Uses and Administration

Carbasalate calcium is a 1:1 complex of calcium acetylsalicylate and urea. It is metabolised to aspirin after absorption and thus has the actions of aspirin (p.23). Carbasalate calcium is given in oral doses equivalent to about 400 to 800 mg of aspirin every 4 to 8 hours up to a maximum of about 3 g daily for pain or fever. Carbasalate calcium has also been used in the management of thromboembolic disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Iromin; Vascal; ***Neth.:*** Ascal; ***Port.:*** Ascal; ***Spain:*** Ascal; ***Switz.:*** Alcacyl.

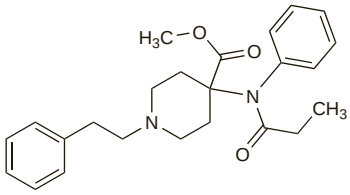
Multi-ingredient: ***Austria:*** Irocopar c C; Irocophan; Iromin-Chinin-C; ***Cz.:*** Cephalgan†; ***Fr.:*** Cephalgan†; ***Switz.:*** Alca-C.

Carfentanil Citrate *(USAN, rINNM)* ⊗

Carfentanil, Citrate de; Carfentanili Citras; Citrato de carfentanilo; R-33799. Methyl 1-phenethyl-4-(*N*-phenylpropionamido)isonipecotate citrate.

Карфентанила Цитрат

$C_{24}H_{30}N_2O_3,C_6H_8O_7$ = 586.6.
CAS — 59708-52-0 (carfentanil); 61380-27-6 (carfentanil citrate).



(carfentanil)

Profile

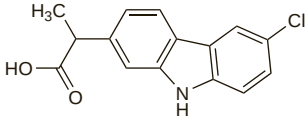
Carfentanil citrate is an opioid analgesic related to fentanyl (p.55). It is used in veterinary medicine.

Carprofen *(BAN, USAN, rINN)*

C-5720; Carprofène; Carprofeno; Carprofenum; Karprofeeni; Karprofen; Ro-20-5720/000. (±)-2-(6-Chlorocarbazol-2-yl)propionic acid.

Карпрофен

$C_{15}H_{12}ClNO_2$ = 273.7.
CAS — 53716-49-7.
ATC Vet — QM01AE91.



Pharmacopoeias. In *Eur.* (see p.vii) and *US* for veterinary use only.
Ph. Eur. 6.2 (Carprofen for Veterinary Use). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in acetone; soluble in methyl alcohol; slightly soluble in isopropyl alcohol. It exhibits polymorphism. Protect from light.
USP 31 (Carprofen). A white crystalline powder. Practically insoluble in water; freely soluble in acetone, in ether, in ethyl acetate, and in solutions of sodium carbonate and of sodium hydroxide. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Profile

Carprofen, a propionic acid derivative, is an NSAID (p.96) used in veterinary medicine.

Adverse effects. A pruritic, erythematous, eczematous eruption developed in a 27-year-old woman after occupational exposure to carprofen.[1] Patch testing showed a strong positive photoallergic reaction to carprofen.

1. Walker SL, *et al.* Occupational photoallergic contact dermatitis in a pharmaceutical worker manufacturing carprofen, a canine nonsteroidal anti-inflammatory drug. *Br J Dermatol* 2006; **154:** 569–70.

Preparations

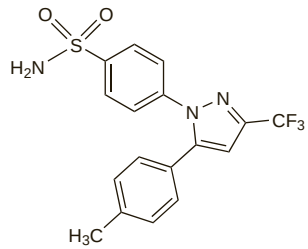
USP 31: Carprofen Tablets.

Celecoxib *(BAN, USAN, rINN)*

Célécoxib; Celecoxibum; Celekoxib; SC-58635; Selekoksib; Selekoksibi; YM-177. *p*-[5-*p*-Tolyl-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide.

Целекоксиб

$C_{17}H_{14}F_3N_3O_2S$ = 381.4.
CAS — 169590-42-5.
ATC — L01XX33; M01AH01.
ATC Vet — QL01XX33; QM01AH01.



Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Serious skin reactions such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with celecoxib. Other hypersensitivity reactions, including anaphylaxis and angioedema, have also occurred. Celecoxib should be stopped at the first signs of hypersensitivity. Some of these reactions have been seen in patients with a history of allergic reactions to sulfonamides and the use of celecoxib is contra-indicated in such patients.

Celecoxib should not be used after coronary artery bypass surgery as there may be an increased risk of adverse effects such as myocardial infarction and stroke. It should be used with caution, if at all, in patients with a history of ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease; it should also be used with caution in patients with significant risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and diabetes mellitus. For further details see Effects on the Cardiovascular System, below.

Therapy is contra-indicated in patients with moderate to severe heart failure (NYHA class II to IV), inflammatory bowel disease, and renal impairment associated with a creatinine clearance of less than 30 mL/minute. Celecoxib should also not be used in patients with severe hepatic impairment (Child-Pugh category C). Caution is recommended when using celecoxib in dehydrated patients; rehydration may be advisable before giving celecoxib.

