Butorphanol Tartrate *(BANM, USAN, rINNM)*

levo-BC-2627 (butorphanol); Butorfanolitartraatti; Butorfanoltartrat; Butorphanol, Tartrate de; Butorphanoli Tartras; Tartrato de butorfanol. (–)-17-(Cyclobutylmethyl)morphinan-3,14-diol hydrogen tartrate.

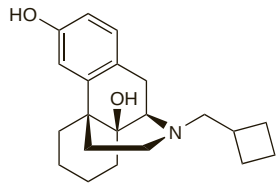
Буторфанола Тартрат

$C_{21}H_{29}NO_2.C_4H_6O_6$ = 477.5.

CAS — 42408-82-2 (butorphanol); 58786-99-5 (butorphanol tartrate).

ATC — N02AF01.

ATC Vet — QN02AF01.



(butorphanol)

Pharmacopoeias. In *US.*

USP 31 (Butorphanol Tartrate). A white powder. Its solutions are slightly acidic. Sparingly soluble in water; insoluble in alcohol, in chloroform, in ether, in ethyl acetate, and in hexane; slightly soluble in methyl alcohol; soluble in dilute acids. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Butorphanol may have a lower potential for producing dependence than pure agonists such as morphine. However, it has been subject to abuse (see under Precautions, below). Abruptly stopping chronic butorphanol has produced a less severe withdrawal syndrome than with morphine.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102, and for Pentazocine, p.112.

Headache, and feelings of floating may also occur. Hallucinations and other psychotomimetic effects are rare and have been reported less frequently than with pentazocine. In addition insomnia and nasal congestion may occur frequently when butorphanol is given intranasally.

Because butorphanol has opioid agonist and antagonist activity, naloxone is the recommended antagonist for the treatment of overdosage.

Effects on the respiratory system. Butorphanol 2 mg produces a similar degree of respiratory depression to morphine 10 mg, but a ceiling effect is apparent with higher doses of butorphanol.[1] It has been reported to be a less potent respiratory depressant than fentanyl,[2] but more potent than nalbuphine.[3]

1. Nagashima H, *et al.* Respiratory and circulatory effects of intravenous butorphanol and morphine. *Clin Pharmacol Ther* 1976; **19:** 738–45.
2. Dryden GE. Voluntary respiratory effects of butorphanol and fentanyl following barbiturate induction: a double-blind study. *J Clin Pharmacol* 1986; **26:** 203–7.
3. Zucker JR, *et al.* Respiratory effects of nalbuphine and butorphanol in anesthetized patients. *Anesth Analg* 1987; **66:** 879–81.

Precautions

As for Opioid Analgesics in general, p.103.

Although cardiovascular effects may be less than with pentazocine, butorphanol should generally be avoided after myocardial infarction.

Butorphanol may precipitate withdrawal symptoms if given to patients physically dependent on opioids. The dosage regimen of butorphanol may need to be adjusted in the elderly and in patients with hepatic or renal impairment.

Abuse. A WHO expert committee considered in 2006 that the likelihood of butorphanol abuse was low and was not great enough to warrant international control.[1] Abuse had been reported infrequently and only in a few countries. The committee also commented that, pharmacologically, intranasal preparations of butorphanol do not appear to differ in their abuse potential from parenteral preparations; however, other factors such as availability and usage patterns may affect the likelihood of abuse. Indeed, US licensed product information states that there have been more reports of abuse with intranasal preparations than with injectable ones.

Cases of butorphanol abuse have been published[2,3] including a report of fibrous myopathy associated with chronic intramuscular abuse.

1. WHO. WHO expert committee on drug dependence: thirty-fourth report. *WHO Tech Rep Ser 942* 2006. Also available at: http://libdoc.who.int/trs/WHO_TRS_942_eng.pdf (accessed 26/06/08)
2. Wagner JM, Cohen S. Fibrous myopathy from butorphanol injections. *J Rheumatol* 1991; **18:** 1934–5.
3. Loder E. Post-marketing experience with an opioid nasal spray for migraine: lessons for the future. *Cephalalgia* 2006; **26:** 89–97.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given butorphanol, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

In a study[2] of 12 women, butorphanol was detected in breast milk after both intramuscular and oral doses. However, the milk-to-plasma ratio after a 2-mg intramuscular dose (0.7) was significantly less than that after an 8-mg oral dose (1.9). Although the mothers were not breast feeding at the time of the study, the authors concluded that the potential for any adverse effects on nursing infants after maternal butorphanol use would be minimal.

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 26/06/08)
2. Pittman KA, *et al.* Human perinatal distribution of butorphanol. *Am J Obstet Gynecol* 1980; **138:** 797–800.

