form, and in benzene; slightly soluble in carbon disulfide. Store in a cool place in airtight containers. Protect from light.

Adverse Effects

A warm, stinging, or burning sensation may occur at the site of application; this usually disappears after a few days of use but may persist longer if applications are less frequent than recommended (see Uses and Administration, below). Coughing, sneezing, or other signs of respiratory irritation may occur if dried residue from topical preparations is inhaled.

Precautions

Capsaicin should be handled with care. Particles should not be inhaled nor come into contact with any part of the body.

For topical application, contact with eyes and broken or irritated skin should be avoided. The hands should be washed after application of the cream, unless the hands are the treated areas, in which case, they should be washed 30 minutes after application. If bandages are used to cover treated areas they should not be wound too tightly. Heating pads should not be used with capsaicin, and patients should avoid taking a hot bath or shower immediately before or after application, as the burning sensation may be exacerbated. Thick applications of the cream should be avoided.

Uses and Administration

Capsaicin is the active principle of the dried ripe fruits of *Capsicum* spp. It is used as a topical analgesic (p.5) in painful conditions such as postherpetic neuralgia after the lesions have healed, diabetic neuropathy, osteoarthritis, and rheumatoid arthritis. Capsaicin is usually applied sparingly 3 or 4 times daily (and not more often than every 4 hours) as a 0.025% or 0.075% cream; in the UK these creams are not licensed for use in children, but in the USA they may be used in children over 2 years of age. A more concentrated cream containing 0.25% capsaicin is available in some countries.

Capsaicin cream should be rubbed well into the skin until little or no residue is left on the surface. Therapeutic response may not be evident for 1 to 2 weeks for arthritic disorders, or 2 to 4 weeks for neuralgias (or even longer if the head or neck are involved). For the management of painful diabetic neuropathy, licensed UK product information recommends that capsaicin should only be used under specialist supervision and that treatment should be reviewed after the first 8 weeks and regularly re-evaluated thereafter.

Although not a counter-irritant itself, capsaicin has been included in rubefacient preparations for the relief of muscular and rheumatic pain.

Action. The action of capsaicin and related compounds (vanilloids) are complex and still being investigated. Capsaicin has been found to produce burning pain[1,2] by activating specific vanilloid receptors such as TRPV1 (transient receptor potential channel, vanilloid subfamily member 1) which are also stimulated by heat and acids. TRPV1 is expressed by nerves and other tissues such as the keratinocytes of the epidermis, bladder urothelium and smooth muscle, and liver.

The analgesic effect of capsaicin has been suggested to be due to both depletion of substance P from local sensory C-type nerve fibres[3-7] and to the desensitisation of vanilloid receptors.[1,2,8] Since the effect of capsaicin does not rely on vasodilatation in the skin it is therefore not considered to be a traditional counter-irritant.

1. Szallasi A, Blumberg PM. Vanilloid (capsaicin) receptors and mechanisms. *Pharmacol Rev* 1999; **51:** 159–211.
2. Cortright DN, Szallasi A. Biochemical pharmacology of the vanilloid receptor TRPV1: an update. *Eur J Biochem* 2004; **271:** 1814–19.
3. Rumsfield JA, West DP. Topical capsaicin in dermatologic and peripheral pain disorders. *DICP Ann Pharmacother* 1991; **25:** 381–7.
4. Cordell GA, Araujo OE. Capsaicin: identification, nomenclature, and pharmacotherapy. *Ann Pharmacother* 1993; **27:** 330–6.
5. Winter J, *et al.* Capsaicin and pain mechanisms. *Br J Anaesth* 1995; **75:** 157–68.
6. Del Bianco E, *et al.* The effects of repeated dermal application of capsaicin to the human skin on pain and vasodilatation induced by intradermal injection of acid and hypertonic solutions. *Br J Clin Pharmacol* 1996; **41:** 1–6.
7. Fusco BM, Giacovazzo M. Peppers and pain: the promise of capsaicin. *Drugs* 1997; **53:** 909–14.
8. Tominaga M, Julius D. Capsaicin receptor in the pain pathway. *Jpn J Pharmacol* 2000; **83:** 20–4.

Headache. Prevention of attacks of *cluster headache* (p.616) by repeated application of capsaicin to the nasal mucosa has been reported.[1] The *Z*-isomer (zucapsaicin; civamide) has also been found to be modestly effective.[2]

Repeated nasal application of capsaicin has also been found to be effective in *chronic migraine*.[3]

1. Fusco BM, *et al.* Preventative effect of repeated nasal applications of capsaicin in cluster headache. *Pain* 1994; **59:** 321–5.
2. Saper JR, *et al.* Intranasal civamide for the treatment of episodic cluster headaches. *Arch Neurol* 2002; **59:** 990–4.
3. Fusco BM, *et al.* Repeated intranasal capsaicin applications to treat chronic migraine. *Br J Anaesth* 2003; **90:** 812.