Celecoxib treatment may need to be stopped if signs or symptoms of organ toxicity develop.

Incidence of adverse effects. A prescription-event monitoring study[1] conducted after the introduction of celecoxib in England in May 2000 found that the most common adverse events reported were gastrointestinal effects including dyspepsia (4.7% of all events), abdominal pain (1.8%), nausea or vomiting (1.6%), and diarrhoea (1.4%). Rash (1.2%) was also common. Uncommon events included anaemia, cough, anxiety, hypertension, visual disturbances, and insomnia. Blood dyscrasias, gastrointestinal bleeds, myocardial infarction, heart failure, abnormal liver function tests, nephritis, confusion, hallucinations, serious skin disorders, anaphylaxis, and bronchospasm were rare.

1. Layton D, *et al.* Safety profile of celecoxib as used in general practice in England: results of a prescription-event monitoring study. *Eur J Clin Pharmacol* 2004; **60:** 489–501.

Breast feeding. Licensed product information recommends that celecoxib should not be used in breast-feeding women because of the potential for serious adverse effects in nursing infants.

No adverse effects were noted in 2 older infants (aged 17 and 22 months) whose mothers took celecoxib while breast feeding.[1] The authors of this report also measured celecoxib plasma concentrations in 2 other women; from these values, the average milk-to-plasma ratio was calculated to be 0.23 and infant exposure was estimated at about 0.3% of the weight-adjusted maternal dose. Similar values have also been estimated from a study of blood and milk concentrations of celecoxib in 6 women.[2]

1. Hale TW, *et al.* Transfer of celecoxib into human milk. *J Hum Lact* 2004; **20:** 397–403.
2. Gardiner SJ, *et al.* Quantification of infant exposure to celecoxib through breast milk. *Br J Clin Pharmacol* 2006; **61:** 101–4.

Effects on the blood. Severe methaemoglobinaemia has been reported in an elderly patient after taking celecoxib for 1 month.[1]

1. Kaushik P, *et al.* Celecoxib-induced methemoglobinemia. *Ann Pharmacother* 2004; **38:** 1635–8.

Effects on the cardiovascular system. Prelicensing studies did not report any increased risk of serious cardiovascular effects in patients given celecoxib.[1,2] Nonetheless, by February 2001 the UK CSM had received a small number of reports[3] of *myocardial infarction* or *ischaemia* associated with the selective cyclo-oxygenase-2 (COX-2) inhibitors. There have also been 3 cases of *torsade de pointes* associated with celecoxib use.[4] Subsequently, in September 2004, the COX-2 inhibitor rofecoxib was generally withdrawn worldwide by the manufacturer after further reports of cardiovascular adverse effects (see p.121) and this has prompted re-evaluation of the safety of other selective COX-2 inhibitors.

In December 2004 a large study of celecoxib for prevention of colon polyps (the APC study) was halted because of an increased risk of cardiovascular events (including death from cardiovascular causes, myocardial infarction, stroke, and heart failure) in patients receiving the drug compared with those receiving placebo.[5] The results of this long-term study suggested that there was a 2.8-fold increase in the risk of such events in patients taking either celecoxib 400 or 800 mg daily and that the increase was dose-related. The possibility of a dose-adverse effect relationship was supported by some at-the-time unpublished studies, the PreSAP and ADAPT studies, that showed no increase in the risk of cardiovascular effects with celecoxib 400 mg daily when compared with placebo.[6] These studies[7,8] have since been published and their finished reports were less reassuring than initially thought. The risk of serious cardiovascular events was found to be increased in the celecoxib group when compared with the placebo group although the difference was not significant. In addition, an update[9] of the original APC study confirmed that the risk of adverse cardiovascular events was significantly increased for both high-dose (800 mg daily) and low-dose (400 mg daily) celecoxib when compared with placebo treatment; however, high-dose treatment was associated with the greatest risk. Increases in blood pressure were also more likely with both celecoxib groups than with placebo. An analysis[10] using pooled data from the APC and PreSAP studies provides further evidence of an increased cardiovascular risk with celecoxib.

Based on the findings of the above studies, EU regulatory authorities[11-13] recommend that:

- selective COX-2 inhibitors should not be used in patients with established ischaemic heart disease or cerebrovascular disease; they are also contra-indicated in those with peripheral arterial disease
- patients with risk factors for heart disease such as hypertension, hyperlipidaemia, diabetes, and smoking should be carefully monitored if given selective COX-2 inhibitors
- all patients should be assessed individually on the risks and benefits of selective COX-2 inhibitor treatment, particularly cardiovascular and gastrointestinal risk factors, and alternative treatments considered

Similar advice has also been issued by the FDA;[14] however, the only absolute contra-indication is in the immediate postoperative period after coronary artery bypass surgery. (In the USA celecoxib is currently the only available selective COX-2 inhibitor.)

