Profile
Proquazone is an NSAID (p.96) that has been used orally and rectally in musculoskeletal and joint disorders.

Preparations
Proprietary Preparations (details are given in Part 3)
Hung.: Biarison†; ***Turk.:*** Biarison.

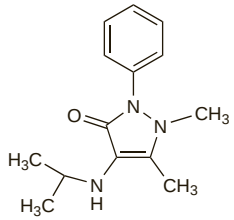
Ramifenazone *(rINN)*

Isopropylaminophenazone; Isopyrin; Ramifenazona; Ramifénazone; Ramifenazonum. 4-Isopropylamino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one.

Рамифеназон

$C_{14}H_{19}N_3O$ = 245.3.

CAS — 3615-24-5.



NOTE. The name Isopyrin has also been applied to isoniazid.

Profile
Ramifenazone is an NSAID (p.96) that has been used in preparations for painful and inflammatory conditions; it has also been used in veterinary medicine. Ramifenazone has been given as the hydrochloride and the salicylate.

Remifentanil Hydrochloride

(BANM, USAN, rINNM) ⊗

GI-87084B; Hidrocloruro de remifentanilo; Rémifentanil, Chlorhydrate de; Remifentanili Hydrochloridum. 4-Carboxyl-4-(*N*-phenylpropionamido)-1-piperidine propionic acid dimethyl ester monohydrate.

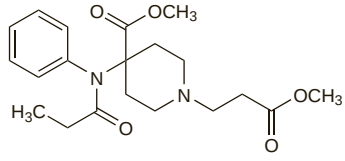
Ремифентанила Гидрохлорид

$C_{20}H_{28}N_2O_5$,HCl = 412.9.

CAS — 132539-07-2.

ATC — N01AH06.

ATC Vet — QN01AH06.



(remifentanil)

Incompatibility. Remifentanil hydrochloride should not be mixed in the same intravenous solution as blood products. UK licensed product information states that it should not be mixed with lactated Ringer's injection with or without 5% glucose; however, in the USA the product literature states that remifentanil hydrochloride is stable for 4 hours at room temperature after reconstitution and dilution to 20 to 250 micrograms/mL with lactated Ringer's injection and for 24 hours if lactated Ringer's with 5% glucose is used. Incompatibilities have been reported between chlorpromazine hydrochloride 2 mg/mL and remifentanil 25 micrograms/mL (as the hydrochloride) in 5% glucose and cefoperazone sodium 40 mg/mL or amphotericin B 0.6 mg/mL and remifentanil 250 micrograms/mL (as the hydrochloride) in 5% glucose.[1]

1. Trissel LA, *et al.* Compatibility of remifentanil hydrochloride with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 2192–6.

Dependence and Withdrawal
As for Opioid Analgesics, p.101.

Adverse Effects and Treatment
As for Opioid Analgesics in general, p.102 and for Fentanyl, p.56.

Precautions
As for Opioid Analgesics in general, p.103.

Administration. Remifentanil hydrochloride injections containing glycine should not be given by the epidural or intrathecal routes.

Hepatic impairment. Although the pharmacokinetics of remifentanil are not changed in patients with severe hepatic impairment, such patients may be more sensitive to the respiratory depressant effects and should be monitored with doses titrated to individual requirements.

Renal impairment. The pharmacokinetics of remifentanil are not changed in patients with severe renal impairment (a creatinine clearance of less than 10 mL/minute) and licensed product information states that the carboxylic acid metabolite is unlikely to accumulate to clinically active concentrations in such patients after remifentanil infusions given for up to 3 days. Dosage adjustment is considered to be unnecessary. This is supported by pharmacokinetic studies[1,2] in intensive care patients with renal impairment given remifentanil infusions at a rate of 100 to 150 nanograms/kg per minute for up to 3 days.

1. Breen D, *et al.* Offset of pharmacodynamic effects and safety of remifentanil in intensive care unit patients with various degrees of renal impairment. *Crit Care* 2004; **8:** R21–R30.
2. Pitsiu M, *et al.* Pharmacokinetics of remifentanil and its major metabolite, remifentanil acid, in ICU patients with renal impairment. *Br J Anaesth* 2004; **92:** 493–503.

