] in a 55-year-old man given relatively low doses of intravenous hydromorphone with a total daily dose of 4 mg on day 1 and 6 mg on day 2; symptoms resolved when the drug was stopped on day 3. A chart review[2] for neuroexcitatory symptoms in 48 patients with terminal illnesses on hydromorphone found 13 cases of agitation, 9 of myoclonus, and 4 of seizures; maximal dose and treatment duration were noted to increase the risk of neurotoxicity.

1. Patel S, *et al.* A myoclonic reaction with low-dose hydromorphone. *Ann Pharmacother* 2006; **40:** 2068–70.
2. Thwaites D, *et al.* Hydromorphone neuroexcitation. *J Palliat Med* 2004; **7:** 545–50.

Interactions

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

Alcohol. The FDA received data from pharmacokinetic studies in healthy subjects which showed that significantly higher peak plasma concentrations of hydromorphone were achieved, as a result of dose-dumping, when alcohol was ingested with once-daily hydromorphone modified-release capsules (*Palladone;*

Purdue Frederick, USA); these increases were considered potentially lethal, even in opioid-tolerant patients.[1] Subsequently, this formulation was voluntarily withdrawn by the US manufacturer in July 2005.

1. Food and Drug Administration. FDA alert for healthcare professionals: alcohol-Palladone interaction (issued 13th July, 2005). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/hydromorphoneHCP.pdf (accessed 26/06/08)

Pharmacokinetics

Hydromorphone hydrochloride is rapidly but incompletely absorbed from the gastrointestinal tract after oral doses; peak plasma concentrations occur within 0.5 to 1 hour. Oral bioavailability is about 50% as it undergoes extensive first-pass metabolism. Hydromorphone is about 8 to 19% bound to plasma proteins. A plasma elimination half-life of about 2.5 hours has been reported after oral or intravenous doses. Hydromorphone appears to be widely distributed in the tissues; it crosses the placenta and is distributed into breast milk. It is extensively metabolised by glucuronidation in the liver and excreted in the urine mainly as conjugated hydromorphone, dihydroisomorphine, and dihydromorphine.

◊ References.

1. Vallner JJ, *et al.* Pharmacokinetics and bioavailability of hydromorphone following intravenous and oral administration to human subjects. *J Clin Pharmacol* 1981; **21:** 152–6.
2. Parab PV, *et al.* Pharmacokinetics of hydromorphone after intravenous, peroral and rectal administration to human subjects. *Biopharm Drug Dispos* 1988; **9:** 187–99.
3. Vashi V, *et al.* Clinical pharmacology and pharmacokinetics of once-daily hydromorphone hydrochloride extended-release capsules. *J Clin Pharmacol* 2005; **45:** 547–54.

Uses and Administration

Hydromorphone hydrochloride, a phenanthrene derivative, is an opioid analgesic (p.104). It is related to morphine (p.89) but with a greater analgesic potency. Hydromorphone hydrochloride is used for the relief of moderate to severe pain and for the relief of non-productive cough.

In the treatment of **pain**, hydromorphone hydrochloride is a useful alternative to morphine for subcutaneous use since its greater solubility in water allows a smaller dose volume. After injection onset of action usually occurs within 15 minutes and analgesia is reported to last for more than 5 hours; after oral doses onset of analgesia is usually within 30 minutes. It is given by subcutaneous or intramuscular injection in initial doses of 1 to 2 mg every 4 to 6 hours as necessary. It may also be given by slow intravenous injection or by intravenous or subcutaneous infusion, with doses adjusted according to individual requirements. Higher parenteral doses may be given to opioid-tolerant patients using a highly concentrated solution containing 10 mg/mL that allows smaller dose volumes. In the UK, the initial oral dose is 1.3 mg every 4 hours; thereafter the dose may be increased as necessary. In the USA, initial oral doses of 2 mg may be given every 4 to 6 hours; doses may be increased to 4 mg or more for severe pain. Modified-release preparations are available for less frequent administration, but see Alcohol, under Interactions, above. By rectum, the usual dose is 3 mg every 6 to 8 hours.

For the relief of non-productive **cough** hydromorphone hydrochloride is given, as a syrup, in doses of 1 mg repeated every 3 to 4 hours.

◊ References.