COX-2 inhibitors such as celecoxib do not possess the intrinsic antiplatelet activity associated with aspirin and possibly other non-selective NSAIDs and consequently do not provide protection against ischaemic cardiac events.[3,15]

1. Silverstein FE, *et al.* Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *JAMA* 2000; **284:** 1247–55.
2. White WB, *et al.* Comparison of thromboembolic events in patients treated with celecoxib, a cyclooxygenase-2 specific inhibitor, versus ibuprofen or diclofenac. *Am J Cardiol* 2002; **89:** 425–30.
3. CSM/MCA. COX-2 selective NSAIDs lack antiplatelet activity. *Current Problems* 2001; **27:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)
4. Pathak A, *et al.* Celecoxib-associated torsade de pointes. *Ann Pharmacother* 2002; **36:** 1290–1.
5. Solomon SD, *et al.* Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005; **352:** 1071–80.
6. FDA. Celecoxib (marketed as Celebrex) (issued 7th April 2005). Available at: http://www.fda.gov/cder/drug/infopage/celebrex/celebrex-hcp.pdf (accessed 01/11/07)
7. Arber N, *et al.* Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med* 2006; **355:** 885–95.
8. ADAPT Research Group. Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's disease anti-inflammatory prevention trial (ADAPT). Available at: http://clinicaltrials.plosjournals.org/archive/1555-5887/1/7/pdf/10.1371_journal.pctr.0010033-L.pdf (accessed 01/11/07)
9. Bertagnolli MM, *et al.* Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med* 2006; **355:** 873–84.

10. Solomon SD, *et al.* Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. *Circulation* 2006; **114:** 1028–35.
11. MHRA. Updated advice on the safety of selective COX-2 inhibitors. Message from Professor G Duff, Chairman of CSM (issued 17th February, 2005). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019458&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)
12. EMEA. European Medicines Agency announces regulatory action on COX-2 inhibitors (issued 17th February, 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/6275705en.pdf (accessed 29/08/08)
13. EMEA. European Medicines Agency concludes action on COX-2 inhibitors (issued 27th June, 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/20776605en.pdf (accessed 01/11/07)
14. FDA. FDA issues public health advisory recommending limited use of cox-2 inhibitors: agency requires evaluation of prevention studies involving cox-2 selective agents. (issued 23rd December, 2004). Available at: http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01336.html (accessed 01/11/07)
15. Bing RJ, Lomnicka M. Why do cyclo-oxygenase-2 inhibitors cause cardiovascular events? *J Am Coll Cardiol* 2002; **39:** 521–2.

Effects on the gastrointestinal tract. It is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of the NSAIDs, and that the selective inhibition of the other isoform, COX-2, by NSAIDs such as celecoxib may cause less gastrotoxicity than the non-selective inhibition of the traditional NSAIDs.

Results from controlled studies suggested that NSAIDs selective for COX-2 were associated with a lower incidence of serious gastrointestinal effects. In a placebo-controlled study[1] the incidence of endoscopically determined gastroduodenal ulcers in patients taking celecoxib for rheumatoid arthritis (dose range 200 to 800 mg daily) was not significantly different to that seen with the placebo group. Another study[2] in patients taking celecoxib at supratherapeutic doses (800 mg daily) concluded that there was a lower combined incidence of symptomatic gastrointestinal ulcers and ulcer complications (bleeding, perforation, and obstruction) after 6 months of treatment when compared with non-selective NSAIDS (ibuprofen 2.4 g daily or diclofenac 150 mg daily). However, the incidence of ulcer complications alone was not significantly different to that seen with other NSAIDs. A re-analysis of the study by the FDA, including both the 6-month and full-term data, also found that there was no significant reduction in the rate of ulcer complications with celecoxib compared with the non-selective NSAIDs although, in subjects not taking aspirin, there was a strong trend in favour of celecoxib compared to ibuprofen.[3] The risk of ulcer complications was also significantly increased in celecoxib users taking concomitant low-dose aspirin.[2] A later systematic review[4] of studies of patients receiving celecoxib or NSAIDs for at least 12 weeks claimed to show improved gastrointestinal safety and tolerability in those receiving celecoxib (including in patients also taking low-dose aspirin) but this has been criticised on grounds of data selection.[5,6]

It has been noted that the use of aspirin appears to nullify any potential protective effect of COX-2 selectivity by celecoxib.[7,8]

There have been individual case reports of gastrotoxicity with celecoxib.[9-11]