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

Pharmacokinetics
After parenteral doses remifentanil hydrochloride has a rapid onset and short duration of action. Its effective biological half-life is about 3 to 10 minutes and is independent of dose. Remifentanil is about 70% bound to plasma proteins, mainly to α_1-acid glycoprotein. It is hydrolysed by non-specific esterases in blood and tissues to an essentially inactive carboxylic acid metabolite. About 95% of a dose of remifentanil is excreted in the urine as the metabolite. Studies in *animals* suggest that remifentanil may cross the placenta and is distributed into breast milk.

◊ Licensed product information for remifentanil gives values for a three-compartment pharmacokinetic model with a rapid distribution half-life of 1 minute, a slower distribution half-life of 6 minutes, and a terminal elimination half-life of 10 to 20 minutes.

References.

1. Egan TD. Remifentanil pharmacokinetics and pharmacodynamics: a preliminary appraisal. *Clin Pharmacokinet* 1995; **29:** 80–94.
2. Egan TD. Pharmacokinetics and pharmacodynamics of remifentanil: an update in the year 2000. *Curr Opin Anaesthesiol* 2000; **13:** 449–55.
3. Ross AK, *et al.* Pharmacokinetics of remifentanil in anesthetized pediatric patients undergoing elective surgery or diagnostic procedures. *Anesth Analg* 2001; **93:** 1393–1401.

Uses and Administration
Remifentanil, an anilidopiperidine derivative, is an opioid analgesic (p.104) related to fentanyl (p.58). It is a short-acting μ-receptor opioid agonist used for analgesia during induction and/or maintenance of general anaesthesia. It is also used to provide analgesia into the immediate postoperative period, and may be used as the analgesic component of local or regional anaesthesia with or without benzodiazepine sedation. Remifentanil is also used to provide analgesia and sedation in mechanically ventilated patients under intensive care.

Remifentanil is given intravenously as the hydrochloride, usually by infusion. Its onset of action is within 1 minute and the duration of action is 5 to 10 minutes. Doses are expressed in terms of the base; remifentanil hydrochloride 1.1 mg is equivalent to about 1 mg of remifentanil. Initial doses for anaesthesia in elderly patients should be half the recommended adult doses and then titrated to individual requirements. Obese patients may require doses based on their ideal (lean) bodyweight. For details of doses in children, see below.

When used to provide **analgesia** during *induction* of anaesthesia an intravenous infusion is given in doses of 0.5 to 1 micrograms/kg per minute. An additional initial intravenous bolus of 1 microgram/kg may be given over 30 to 60 seconds particularly if the patient is to be intubated less than 8 minutes after the start of the infusion.

For provision of analgesia during *maintenance* of anaesthesia in ventilated patients, usual infusion doses range from 0.05 to 2 micrograms/kg per minute depending on the anaesthetic drug employed and adjusted according to response. Supplemental intravenous boluses of 0.5 to 1 micrograms/kg may be given every 2 to 5 minutes in response to light anaesthesia or intense surgical stress. The infusion dosage in spontaneous respiration is initially 0.04 micrograms/kg per minute adjusted according to response within a usual range of 0.025 to 0.1 micrograms/kg per minute. Bolus doses are not recommended during spontaneous ventilation.

For continuation of analgesia into the immediate *postoperative* period typical doses by intravenous infusion have ranged from 100 to 200 nanograms/kg per minute; supplemental intravenous bolus doses are not recommended during the postoperative period.

To provide **analgesia and sedation** in ventilated patients under intensive care, remifentanil is given as an intravenous infusion at an initial rate of 100 to 150 nanograms/kg per minute. Doses should then be titrated to provide adequate analgesia and sedation; a period of 5 minutes should be allowed between dose adjustments. Additional sedative drugs should be given to those patients inadequately sedated with remifentanil infusions of 200 nanograms/kg per minute. An increase in the rate of remifentanil infusion may be necessary if additional analgesia is required to cover stimulating or painful procedures such as wound dressing. Doses of up to 750 nanograms/kg per minute have been given to some patients. Bolus doses of remifentanil are not recommended in intensive care.