Micturition disorders. Intravesical capsaicin has been tried for painful bladder disorders and to treat bladder detrusor hyperreflexia.[1-9] Results have been variable, and the characteristic sensory effects of capsaicin make blinding of studies difficult, but some patients have reported benefit particularly those with neurological bladder disorders. Instillation into the ureter has also been tried in the management of the loin pain/haematuria syndrome.[10]

1. Lazzeri M, *et al.* Intravesical capsaicin for treatment of severe bladder pain: a randomized placebo controlled study. *J Urol (Baltimore)* 1996; **156:** 947–52.
2. de Sèze M, *et al.* Capsaicin and neurogenic detrusor hyperreflexia: a double-blind placebo-controlled study in 20 patients with spinal cord lesions. *Neurourol Urodyn* 1998; **17:** 513–23.
3. Petersen T, *et al.* Intravesical capsaicin in patients with detrusor hyper-reflexia: a placebo-controlled cross-over study. *Scand J Urol Nephrol* 1999; **33:** 104–10.
4. de Sèze M, *et al.* Intravesical instillation of capsaicin in urology: a review of the literature. *Eur Urol* 1999; **36:** 267–77.
5. de Sèze M, *et al.* Capsaïcine intravésicale et hyperréflexie du détrusor: expérience de 100 instillations sur une période de cinq ans. *Ann Readapt Med Phys* 2001; **44:** 514–24.
6. Szallasi A, Fowler CJ. After a decade of intravesical vanilloid therapy: still more questions than answers. *Lancet Neurol* 2002; **1:** 167–72.
7. de Sèze M, *et al.* Intravesical capsaicin versus resiniferatoxin for the treatment of detrusor hyperreflexia in spinal cord injured patients: a double-blind, randomized, controlled study. *J Urol (Baltimore)* 2004; **171:** 251–5.
8. Lazzeri M, *et al.* Intravesical vanilloids and neurogenic incontinence: ten years experience. *Urol Int* 2004; **72:** 145–9.
9. El-Mahrouky AS, *et al.* The effect of intravesical capsaicin and resiniferatoxin in neurogenic bladder dysfunction. *Adv Exp Med Biol* 2003; **539:** 359–79.
10. Bultitude MI. Capsaicin in treatment of loin pain/haematuria syndrome. *Lancet* 1995; **345:** 921–2.

Neuropathic pain. Capsaicin has been tried topically in various types of pain including neuropathic pain, which does not generally respond to conventional systemic analgesics. Topical capsaicin is used in the management of diabetic neuropathy (p.6) and postherpetic neuralgia (p.9), but while a meta-analysis[1] of randomised, double-blind, placebo-controlled studies and later studies[2] suggested that it is effective in painful diabetic neuropathy the evidence for efficacy in postherpetic neuralgia was considered[1] to be less convincing. Another meta-analysis[3] and a systematic review[4] have suggested that capsaicin was of benefit in neuropathic pain, although this effect may be modest.[4] The difficulty of blinding in placebo-controlled trials of capsaicin has also been noted, because of the burning sensation it produces. Other types of pain syndrome for which capsaicin has been tried include reflex sympathetic dystrophy (see Complex Regional Pain Syndrome, p.6), postmastectomy neuroma, amputation stump pain, chronic neck pain, and the pain of oral mucositis.[5]

See also Rheumatic Disorders, below for use in musculoskeletal pain.

1. Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin. *Eur J Clin Pharmacol* 1994; **46:** 517–22.
2. Biesbroeck R, *et al.* A double-blind comparison of topical capsaicin and oral amitriptyline in painful diabetic neuropathy. *Adv Therapy* 1995; **12:** 111–20.
3. Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain* 1997; **73:** 123–39.
4. Mason L, *et al.* Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ* 2004; **328:** 991–4.
5. Hautkappe M, *et al.* Review of the effectiveness of capsaicin for painful cutaneous disorders and neural dysfunction. *Clin J Pain* 1998; **14:** 97–106.