1. Simon LS, *et al.* Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA* 1999; **282:** 1921–8.
2. Silverstein FE, *et al.* Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *JAMA* 2000; **284:** 1247–55.
3. FDA. Celebrex capsules (celecoxib) NDA 20-998/S009—Medical Officer Review. 2000. Available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_03_med.pdf (accessed 01/11/07)
4. Deeks JJ, *et al.* Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. *BMJ* 2002; **325:** 619–23.
5. Jüni P, *et al.* Systematic review of celecoxib for osteoarthritis and rheumatoid arthritis: problems compromise review's validity. *BMJ* 2003; **326:** 334.
6. Metcalfe S, *et al.* Systematic review of celecoxib for osteoarthritis and rheumatoid arthritis: celecoxib's relative gastrointestinal safety is overstated. *BMJ* 2003; **326:** 334–5.
7. Lichtenstein DR, Wolfe MM. COX-2-selective NSAIDs: new and improved? *JAMA* 2000; **284:** 1297–9.
8. Bates DE, Lemaire JB. Possible celecoxib-induced gastroduodenal ulceration. *Ann Pharmacother* 2001; **35:** 782–3.
9. Mohammed S, Croom DW. Gastropathy due to celecoxib, a cyclooxygenase-2 inhibitor. *N Engl J Med* 1999; **340:** 2005–6.
10. Adverse Drug Reactions Advisory Committee (ADRAC). Celecoxib: early Australian reporting experience. *Aust Adverse Drug React Bull* 2000; **19:** 6–7. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0006.pdf (accessed 29/08/08)
11. Adverse Drug Reactions Advisory Committee (ADRAC). Serious gastrointestinal effects with celecoxib and rofecoxib. *Aust Adverse Drug React Bull* 2003; **22:** 15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0308.htm (accessed 01/11/07)

Effects on the kidneys. Increasing evidence suggests that selective cyclo-oxygenase-2 (COX-2) inhibitors such as celecoxib appear to have adverse effects on renal function similar to those of the non-selective NSAIDs (see p.98).

Some references to the adverse renal effects of celecoxib.

1. Boyd IW, *et al.* COX-2 inhibitors and renal failure: the triple whammy revisited. *Med J Aust* 2000; **173:** 274.
2. Perazella MA, Tray K. Selective cyclooxygenase-2 inhibitors: a pattern of nephrotoxicity similar to traditional nonsteroidal anti-inflammatory drugs. *Am J Med* 2001; **111:** 64–7.
3. Graham MG. Acute renal failure related to high-dose celecoxib. *Ann Intern Med* 2001; **135:** 69–70.
4. Alkhuja S, *et al.* Celecoxib-induced nonoliguric acute renal failure. *Ann Pharmacother* 2002; **36:** 52–4.
5. Ahmad SR, *et al.* Renal failure associated with the use of celecoxib and rofecoxib. *Drug Safety* 2002; **25:** 537–44.
6. Alper AB, *et al.* Nephrotic syndrome and interstitial nephritis associated with celecoxib. *Am J Kidney Dis* 2002; **40:** 1086–90.
7. Akhund L, *et al.* Celecoxib-related renal papillary necrosis. *Arch Intern Med* 2003; **163:** 114–15.
8. Markowitz GS, *et al.* Membranous glomerulopathy and acute interstitial nephritis following treatment with celecoxib. *Clin Nephrol* 2003; **59:** 137–42.
9. Brewster UC, Perazella MA. Acute tubulointerstitial nephritis associated with celecoxib. *Nephrol Dial Transplant* 2004; **19:** 1017–18.
10. Clifford TM, *et al.* Celecoxib-induced nephrotoxicity in a renal transplant recipient. *Pharmacotherapy* 2005; **25:** 773–7.

Effects on the liver. Cholestatic hepatitis developed in a 54-year-old woman taking celecoxib;[1] her liver function tests improved and her symptoms resolved after drug withdrawal. Despite the temporal relationship between celecoxib use and the onset of hepatotoxicity, the manufacturers have stated that current evidence does not support such a relationship.[2] Other cases[3,4] have since been reported.

For a case of acute hepatitis with pancreatitis, see Pancreatitis, below.

1. O'Beirne JP, Cairns SR. Cholestatic hepatitis in association with celecoxib. *BMJ* 2001; **323:** 23.
2. Arellano FM, *et al.* Case of cholestatic hepatitis with celecoxib did not fulfil international criteria. *BMJ* 2002; **324:** 789–90.
3. Grieco A, *et al.* Acute cholestatic hepatitis associated with celecoxib. *Ann Pharmacother* 2002; **36:** 1887–9.
4. Chamouard P, *et al.* Prolonged cholestasis associated with short-term use of celecoxib. *Gastroenterol Clin Biol* 2005; **29:** 1286–8.

Effects on the lungs. Report of a case of pulmonary oedema and possible pneumonitis in a patient taking celecoxib.[1]

1. Olin JL, *et al.* Pulmonary edema and possible pneumonitis associated with celecoxib. *Ann Pharmacother* 2004; **38:** 1086.

Effects on the nervous system. Acute neuropsychiatric reactions such as confusion, somnolence, and insomnia, have occurred after celecoxib use.[1] There has also been a case report of aseptic meningitis.[2]

1. Adverse Drug Reations Advisory Committee (ADRAC). Acute neuropsychiatric events with celecoxib and rofecoxib. *Aust Adverse Drug React Bull* 2003; **22:** 3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0302.pdf (accessed 01/11/07)
2. Papaioannides DH, *et al.* Aseptic meningitis possibly associated with celecoxib. *Ann Pharmacother* 2004; **38:** 172.