Pregnancy. Two instances of sinusoidal fetal heart rate pattern were noted out of 188 consecutive cases of butorphanol use in active-phase labour.[1] Visual hallucinations and paranoid delusions developed in a woman on receiving a 1-mg intravenous injection of butorphanol early in labour; the psychosis had resolved 40 hours after the injection and was not noted on follow-up 2 weeks later.[2]

1. Welt SI. Sinusoidal fetal heart rate and butorphanol administration. *Am J Obstet Gynecol* 1985; **152:** 362–3.
2. Davis A, *et al.* Acute psychosis associated with butorphanol. *J Neuropsychiatr Clin Neurosci* 1998; **10:** 236–7.

Interactions

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

Antimigraine drugs. No pharmacokinetic interactions were reported when butorphanol nasal spray and subcutaneous *sumatriptan* were used together within a minute of each other in healthy subjects.[1] However, another study[2] in healthy subjects found that the AUC and maximum plasma concentration of intranasal butorphanol were reduced by about 29% and 38%, respectively when given 1 minute after intranasal sumatriptan. No such effect was noted when administration was separated by 30 minutes. It was suggested that sumatriptan may reduce butorphanol absorption by inducing transient nasal vasoconstriction.

1. Srinivas NR, *et al.* Lack of pharmacokinetic interaction between butorphanol tartrate nasal spray and sumatriptan succinate. *J Clin Pharmacol* 1995; **35:** 432–7.
2. Vachharajani NN, *et al.* A pharmacokinetic interaction study between butorphanol and sumatriptan nasal sprays in healthy subjects: importance of the timing of butorphanol administration. *Cephalalgia* 2002; **22:** 282–7.

Pharmacokinetics

Butorphanol is absorbed from the gastrointestinal tract but it undergoes extensive first-pass metabolism. Peak plasma concentrations occur 0.5 to 1 hour after intramuscular and intranasal doses and 1 to 1.5 hours after oral doses. Butorphanol has a plasma elimination half-life of about 4.5 hours. About 80% is bound to plasma proteins.

Butorphanol is extensively metabolised in the liver through hydroxylation, *N*-dealkylation, and conjugation, only 5% being excreted unchanged. Excretion is mainly in the urine; about 15% of a parenteral dose is excreted in the bile. It crosses the placenta and is distributed into breast milk.

Administration. *INTRANASAL ROUTE.* References.

1. Davis GA, *et al.* Pharmacokinetics of butorphanol tartrate administered from single-dose intranasal sprayer. *Am J Health-Syst Pharm* 2004; **61:** 261–6.
2. Davis GA, *et al.* Bioavailability of intranasal butorphanol administered from a single-dose sprayer. *Am J Health-Syst Pharm* 2005; **62:** 48–53.
3. Wermeling DP, *et al.* Pharmacokinetics, bioequivalence, and spray weight reproducibility of intranasal butorphanol after administration with 2 different nasal spray pumps. *J Clin Pharmacol* 2005; **45:** 969–73.

Uses and Administration

Butorphanol tartrate, a phenanthrene derivative, is an opioid analgesic (p.104) with opioid agonist and antagonist properties; it is pharmacologically similar to pentazocine (p.113). Butorphanol is used for the relief of moderate to severe pain, including the pain of labour, and as an adjunct to anaesthesia. Onset of analgesia occurs within 15 minutes of intramuscular injection or an intranasal dose and may last for 3 to 4 hours after parenteral doses or for 4 to 5 hours after intranasal doses.

For the relief of moderate to severe **pain**, butorphanol tartrate is given in doses of 1 to 4 mg (usually 2 mg) by intramuscular injection or in doses of 0.5 to 2 mg (usually 1 mg) by intravenous injection every 3 to 4 hours. It may also be given as a nasal spray, in usual doses of 1 mg (1 spray in 1 nostril), repeated after 60 to 90 minutes, if necessary. This sequence may be repeated after 3 to 4 hours as needed. An initial dose of 2 mg (1 spray in each nostril) may be given for severe pain, but should not be repeated until 3 to 4 hours later.

In *obstetric analgesia* 1 to 2 mg may be given by intramuscular or intravenous injection during early labour in women at term. This dose may be repeated after 4 hours if necessary but an alternative analgesic should be used if delivery is expected within 4 hours.

In **anaesthesia**, 2 mg may be given intramuscularly for premedication 60 to 90 minutes before surgery. For use in balanced anaesthesia, a usual dose is 2 mg given intravenously shortly before induction and/or 0.5 to 1 mg given intravenously in increments during anaesthesia. The total dose needed varies but most patients require 4 to 12.5 mg.