Pruritus. Substance P is a possible mediator of itch sensations and since capsaicin acts as a depletor of substance P it has been tried in the relief of pruritus (p.1582) associated with various diseases and haemodialysis.[1-7] It has also been used to provide relief from pruritus induced by hetastarch[8] and for the itch and pain associated with PUVA therapy.[9,10]

1. Breneman DL, *et al.* Topical capsaicin for treatment of hemodialysis-related pruritus. *J Am Acad Dermatol* 1992; **26:** 91–4.
2. Leibsohn E. Treatment of notalgia paresthetica with capsaicin. *Cutis* 1992; **49:** 335–6.
3. Fölster-Holst R, Brasch J. Effect of topically applied capsaicin on pruritus in patients with atopic dermatitis. *J Dermatol Treat* 1996; **7:** 13–15.
4. Hautmann G, *et al.* Aquagenic pruritus, PUVA and capsaicin treatments. *Br J Dermatol* 1994; **131:** 920–1.
5. Ständer S, *et al.* Treatment of prurigo nodularis with topical capsaicin. *J Am Acad Dermatol* 2001; **44:** 471–8.
6. Lysy J, *et al.* Topical capsaicin— a novel and effective treatment for idiopathic intractable pruritus ani: a randomised, placebo controlled, crossover study. *Gut* 2003; **52:** 1323–6.
7. Hautkappe M, *et al.* Review of the effectiveness of capsaicin for painful cutaneous disorders and neural dysfunction. *Clin J Pain* 1998; **14:** 97–106.
8. Szeimies R-M, *et al.* Successful treatment of hydroxyethyl starch-induced pruritus with topical capsaicin. *Br J Dermatol* 1994; **131:** 380–2.
9. Burrows NP, Norris PG. Treatment of PUVA-induced skin pain with capsaicin. *Br J Dermatol* 1994; **131:** 584–5.
10. Kirby B, Rogers S. Treatment of PUVA itch with capsaicin. *Br J Dermatol* 1997; **137:** 152.

Psoriasis. Since substance P has been implicated in the pathophysiology of several inflammatory dermatological processes, capsaicin, a substance P depletor, has been tried with some benefit in a number of skin disorders including psoriasis.[1-3]

The usual management of psoriasis is discussed on p.1583.

1. Bernstein JE, *et al.* Effects of topically applied capsaicin on moderate and severe psoriasis vulgaris. *J Am Acad Dermatol* 1986; **15:** 504–7.
2. Ellis CN, *et al.* A double-blind evaluation of topical capsaicin in pruritic psoriasis. *J Am Acad Dermatol* 1993; **29:** 438–42.
3. Hautkappe M, *et al.* Review of the effectiveness of capsaicin for painful cutaneous disorders and neural dysfunction. *Clin J Pain* 1998; **14:** 97–106.

Rheumatic disorders. Topical capsaicin is used for the temporary relief of the pain of arthritis. From the results of a meta-analysis[1] of randomised, double-blind, placebo-controlled studies and later studies[2,3] it appears that capsaicin is effective in easing the pain of osteoarthritis (p.11) but its role, if any, is unclear; published evidence[4] for efficacy in rheumatoid arthritis (p.11) appears to be limited. A review of use in both neuropathic and musculoskeletal chronic pain concluded that its benefits were at best moderate, but noted that in a minority of patients unresponsive to, or intolerant of, other treatments it might be useful.[5] Capsaicin may be a useful therapy for pain associated with primary fibromyalgia[6] (see under Soft Tissue Rheumatism, p.13), which responds poorly to conventional treatment.

1. Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin. *Eur J Clin Pharmacol* 1994; **46:** 517–22.
2. Altman RD, *et al.* Capsaicin cream 0.025% as monotherapy for osteoarthritis: a double-blind study. *Semin Arthritis Rheum* 1994; **23** (suppl 3): 25–33.
3. McCleane G. The analgesic efficacy of topical capsaicin is enhanced by glyceryl trinitrate in painful osteoarthritis: a randomized, double blind, placebo controlled study. *Eur J Pain* 2000; **4:** 355–60.
4. Deal CL, *et al.* Treatment of arthritis with topical capsaicin: a double-blind trial. *Clin Ther* 1991; **13:** 383–95.
5. Mason L, *et al.* Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ* 2004; **328:** 991–4.
6. McCarty DJ, *et al.* Treatment of pain due to fibromyalgia with topical capsaicin: a pilot study. *Semin Arthritis Rheum* 1994; **23** (suppl 3): 41–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Zostrix; ***Belg.:*** Hansamedic Warmtepleister; ***Braz.:*** Moment; ***Canad.:*** Antiphlogistine Rub A-535 Capsaicin; Arthricare for Women Extra Moisturizing†; Zostrix; ***Chile:*** Presyc; ***Gr.:*** Gelcen; Zacin; ***Indon.:*** Capzacin; ***Irl.:*** Axsain; Zacin; ***Israel:*** Zostrix; ***Mex.:*** Capsidol; ***Norw.:*** Capsina; ***NZ:*** Zostrix; ***Port.:*** Hansaplast Emplastro Termico; Hansaterm; ***Spain:*** Capsicin; Capsicum Farmaya; Capsidol; Gelcen; Hansaterm; Katrum; ***Swed.:*** Capsina; ***Switz.:*** Emplatre antirhumatismal Isola Capsicum N; Emplatre Etoile†; ***UK:*** Axsain; Zacin; ***USA:*** Axsain; Capsin; Capzasin-HP; Capzasin-P; Dolorac; Doublecap; No Pain-HP; R-Gel; Rid-a-Pain HP; Theragen; Zostrix.