Hypersensitivity. A 52-year-old man suffered an allergic vasculitis after 8 days of treatment with celecoxib.[1] Despite intensive treatment the patient died from multiple organ failure and diffuse cutaneous necrolysis. The authors noted that potentially fatal skin reactions have occurred with other sulfa-containing drugs, although there is some evidence suggesting that the potential for cross-reactivity in patients sensitive to sulfonamides is relatively low;[2] nonetheless, licensed product information contra-indicates the use of celecoxib in such patients.

1. Schneider F, *et al.* Fatal allergic vasculitis associated with celecoxib. *Lancet* 2002; **359:** 852–3.
2. Shapiro LE, *et al.* Safety of celecoxib in individuals allergic to sulfonamide: a pilot study. *Drug Safety* 2003; **26:** 187–95.

Pancreatitis. Acute hepatitis and pancreatitis developed in an elderly patient with a reported history of hypersensitivity to sulfonamides who was given celecoxib.[1] Symptoms resolved on stopping the drug. Pancreatitis has also been reported in a patient known to be tolerant of sulfonamides.[2]

Celecoxib was one of the more commonly implicated drugs cited in case reports of drug-induced pancreatitis received by the Adverse Drug Reactions Advisory Committee in Australia.[3]

1. Carrillo-Jimenez R, Nurnberger M. Celecoxib-induced acute pancreatitis and hepatitis: a case report. *Arch Intern Med* 2000; **160:** 553–4.
2. Baciewicz AM, *et al.* Acute pancreatitis associated with celecoxib. *Ann Intern Med* 2000; **132:** 680.
3. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Drug induced pancreatitis. *Aust Adverse Drug React Bull* 2006; **25:** 22. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0612.pdf (accessed 01/11/07)

Interactions

The metabolism of celecoxib is mediated mainly by the cytochrome P450 isoenzyme CYP2C9. Use with other drugs that inhibit or induce or are metabolised by this isoenzyme may result in changes in plasma concentration of celecoxib; fluconazole has increased plasma concentrations of celecoxib and licensed product information recommends that the dose of celecoxib should be halved when given with fluconazole.

Celecoxib is an inhibitor of the isoenzyme CYP2D6 and the potential therefore exists for an effect on drugs metabolised by this enzyme.

For interactions associated with NSAIDs in general, see p.99.

Pharmacokinetics

Celecoxib is absorbed from the gastrointestinal tract, peak plasma concentrations being achieved after about 3 hours. Protein binding is about 97%. Celecoxib is metabolised in the liver mainly by the cytochrome P450 isoenzyme CYP2C9; the three identified metabolites are inactive as inhibitors of COX-1 or COX-2 enzymes. It is eliminated mainly as metabolites in the faeces and urine; less than 3% is recovered as unchanged drug. The effective terminal half-life is about 11 hours. Celecoxib is distributed into breast milk. The pharmacokinetics of celecoxib may vary in different ethnic groups; it has been stated that the area under the curve is elevated in patients of Afro-Caribbean origin, although any clinical significance is unclear.

◊ References.

1. Davies NM, *et al.* Clinical pharmacokinetics and pharmacodynamics of celecoxib: a selective cyclo-oxygenase-2 inhibitor. *Clin Pharmacokinet* 2000; **38:** 225–42.
2. Stempak D, *et al.* Single-dose and steady-state pharmacokinetics of celecoxib in children. *Clin Pharmacol Ther* 2002; **72:** 490–7. Correction. *ibid.* 2006; **80:** 667.
3. Kirchheiner J, *et al.* Influence of CYP2C9 genetic polymorphisms on pharmacokinetics of celecoxib and its metabolites. *Pharmacogenetics* 2003; **13:** 473–80.
4. Lundblad MS, *et al.* Accumulation of celecoxib with a 7-fold higher drug exposure in individuals homozygous for CYP2C9*3. *Clin Pharmacol Ther* 2006; **79:** 287–8.

Uses and Administration

Celecoxib is an NSAID (p.99) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It is used in the treatment of rheumatoid arthritis including juvenile idiopathic arthritis, osteoarthritis, and ankylosing spondylitis, and in the adjunctive treatment of adenomatous colorectal polyps. Celecoxib is also used in the management of acute pain and dysmenorrhoea.

For **osteoarthritis** the recommended oral dose is 200 mg daily given as a single dose or in 2 divided doses. If necessary a dose of 200 mg twice daily may be used. For **rheumatoid arthritis** the dose is 100 to 200 mg given twice daily. Celecoxib is also used for **ankylosing spondylitis** in an initial dose of 200 mg daily, as a single dose or in 2 divided doses. In the USA, the dose may be increased to 400 mg daily after 6 weeks, although if no response is seen at this dose after a further 6 weeks, alternative treatments should be considered. A similar increase is also permitted in UK licensed product information; however, it is recommended that if ineffective, the higher dose should only be continued for 2 weeks before considering alternative treatments. In elderly patients treatment should be begun at the lowest recommended dose.