Remifentanil is also used as an analgesic in patients receiving monitored anaesthesia care. In the USA, it may be given intravenously in a single dose of 1 microgram/kg 90 seconds before the local anaesthetic; alternatively, a dose of 100 nanograms/kg per minute may be given as an intravenous infusion, starting 5 minutes before the local anaesthetic, which should be reduced to 50 nanograms/kg per minute after the local anaesthetic. Subsequent adjustments of 25 nanograms/kg per minute at 5-minute intervals may be made to maintain a balanced analgesia.

Remifentanil has a very rapid offset of action and no residual opioid action remains 5 to 10 minutes after stopping an infusion. When appropriate, alternative analgesics should be given before stopping remifentanil, in sufficient time to provide continuous and more prolonged pain relief.

◊ References and reviews.

1. Patel SS, Spencer CM. Remifentanil. *Drugs* 1996; **52:** 417–27.
2. Duthie DJR. Remifentanil and tramadol. *Br J Anaesth* 1998; **81:** 51–7.
3. Davis PJ, Cladis FP. The use of ultra-short-acting opioids in paediatric anaesthesia: the role of remifentanil. *Clin Pharmacokinet* 2005; **44:** 787–96.
4. Scott LJ, Perry CM. Remifentanil: a review of its use during the induction and maintenance of general anaesthesia. *Drugs* 2005; **65:** 1793–1823. Correction. *ibid.*; 2286.
5. Battershill AJ, Keating GM. Remifentanil: a review of its analgesic and sedative use in the intensive care unit. *Drugs* 2006; **66:** 365–85.
6. Welzing L, Roth B. Experience with remifentanil in neonates and infants. *Drugs* 2006; **66:** 1339–50.

Administration in children. Remifentanil hydrochloride, given by continuous intravenous infusion, is used for analgesia during maintenance of general anaesthesia in children. Usual infusion doses (expressed as the base) for those aged from 1 to 12 years range from 0.05 to 1.3 micrograms/kg per minute depending on the anaesthetic drug employed and adjusted according to response; supplemental intravenous boluses of 1 microgram/kg may be given over at least 30 seconds. US licensed product information also states that neonates and children aged up to 2 months may be given infusion doses of 0.4 to 1 micrograms/kg per minute with supplemental boluses of 1 microgram/kg. Similar doses are suggested in the *BNFC* for use in neonates although in the UK remifentanil is not licensed for use in children under 1 year of age.

Preparations

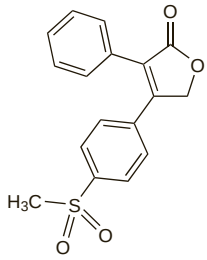
Proprietary Preparations (details are given in Part 3)
Arg.: Remicit; Ultiva; ***Austral.:*** Ultiva; ***Austria:*** Ultiva; ***Belg.:*** Ultiva; ***Braz.:*** Ultiva; ***Canad.:*** Ultiva; ***Chile:*** Ultiva; ***Cz.:*** Ultiva; ***Denm.:*** Ultiva; ***Fin.:*** Ultiva; ***Fr.:*** Ultiva; ***Ger.:*** Ultiva; ***Gr.:*** Ultiva; ***Hong Kong:*** Ultiva; ***Hung.:*** Ultiva†; ***Irl.:*** Ultiva†; ***Israel:*** Ultiva; ***Ital.:*** Ultiva; ***Mex.:*** Ultiva; ***Neth.:*** Ultiva; ***Norw.:*** Ultiva; ***NZ:*** Ultiva; ***Pol.:*** Ultiva; ***Port.:*** Ultiva; ***S.Afr.:*** Ultiva; ***Singapore:*** Ultiva; ***Spain:*** Ultiva; ***Swed.:*** Ultiva; ***Switz.:*** Ultiva; ***Turk.:*** Ultiva; ***UK:*** Ultiva; ***USA:*** Ultiva; ***Venez.:*** Ultiva.

Rofecoxib *(BAN, USAN, rINN)*

MK-966; MK-0966; Rofécoxib; Rofecoxibum; Rofekoksibi; Rofekoxib. 4-[*p*-(Methylsulfonyl)phenyl]-3-phenyl-2(5*H*)-furanone.

Рофекоксиб

$C_{17}H_{14}O_4S$ = 314.4.
CAS — 162011-90-7.
ATC — M01AH02.
ATC Vet — QM01AH02.