Multi-ingredient: ***Arg.:*** Atomo Desinflamante C; Rati Salil Crema; Rati Salil Flex; ***Austria:*** Rubizon-Rheumagel; ***Canad.:*** Arthricare for Women Multi-Action†; Heet; Menthacin; Midalgan†; ***Cz.:*** Capsicolle; Dr Theiss Rheuma Creme†; ***Fr.:*** Capsic; Cliptol Sport†; ***Ger.:*** Capsamol N†; ***Gr.:*** Ponostop; ***Hong Kong:*** Salomethyl; ***Hung.:*** Nicoflex; ***India:*** Nimulid Nugel; ***Irl.:*** Algipan; Radian-B†; ***Ital.:*** Disalgil†; ***Pol.:*** Capsigel N; Neo-Capsiderm; ***Switz.:*** Emplatre antirhumatismal Isola Capsicum N a l'huile essentielle de Gaultherie; Emplatre Etoile salicylé†; ***UK:*** NatraFlex; ***USA:*** Arthricare Odor Free; Heet; Menthacin; Pain Doctor; Ziks.

Carbasalate Calcium *(BAN, rINN)*

Calcium Acetylsalicylate Carbamide; Calcium Carbaspirin; Carbasalate calcique; Carbasalato cálcico; Carbasalatum calcicum; Carbasalatum Calcium; Carbaspirin Calcium *(USAN)*; Karbasalaattikalsium; Karbasalát vápenatá sůl; Karbasalatkalcium; Karbasalato kalcio druska; Karbaszalát-kálcium. Calcium bis[2-(acetoxy)benzoate]—urea.

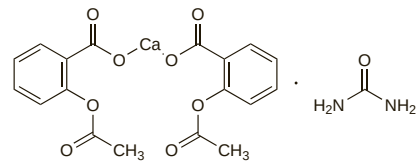
Карбасалат Кальций

$C_{19}H_{18}CaN_2O_9$ = 458.4.

CAS — 5749-67-7.

ATC — B01AC08; N02BA15.

ATC Vet — QB01AC08; QN02BA15.



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

Ph. Eur. 6.2 (Carbasalate Calcium). A white or almost white, crystalline powder. It contains not less than 99.0% and not more than the equivalent of 101.0% of an equimolecular compound of calcium di[2-(acetyloxy)benzoate] and urea, calculated with reference to the anhydrous substance. Freely soluble in water and in dimethylformamide; practically insoluble in acetone and in anhydrous methyl alcohol. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Aspirin, p.20.

Carbasalate calcium, like aspirin, should not generally be given to children because of the risk of Reye's syndrome.

Effects on hearing. As of June 2006 the Netherlands Pharmacovigilance Centre[1] database contained 8 reports of tinnitus and 1 of ototoxicity associated with use of low oral doses of carbasalate calcium (38 or 100 mg usually once daily). The association between low-dose carbasalate calcium and tinnitus was considered to be disproportional.

1. Nederlands Bijwerkingen Centrum. Low dosage carbasalate calcium and tinnitus. Available at: http://www.lareb.nl/documents/kwb_2006_3_carbas.pdf (accessed 12/04/07)

Interactions

For interactions associated with aspirin, see p.23.

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.

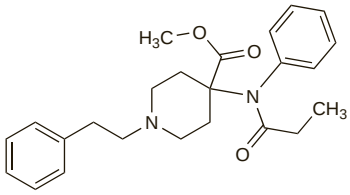
Multi-ingredient: ***Austria:*** Irocopar c C; Irocophan; Iromin-Chinin-C; ***Cz.:*** Cephalgan†; ***Fr.:*** Cephalgan†; ***Switz.:*** Alca-C.

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

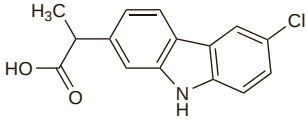
Carfentanil citrate is an opioid analgesic related to fentanyl (p.55). It is used in veterinary medicine.

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

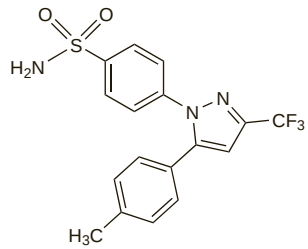
USP 31: Carprofen Tablets.

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.