For doses in children with **juvenile idiopathic arthritis**, see below.

In the treatment of **pain** and **dysmenorrhoea**, an initial dose of 400 mg followed by an additional dose of 200 mg, if necessary, is recommended on the first day; thereafter the dose is 200 mg twice daily.

Celecoxib is also used as an adjunct to standard therapy to reduce the number of adenomatous **colorectal polyps** in patients with familial adenomatous polyposis. For this purpose it may be given in doses of 400 mg twice daily with food.

Reduced doses are recommended in patients with hepatic impairment (see below).

◊ Reviews.

1. Clemett D, Goa KL. Celecoxib: a review of its use in osteoarthritis, rheumatoid arthritis and acute pain. *Drugs* 2000; **59:** 957–80.
2. Frampton JE, Keating GM. Celecoxib: a review of its use in the management of arthritis and acute pain. *Drugs* 2007; **67:** 2433–72.

Administration in children. In the USA, celecoxib is licensed for the treatment of juvenile idiopathic arthritis in children aged 2 years and over. The recommended oral doses, based on body-weight, are:

- 10 kg to 25 kg: 50 mg twice daily
- over 25 kg: 100 mg twice daily

Licensed product information recommends that the contents of a celecoxib capsule may be sprinkled onto apple sauce if a patient has difficulty swallowing the capsules. The sprinkled capsule should be taken immediately; however, it remains stable at a temperature between 2° to 8° for up to 6 hours.

Administration in hepatic impairment. Licensed product information recommends that doses of celecoxib should be reduced by 50% in patients with moderate hepatic impairment (Child-Pugh category B); its use is contra-indicated in those with severe impairment (Child-Pugh category C or a score of 10 or more).

Familial adenomatous polyposis. Celecoxib is used in the treatment of familial adenomatous polyposis, an inherited syndrome known to predispose sufferers to the development of colonic cancer (see p.666). A randomised study[1,2] found that treatment with celecoxib reduced the number of colonic polyps; the authors considered celecoxib to be a useful adjunct to the standard therapy of colectomy.

1. Steinbach G, *et al.* The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 2000; **342:** 1946–52.
2. Phillips RKS, *et al.* A randomised, double blind, placebo controlled study of celecoxib, a selective cyclooxygenase 2 inhibitor, on duodenal polyposis in familial adenomatous polyposis. *Gut* 2002; **50:** 857–60.

Malignant neoplasms. Celecoxib is under investigation as adjuvant therapy in the treatment of cancer;[1-9] preliminary results have been variable. It has also been investigated for chemoprevention of malignancy[10-13] (see also Familial Adenomatous Polyposis, above), but a large study for the prevention of colon cancer was terminated early because of increased cardiovascular risk.[11,12]

1. Dang CT, *et al.* Phase II study of celecoxib and trastuzumab in metastatic breast cancer patients who have progressed after prior trastuzumab-based treatments. *Clin Cancer Res* 2004; **10:** 4062–7.
2. Reardon DA, *et al.* Phase II trial of irinotecan plus celecoxib in adults with recurrent malignant glioma. *Cancer* 2005; **103:** 329–38.
3. Nugent FW, *et al.* Docetaxel and cyclooxygenase-2 inhibition with celecoxib for advanced non-small cell lung cancer progressing after platinum-based chemotherapy: a multicenter phase II trial. *Lung Cancer* 2005; **48:** 267–73.
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9. Chow LWC, *et al.* Serum lipid profiles in patients receiving endocrine treatment for breast cancer—the results from the Celecoxib Anti-Aromatase Neoadjuvant (CAAN) Trial. *Biomed Pharmacother* 2005; **59** (suppl 2): S302–S305.
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12. Bertagnolli MM, *et al.* Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med* 2006; **355:** 873–84.
13. Arber N, *et al.* Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med* 2006; **355:** 885–95.

Musculoskeletal and joint disorders. Celecoxib is used in the treatment of osteoarthritis (p.11) and rheumatoid arthritis (p.11) including juvenile idiopathic arthritis (p.10). However, in the UK it is recommended that the use of celecoxib and other selective cyclo-oxygenase-2 (COX-2) inhibitors be limited to those patients considered to be at high risk of developing serious gastrointestinal problems if given a non-selective NSAID and who do not have pre-existing cardiovascular risk factors (see Adverse Effects, above).

Celecoxib is also used in the treatment of ankylosing spondylitis (see Spondyloarthropathies, p.13).

References.