1. Bruera E, *et al.* A randomized, double-blind, double-dummy, crossover trial comparing the safety and efficacy of oral sustained-release hydromorphone with immediate-release hydromorphone in patients with cancer pain. *J Clin Oncol* 1996; **14:** 1713–17.
2. Miller MG, *et al.* Continuous subcutaneous infusion of morphine vs. hydromorphone: a controlled trial. *J Pain Symptom Manage* 1999; **18:** 9–16.
3. Quigley C. Hydromorphone for acute and chronic pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 26/06/08).
4. Murray A, Hagen NA. Hydromorphone. *J Pain Symptom Manage* 2005; **29** (suppl): S57–S66.
5. Grosset AB, *et al.* Comparative efficacy of oral extended-release hydromorphone and immediate-release hydromorphone in patients with persistent moderate to severe pain: two randomized controlled trials. *J Pain Symptom Manage* 2005; **29:** 584–94.
6. Du Pen S, *et al.* Intrathecal hydromorphone for intractable nonmalignant pain: a retrospective study. *Pain Med* 2006; **7:** 10–15.
7. Chang AK, *et al.* Safety and efficacy of hydromorphone as an analgesic alternative to morphine in acute pain: a randomized clinical trial. *Ann Emerg Med* 2006; **48:** 164–72.

Preparations

USP 31: Hydromorphone Hydrochloride Injection; Hydromorphone Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Dolonovag; ***Austral.:*** Dilaudid; ***Austria:*** Dilaudid; Hydal; ***Belg.:*** Palladone; ***Canad.:*** Dilaudid; Hydromorph; ***Cz.:*** Jurnista; Palladone; ***Denm.:*** Opidol†; Palladon; ***Fin.:*** Palladon; ***Fr.:*** Sophidone; ***Ger.:*** Dilaudid; Palladon; ***Hung.:*** Palladone; ***Irl.:*** Palladone; ***Israel:*** Palladone; ***Mex.:*** Liberaxim; ***Neth.:*** Palladon; ***Norw.:*** Palladon; ***NZ:*** Dilaudid†; ***Port.:*** Jurnista; Palladone; ***Swed.:*** Opidol†; Palladon; ***Switz.:*** Palladon; ***UK:*** Palladone; ***USA:*** Dilaudid; Palladone†.

Multi-ingredient: ***Swed.:*** Dilaudid-Atropin; ***Switz.:*** Dilaudid-Atropin†; ***USA:*** Dilaudid Cough.

Ibuprofen *(BAN, USAN, rINN)*

Ibuprofeeni; Ibuprofén; Ibuprofenas; Ibuprofène; Ibuprofeno; Ibuprofenum; RD-13621; U-18573. 2-(4-Isobutylphenyl)propionic acid.

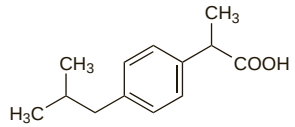
Ибупрофен

$C_{13}H_{18}O_2$ = 206.3.

CAS — 15687-27-1.

ATC — C01EB16; G02CC01; M01AE01; M02AA13.

ATC Vet — QC01EB16; QG02CC01; QM01AE01; QM02AA13.



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

Ph. Eur. 6.2 (Ibuprofen). A white or almost white, crystalline powder or colourless crystals. M.p. 75° to 78°. Practically insoluble in water; freely soluble in acetone, in dichloromethane, and in methyl alcohol; it dissolves in dilute solutions of alkali hydroxides and carbonates.

USP 31 (Ibuprofen). A white to off-white crystalline powder having a slight characteristic odour. Practically insoluble in water; very soluble in alcohol, in acetone, in chloroform, and in methyl alcohol; slightly soluble in ethyl acetate. Store in airtight containers.

Ibuprofen Lysine *(USAN)*

Ibuprofen Lysinate; Soluphene. Lysine 2-(4-isobutylphenyl)propionate.

Ибупрофен Лизин

$C_{19}H_{32}N_2O_4$ = 352.5.

CAS — 57469-77-9.

ATC — C01EB16; G02CC01; M01AE01; M02AA13.

ATC Vet — QC01EB16; QG02CC01; QM01AE01; QM02AA13.

Stability. Solutions of ibuprofen lysine in Water for Injections stored at room temperature were found to be most stable when protected from light.[1]

1. Volonté MG, *et al.* Stability of ibuprofen in injection solutions. *Am J Health-Syst Pharm* 2005; **62:** 630–3.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96. Ibuprofen may be better tolerated than other NSAIDs.

Adverse effects that may be associated with the use of ibuprofen injection in premature **neonates** include intraventricular haemorrhage, periventricular leucomalacia, bronchopulmonary dysplasia, pulmonary haemorrhage, necrotising enterocolitis, intestinal perforation, oliguria, fluid retention, and haematuria; hypoxaemia and gastrointestinal haemorrhage have also been reported. In addition ibuprofen injection should not be given to neonates with life-threatening infection, with significant renal impairment, or with known or suspected necrotising enterocolitis. Infants who are bleeding (especially gastrointestinal bleeding or intracranial haemorrhage) or who have thrombocytopenia or coagulation defects should also not be given parenteral ibuprofen, and those given it should be monitored during treatment for signs of bleeding. Renal function should 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.