Profile

Rofecoxib is an NSAID (p.96) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It was given orally for symptomatic relief in the treatment of osteoarthritis and rheumatoid arthritis, and in the management of acute pain, dysmenorrhoea, and migraine but was generally withdrawn worldwide after reports of cardiovascular adverse effects (see below).

Rofecoxib has been applied topically in some countries.

Effects on the cardiovascular system. As of February 2001, the UK CSM had received a small number of reports of *myocardial infarction* or *ischaemia* associated with the selective cyclo-oxygenase-2 (COX-2) inhibitors.[1] At that time it noted that COX-2 inhibitors such as rofecoxib did not possess the intrinsic antiplatelet activity associated with aspirin, and consequently did not provide protection against ischaemic cardiac events. Data from a large, randomised study also showed the incidence of myocardial infarction to be greater in patients taking rofecoxib than in those taking naproxen.[2] Postmarketing surveillance of rofecoxib continued to provide further case reports of adverse cardiovascular effects. In addition, results of the then unpublished APPROVe study of rofecoxib for prevention of adenomatous polyposis indicated that the risk of myocardial infarction and stroke was markedly increased in patients receiving the drug compared to those on placebo; however, this difference was only apparent after 18 months of treatment. As a result, the study was stopped early and, in September 2004, the manufacturer generally withdrew rofecoxib worldwide. The cardiovascular findings from the APPROVe study were published in 2005;[3] the results showed a twofold increase in the risk of adverse cardiovascular events in patients receiving rofecoxib 25 mg daily when compared with those on placebo. More recently, 1-year follow-up data for patients in the APPROVe study has been released. In a statement from the manufacturer,[4] it is noted that in the year after rofecoxib was stopped there was no statistically significant difference in the risk of confirmed thrombotic cardiovascular events in those patients who had previously taken rofecoxib compared with those who had been given placebo; however, when data from both the on- and off-treatment periods were considered together, the difference in the risk of cardiovascular events between the rofecoxib and the placebo groups remained significant. Combined data from the on- and off-treatment periods also showed that there was an increased risk of confirmed heart attacks and ischaemic strokes in the rofecoxib group when compared to the placebo group. (The data for ischaemic stroke were later published.[5]) Similar data, suggesting a 1.5-fold increase in risk of thrombotic events with rofecoxib, were reported from a study of adjuvant use for colorectal cancer.[6] A cumulative meta-analysis also indicated an increased risk of myocardial infarction in patients receiving rofecoxib.[7]

Subsequent investigation by US and European regulatory authorities has confirmed that other COX-2 inhibitors are also associated with some increased cardiovascular risk (see under Celecoxib, p.34), as are some non-selective NSAIDs (see Thrombotic Events, p.97).

A review[8] of prospective studies evaluating the effect of selective COX-2 inhibitors on blood pressure was unable to determine if there was any association between the use of these drugs and blood pressure elevations. Of the studies considered, a randomised study in elderly, hypertensive patients with osteoarthritis has suggested that the risk of developing *increased systolic blood pressure* is greater in those patients receiving rofecoxib than in those receiving celecoxib.[9] However, the manufacturers of rofecoxib have pointed out that the trial used doses of rofecoxib greater than those recommended for elderly or hypertensive patients.