1. Bensen WG, *et al.* Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. *Mayo Clin Proc* 1999; **74:** 1095–1105.
2. Simon LS, *et al.* Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA* 1999; **282:** 1921–28.
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8. Barkhuizen A, *et al.* Celecoxib is efficacious and well tolerated in treating signs and symptoms of ankylosing spondylitis. *J Rheumatol* 2006; **33:** 1805–12.
9. Luyten FP, *et al.* A prospective randomised multicentre study comparing continuous and intermittent treatment with celecoxib in patients with osteoarthritis of the knee or hip. *Ann Rheum Dis* 2007; **66:** 99–106.

Palmar-plantar erythrodysesthesia syndrome. Celecoxib has been investigated in the treatment of capecitabine-induced hand-foot (palmar-plantar erythrodysesthesia) syndrome; for references, see under Adverse Effects and Precautions of Capecitabine, p.692.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Algybrex; Celebrex; Celemax†; Cloxib†; Coxel†; Coxtenk; Niflam†; Radicacine; Tisorek†; ***Austral.:*** Celebrex; ***Austria:*** Celebrex; Solexa; ***Belg.:*** Celebrex; ***Braz.:*** Celebra; ***Canad.:*** Celebrex; ***Chile:*** Celebra; ***Cz.:*** Celebrex; Onsenal; ***Denm.:*** Celebra; ***Fin.:*** Celebra; ***Fr.:*** Celebrex; Onsenal; ***Ger.:*** Celebrex; ***Gr.:*** Aclarex; Celebrex; ***Hong Kong:*** Celebrex; ***Hung.:*** Celebrex; ***India:*** Celedol; Celib; Cobix; Orthocel; Ultracele†; Zycel; ***Indon.:*** Celebrex; ***Irl.:*** Celebrex; ***Israel:*** Celcox; Celebra; ***Ital.:*** Artilog†; Celebrex; Solexa†; ***Malaysia:*** Celebrex; ***Mex.:*** Celebrex; ***Neth.:*** Celebrex; Onsenal; Solexa; ***Norw.:*** Celebra; Onsenal; ***NZ:*** Celebrex; ***Philipp.:*** Celebrex; Flamar; ***Pol.:*** Celebrex; ***Port.:*** Celebrex; Onsenal; Solexa; ***Rus.:*** Celebrex (Целебрекс); ***S.Afr.:*** Celebrex; ***Singapore:*** Celebrex; ***Spain:*** Celebrex; Onsenal; ***Swed.:*** Celebra; Onsenal; ***Switz.:*** Celebrex; ***Thai.:*** Celebrex; ***UK:*** Celebrex; ***USA:*** Celebrex; ***Venez.:*** Celebrex†; Cexb.

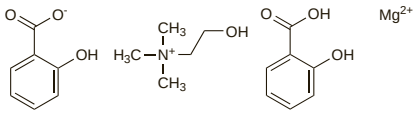
Choline Magnesium Trisalicylate

Trisalicilato de colina y magnesio.

Холин Магнезиум Трисалицилаты

$C_{26}H_{29}O_{10}NMg$ = 539.8.

CAS — 64425-90-7.



Adverse Effects, Treatment, and Precautions

As for Aspirin, p.20.

The use of aspirin and other acetylated salicylates is generally not recommended for children unless specifically indicated, because of the risk of Reye's syndrome. US licensing information extends this precaution to choline magnesium trisalicylate.

Effects on the liver. References.

1. Cersosimo RJ, Matthews SJ. Hepatotoxicity associated with choline magnesium trisalicylate: case report and review of salicylate-induced hepatotoxicity. *Drug Intell Clin Pharm* 1987; **21:** 621–5.
2. Nadkarni MM, *et al.* Eosinophilic hepatitis after ingestion of choline magnesium trisalicylate. *Am J Gastroenterol* 1992; **87:** 151–3.

Interactions

For interactions associated with salicylates, see Aspirin, p.23.

Uses and Administration

Choline magnesium trisalicylate is a combination of the salicylic acid derivatives choline salicylate (p.36) and magnesium salicylate (p.79). It has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (p.23). After oral administration, choline magnesium trisalicylate dissociates and the salicylate moiety is rapidly absorbed. Each unit dose of 500 mg of salicylate is provided by about 293 mg of choline salicylate with 362 mg of magnesium salicylate (anhydrous). Choline magnesium trisalicylate has been used in osteoarthritis, rheumatoid arthritis, and other arthritides in oral doses equivalent to 1 or 1.5 g of salicylate twice daily; doses may also be given as a single daily dose if required. A dose of 750 mg given three times daily may be more suitable for elderly patients. Choline magnesium trisalicylate is also used in similar doses in the general management of other forms of pain and for fever.

Preparations

Proprietary Preparations (details are given in Part 3)

Canad.: Trilisate†; ***USA:*** Trilisate†.

Choline Salicylate *(BAN, USAN, rINN)*

Choline, Salicylate de; Cholini Salicylas; Koliinisalisylaatti; Kolinsalicylat; Salicilato de colina. (2-Hydroxyethyl)trimethylammonium salicylate.