Dosage adjustment may be needed in the elderly. When given by injection the initial dose of butorphanol for pain should be half the usual initial adult dose. Subsequent doses should be determined by the patient's response; a dosage interval of at least 6 hours has been recommended. For nasal use the initial dose should be limited to 1 mg followed by 1 mg after 90 to 120 minutes if necessary; subsequent doses if required should generally be given at intervals of not less than 6 hours. Similar recommendations have also been made for patients with hepatic or renal impairment, see below.

◊ References.

1. Atkinson BD, *et al.* Double-blind comparison of intravenous butorphanol (Stadol) and fentanyl (Sublimaze) for analgesia during labor. *Am J Obstet Gynecol* 1994; **171:** 993–8.
2. Gillis JC, *et al.* Transnasal butorphanol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute pain management. *Drugs* 1995; **50:** 157–75.
3. Commiskey S, *et al.* Butorphanol: effects of a prototypical agonist-antagonist analgesic on κ-opioid receptors. *J Pharmacol Sci* 2005; **98:** 109–16.

Administration in hepatic or renal impairment. The dosage of butorphanol may need to be adjusted in patients with hepatic or renal impairment. When given by injection the initial dose for pain should be half the usual initial adult dose (see above). Subsequent doses should be determined by the patient's response; a dosage interval of at least 6 hours has been recommended. For nasal use the initial dose should be limited to 1 mg followed by 1 mg after 90 to 120 minutes if necessary; subsequent doses if required should generally be given at intervals of not less than 6 hours.

Headache. Butorphanol has been advocated for use as a nasal spray in the treatment of migraine, but there have been problems with abuse and dependence (see above) and its place in therapy, if any, still remains to be established. See also Antimigraine Drugs, under Interactions, above.

References.

1. Freitag FG. The acute treatment of migraine with transnasal butorphanol (TNB). *Headache Q* 1993; **4** (suppl 3): 22–8.
2. Hoffert MJ, *et al.* Transnasal butorphanol in the treatment of acute migraine. *Headache* 1995; **35:** 65–9.
3. Melanson SW, *et al.* Transnasal butorphanol in the emergency department management of migraine headache. *Am J Emerg Med* 1997; **15:** 57–61.

Pruritus. Results from a small study[1] of 6 patients with severe opioid-induced pruritus unresponsive to diphenhydramine, and from a case series of 5 patients with intractable pruritus from other causes,[2] suggest that intranasal butorphanol may be an effective treatment. Doses have ranged from 1 mg every other day to 2 mg every 4 to 6 hours.

1. Dunteman E, *et al.* Transnasal butorphanol for the treatment of opioid-induced pruritus unresponsive to antihistamines. *J Pain Symptom Manage* 1996; **12:** 255–60.
2. Dawn AG, Yosipovitch G. Butorphanol for treatment of intractable pruritus. *J Am Acad Dermatol* 2006; **54:** 527–31.

Preparations

USP 31: Butorphanol Tartrate Injection; Butorphanol Tartrate Nasal Solution.

Proprietary Preparations (details are given in Part 3)
Canad.: Stadol†; ***Chile:*** Stadol†; ***Cz.:*** Beforal†; Moradol†; ***India:*** Butrum; ***Mex.:*** Stadol; ***Philipp.:*** Stadol; ***Rus.:*** Stadol (Стадол); ***USA:*** Stadol.

Capsaicin

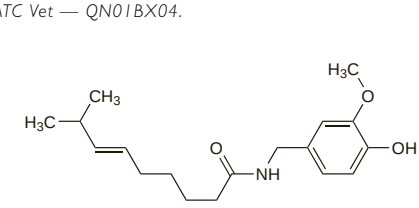
Capsaicina; Capsaicinum; Kapsaicin; Kapsaicyna; Kapsaisiini. (*E*)-8-Methyl-*N*-vanillylnon-6-enamide.

$C_{18}H_{27}NO_3$ = 305.4.

CAS — 404-86-4.

ATC — N01BX04.

ATC Vet — QN01BX04.



NOTE. Do not confuse capsaicin with capsicin, which is capsicum oleoresin (see Capsicum, p.2276).

Pharmacopoeias. In *US.*

USP 31 (Capsaicin). An off-white powder. M.p. 57° to 66°. Practically insoluble in cold water; soluble in alcohol, in chloro-

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.

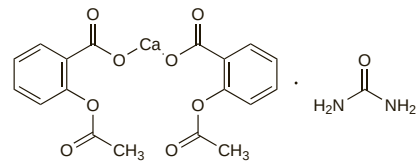
Карбасалат Кальций

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