1. 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 08/11/07)
2. Bombardier C, *et al.* Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000; **343:** 1520–8.
3. Bresalier RS, *et al.* Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005; **352:** 1092–1102. Correction. *ibid.* 2006; **355:** 221.
4. Merck, USA. Merck announces preliminary analyses of off-drug extension of APPROVe study (issued 11th May, 2006). Available at: http://www.merck.com/newsroom/press_releases/corporate/2006_0511.html (accessed 08/11/07)
5. Afilalo J, *et al.* Long-term risk of ischemic stroke associated with rofecoxib. *Cardiovasc Drugs Ther* 2007; **21:** 117–20.
6. Kerr DJ, *et al.* Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer. *N Engl J Med* 2007; **357:** 360–9.
7. Jüni P, *et al.* Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet* 2004; **364:** 2021–9.
8. Johnson DL, *et al.* Effect of cyclooxygenase-2 inhibitors on blood pressure. *Ann Pharmacother* 2003; **37:** 442–6.
9. Whelton A, *et al.* Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. *Am J Ther* 2001; **8:** 85–95.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Antidol†; Blokium Cox†; Coxiro†; Foldoxx†; Toloxane†; Vioxx†; ***Austral.:*** Vioxx†; ***Austria:*** Ceoxx†; Coxxil†; Vioxx†; ***Belg.:*** Vioxx†; ***Braz.:*** Vioxx†; ***Canad.:*** Vioxx†; ***Chile:*** Ceoxx†; ***Cz.:*** Vioxx†; ***Denm.:*** Vioxx†; Vioxxalt†; ***Fin.:*** Vioxx†; ***Fr.:*** Vioxx†; ***Ger.:*** Vioxx†; ***Gr.:*** Peroxx†; Vioxx†; ***Hong Kong:*** Vioxx†; ***Hung.:*** Vioxx†; ***India:*** Alrof†; Dolib†; Rofetab†; Rofib; Rofixx†; Rofiz; Versatil†; ***Irl.:*** Ceoxx†; Vioxx†; ***Israel:*** Vioxx†; ***Ital.:*** Arofexx†; Coxxil†; Dolcoxx†; Dolostop†; Miraxx†; Vioxx†; ***Malaysia:*** Vioxx†; ***Mex.:*** Vioxx†; ***Neth.:*** Vioxx†; ***Norw.:*** Vioxx†; ***NZ:*** Vioxx†; ***Port.:*** Ceoxx†; Coxxil†; Vioxx†; ***S.Afr.:*** Vioxx†; ***Singapore:*** Vioxx†; ***Spain:*** Ceoxx†; Vioxx†; ***Swed.:*** Vioxx†; Vioxxakut†; ***Switz.:*** Vioxx†; ***Thai.:*** Vioxx†; ***UK:*** Vioxx†; ***USA:*** Vioxx†; ***Venez.:*** Vioxx†.

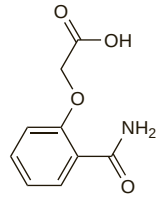
Multi-ingredient: ***India:*** Rofecip Plus†.

Salamidacetic Acid

Carbamoylphenoxyacetic acid; Salamidacético, ácido; Salicylamide *O*-acetic acid. (2-Carbamoylphenoxy)acetic acid.

Натрия Салициламидацетат (sodium salamidacetate)

$C_9H_9NO_4$ = 195.2.
CAS — 25395-22-6 (salamidacetic acid); 3785-32-8 (sodium salamidacetate).



Profile

Salamidacetic acid is a salicylic acid derivative (see Aspirin, p.20) that has also been used as the sodium and diethylamine salts for the treatment of musculoskeletal and joint disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Akistin; ***Ger.:*** Clinit N†.

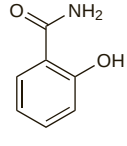
Multi-ingredient: ***Austria:*** Ambene; Rheumesser; ***Ger.:*** Caye Rheuma-Balsam; ***Rus.:*** Ambene (Амбене); ***Thai.:*** Trabit†.

Salicylamide *(BAN, rINN)*

Salicilamida; Salicylamid; Salicylamidum; Salisyyliamidi. 2-Hydroxybenzamide.

Салициламид

$C_7H_7NO_2$ = 137.1.
CAS — 65-45-2.
ATC — N02BA05.
ATC Vet — QN02BA05.



Pharmacopoeias.

In *Pol.* and *US.*

USP 31 (Salicylamide). A white practically odourless crystalline powder. Slightly soluble in water and in chloroform; soluble in alcohol and in propylene glycol; freely soluble in ether and in solutions of alkalis.

Profile

Salicylamide is a salicylic acid derivative (see Aspirin, p.20) but is not hydrolysed to salicylate; it is almost completely metabolised to inactive metabolites during absorption and on first pass through the liver. It is given in usual oral doses of 325 to 650 mg or more, usually with other analgesics, three or four times daily for pain and fever. Salicylamide has also been applied topically in rubefacient preparations in concentrations of up to about 5% for the relief of muscular and rheumatic pain.