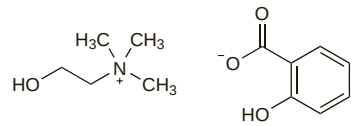
Холина Салицилат

$C_{12}H_{19}NO_4$ = 241.3.

CAS — 2016-36-6.

ATC — N02BA03.

ATC Vet — QN02BA03.



Pharmacopoeias. *Br.* includes a solution.

BP 2008 (Choline Salicylate Solution). An aqueous solution containing 47.5 to 52.5% of choline salicylate. It is a clear colourless liquid. It may contain a suitable antimicrobial preservative.

Profile

Choline salicylate is a salicylic acid derivative (see Aspirin, p.20) used in the treatment of pain and fever, and in the management of rheumatic disorders. In terms of salicylate content, choline salicylate 435 mg is equivalent to about 325 mg of aspirin. Choline salicylate is given orally in doses of 435 to 870 mg every four hours as necessary for pain and fever, and in doses of 4.8 to 7.2 g daily in divided doses for rheumatic disorders.

Choline salicylate is also used as a local analgesic. Solutions containing up to about 20% choline salicylate are used in ear disorders such as the relief of pain in otitis media and externa but are considered to be of doubtful value; they are also used to soften ear wax as an aid to removal (see p.1725). An 8.7% gel is used for lesions of the mouth (p.1700). Choline salicylate has also been applied topically in a rubefacient preparation for the relief of muscular and rheumatic pain.

Choline salicylate is also given in the form of choline magnesium trisalicylate (see above).

Adverse effects. A 21-month-old boy developed salicylate poisoning after his mother had rubbed the contents of 3 tubes of *Bonjela* teething ointment (containing a total of 2.61 g of choline salicylate) on his gums over 48 hours.[1]

In another case, an 8-year-old boy with G6PD deficiency developed an oral mucosal burn a few hours after application of about half a tube of *Teejel* oral gel.[2] He developed mouth ulcers and displayed signs of apathy, lethargy, and nasal congestion 3 days after exposure. His condition improved after a week. The authors felt that G6PD deficiency may have been a contributing factor in the occurrence of adverse effects.

1. Paynter AS, Alexander FW. Salicylate intoxication caused by teething ointment. *Lancet* 1979; **ii:** 1132.
2. Sapir S, Bimstein E. Cholinsalicylate gel induced oral lesion: report of case. *J Clin Pediatr Dent* 2000; **24:** 103–6.

REYE'S SYNDROME. The link between aspirin use in children and the development of Reye's syndrome is established although the evidence for other salicylates could not be adequately evaluated (see p.22). However, a 20-month-old boy who had received a teething gel containing choline salicylate (applied in doses of 1.31 g daily, equivalent to acetylsalicylate 100 mg/kg daily, which exceeds the recommended dose) developed Reye's syndrome following a viral illness.[1] The authors noted that the MHRA in the UK were aware of two earlier reports suggesting an association between choline salicylate and Reye's syndrome.

1. Oman TK, *et al.* Topical choline salicylates implicated in Reye's syndrome. *BMJ* 2008; **336:** 1376.

Preparations

BP 2008: Choline Salicylate Ear Drops; Choline Salicylate Oromucosal Gel.

Proprietary Preparations (details are given in Part 3)

Arg.: Dercolina; ***Austral.:*** Applicaine; Herron Baby Teething Gel; Ora-Sed Jel; ***Belg.:*** Teejel; ***Ger.:*** Audax†; ***Hong Kong:*** Ora-Sed; ***India:*** Gelora; Zytee; ***Irl.:*** Audax; Teejel; ***Israel:*** Teejel; ***NZ:*** Ora-Sed; ***Pol.:*** Cholinex; Otinum; ***Port.:*** Bucagel; ***Rus.:*** Otinum (Отинум); ***Singapore:*** Ora-Sed; ***UK:*** Audax†; Dinnefords Teejel†; ***USA:*** Arthropan†.

Multi-ingredient: ***Arg.:*** Pansoral; ***Austral.:*** Bonjela; Seda-Gel; ***Austria:*** Mundisal; ***Belg.:*** Givalex; ***Cz.:*** Mundisal; ***Fr.:*** Givalex; Pansoral; ***Ger.:*** Givalex†; Mundisal†; ***Gr.:*** Mundisal; ***Hong Kong:*** Bonjela; Dermojela; ***Hung.:*** Mundisal; ***Irl.:*** Bonjela; ***Israel:*** Baby Gum; Bonjela; ***Malaysia:*** Bonjela; Orregel; ***NZ:*** Bonjela; ***Pol.:*** Sachol zel Stomatologiczny; ***Rus.:*** Cholisal (Холисал); Pansoral (Пансорал); ***S.Afr.:*** Bonjela; ***Singapore:*** Bonjela; Soragel; ***Spain:*** Aldo Otico†; ***Switz.:*** Mundisal; Pansoral; Tenderdol; ***Thai.:*** Bonjela; ***UK:*** Bonjela; Earex Plus.