Symptoms of nausea, vomiting, and tinnitus have been reported after ibuprofen overdosage. More serious toxicity is uncommon, but gastric emptying followed by supportive measures is recommended if the quantity ingested within the previous hour exceeds 400 mg/kg.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving ibuprofen, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. The *BNF* also considers the amount of ibuprofen distributed into breast milk to be too small to be harmful to a breast-fed infant. A study[2] estimated that a breast-fed infant would ingest about 0.0008% of the maternal dose. However, licensed product information for some preparations, including some topical preparations, recommends that breast feeding should be avoided during ibuprofen treatment.

1. 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)
2. Walter K, Dilger C. Ibuprofen in human milk. *Br J Clin Pharmacol* 1997; **44:** 211–12.

Children. An analysis[1] of the outcome of treatment of 83 915 children found that the risk of hospitalisation for gastrointestinal bleeding, renal failure, or anaphylaxis was no greater in children given ibuprofen than in those given paracetamol.

1. Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. *JAMA* 1995; **273:** 929–33.

Effects on the blood. Blood disorders including agranulocytosis, aplastic anaemia,[1] pure white-cell aplasia,[2] and thrombocytopenia[3] have been reported in patients taking ibuprofen. Fatal haemolytic anaemia occurred in a man taking ibuprofen and oxazepam.[4]

1. Gryfe CI, Rubenzahl S. Agranulocytosis and aplastic anemia possibly due to ibuprofen. *Can Med Assoc J* 1976; **114:** 877.
2. Mamus SW, *et al.* Ibuprofen-associated pure white-cell aplasia. *N Engl J Med* 1986; **314:** 624–5.
3. Jain S. Ibuprofen-induced thrombocytopenia. *Br J Clin Pract* 1994; **48:** 51.
4. Guidry JB, *et al.* Fatal autoimmune hemolytic anemia associated with ibuprofen. *JAMA* 1979; **242:** 68–9.

Effects on the cardiovascular system. For a discussion of the cardiovascular effects of NSAIDs, including ibuprofen, see p.96.

Effects on the CNS. Aseptic meningitis has occurred in patients taking NSAIDs. A review[1] of NSAID-related CNS adverse effects summarised 23 literature reports of NSAID-associated aseptic meningitis; 17 reports involved ibuprofen, 4 sulindac, 1 naproxen, and 1 tolmetin. Of the 23 reports, 11 were in patients with a diagnosis of SLE. Typically the reaction is seen in patients who have just restarted NSAID therapy after a gap in their treatment. Within a few hours of restarting the NSAID the patient experiences fever, headache, and a stiff neck; abdominal pain may be present. The patient may become lethargic and eventually comatose. Symptoms resolve if the NSAID is stopped. It is believed to be a hypersensitivity reaction but there does not appear to be cross-reactivity between NSAIDs.

Similar conclusions have also been reported more recently.[2] After experience of 2 cases, a review of the literature identified 71 episodes of ibuprofen-induced aseptic meningitis in 36 patients; 22 patients had recurrent episodes after repeated ibuprofen use. An underlying auto-immune connective tissue disorder was noted in 22 patients of whom 14 had SLE, 6 had an undifferentiated or mixed disorder, 1 had rheumatoid arthritis , and 1 had Sjögren's syndrome. In most cases, symptoms developed within 24 hours of starting ibuprofen although 1 patient had been taking ibuprofen for 2 years before the onset of symptoms. Cross-reactivity was reported in only 1 patient who had also developed aseptic meningitis with both naproxen and rofecoxib.

1. Hoppmann RA, *et al.* Central nervous system side effects of nonsteroidal anti-inflammatory drugs: aseptic meningitis, psychosis, and cognitive dysfunction. *Arch Intern Med* 1991; **151:** 1309–13.
2. Rodríguez SC, *et al.* Characteristics of meningitis caused by ibuprofen: report of 2 cases with recurrent episodes and review of the literature. *Medicine* 2006; **85:** 214–20.

Effects on electrolytes. Hyponatraemia has been described in patients receiving ibuprofen;[1-3] other risk factors such as pre-existing renal impairment or use with desmopressin were generally present.

1. Blum M, Aviram A. Ibuprofen induced hyponatraemia. *Rheumatol Rehabil* 1980; **19:** 258–9.
2. Rault RM. Case report: hyponatremia associated with nonsteroidal antiinflammatory drugs. *Am J Med Sci* 1993; **305:** 318–20.
3. García EBG, *et al.* Hyponatraemic coma induced by desmopressin and ibuprofen in a woman with von Willebrand's disease. *Haemophilia* 2003; **9:** 232–4.