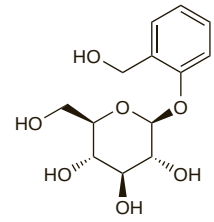
Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Waldheim Rheuma-Creme.

Multi-ingredient: ***Arg.:*** Finagrip†; Funciogrip; Venter; ***Austria:*** Rilfit; Rubriment; Sigmalin B ; Sigmalin B forte; Sigmalin B ohne Coffein; Spalt†; Waldheim Influvidon; Waldheim Sport- und Rheuma-Fluid; ***Belg.:*** Percutalgine; ***Braz.:*** Coristina R; Nogripe; Resprax; Termogripe C†; Vita Grip; ***Denm.:*** Kodamid; Koffisal; ***Fr.:*** Percutalgine; ***Ger.:*** Glutisal†; Salistoperm†; ***Gr.:*** Myalgesic†; ***Hong Kong:*** Antiflu Forte; Antiflu-N-Forte; DF Multi-Symptom; Flu-Zep; Neozep; Qualizep; ***Indon.:*** Cold Cap; Corexin; Neozep; Refagan; ***Ital.:*** Anticorizza†; ***Mex.:*** Artrilan; Butayonacol; ***NZ:*** Calm-U; ***Pol.:*** Reumosol; Scorbolamid; ***Rus.:*** Cefecon N (Цефекон Н); Percutalgine (Перкуталжин)†; ***S.Afr.:*** Colcaps; Flutex Cold and Flu; Histamed Compound; Ilvico; Specific Nerve Pain Remedy; ***Spain:*** Coricidin†; Hubergrip†; Pridio; Rinomicine; Rinomicine Activada; Yendol; ***Switz.:*** Escalgin sans codeine†; Escognipp sans codeine; Grippalgine N†; Osa Gel de dentition; ***Thai.:*** Apracur; Fecol; Percutalgine†; ***UAE:*** Adol Compound; Flukit; ***UK:*** Intralgin†; ***USA:*** Anabar; BC; Be-Flex Plus; By-Ache; Combiflex; Duraxin; Levacet; Lobac; Painaid; Saleto; Stanback Headache; Trim-Elim†; ***Venez.:*** Cotar†; Praxona.

Salix

Corteza de sauce; Écorce de Saule; Fűzfakéreg; Gluosnių žievė; Kora wierzby; Pajunkuori; Sälgbark; Salicis cortex; Saule, écorce de; Vrbová kůra; Weidenbaumrinde; White Willow Bark; Willow Bark.



(salicin)

Pharmacopoeias.

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

Ph. Eur. 6.2 (Willow Bark). The whole or fragmented dried bark of young branches or whole dried pieces of current year twigs of various species of the genus *Salix*, including *Salix purpurea*, *S. daphnoides*, and *S. fragilis*. It contains not less than 1.5% of total salicylic derivatives, expressed as salicin ($C_{13}H_{18}O_7$ = 286.3), calculated with reference to the dried drug. Protect from light.

Profile

Salix contains variable amounts of tannin and also of salicin, which has antipyretic and analgesic actions similar to those of aspirin. Salix has been used in a variety of herbal remedies for painful and inflammatory conditions and for fever. It was once used as a bitter.

Adverse effects. An *anaphylactic reaction* developed in a 25-year-old woman with asthma and a known allergy to aspirin, within 75 minutes of ingesting a dietary supplement containing willow bark extract.[1] The link between salicylate and willow bark allergy was also reported in a carpenter who experienced a widespread *rash*, similar to that he developed with aspirin, when working with willow wood.[2]

1. Boullata JI, *et al.* Anaphylactic reaction to a dietary supplement containing willow bark. *Ann Pharmacother* 2003; **37:** 832–5.
2. Jennings A. Link between salicylate and willow bark. *Pharm J* 2006; **276:** 417.

Pain. Preparations containing willow bark extract have been tried with some success in the treatment of musculoskeletal disorders such as low back pain[1-3] and osteoarthritis.[4] However, the quality of reporting in trials is generally poor and further studies are needed to establish their place in therapy.

1. Chrubasik S, *et al.* Treatment of low back pain exacerbations with willow bark extract: a randomized double-blind study. *Am J Med* 2000; **109:** 9–14.