Preparations

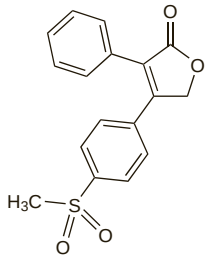
Proprietary Preparations (details are given in Part 3)
Arg.: Remicit; Ultiva; ***Austral.:*** Ultiva; ***Austria:*** Ultiva; ***Belg.:*** Ultiva; ***Braz.:*** Ultiva; ***Canad.:*** Ultiva; ***Chile:*** Ultiva; ***Cz.:*** Ultiva; ***Denm.:*** Ultiva; ***Fin.:*** Ultiva; ***Fr.:*** Ultiva; ***Ger.:*** 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and rheumatoid arthritis, and in the management of acute pain, dysmenorrhoea, and migraine but was generally withdrawn worldwide after reports of cardiovascular adverse effects (see below).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 In addition, results of the then unpublished APPROVe study of rofecoxib for prevention of adenomatous polyposis indicated that the risk of myocardial infarction and stroke was markedly increased in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†.

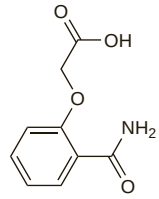
Multi-ingredient: ***India:*** Rofecip Plus†.

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†.

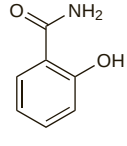
Multi-ingredient: ***Austria:*** Ambene; Rheumesser; ***Ger.:*** Caye Rheuma-Balsam; ***Rus.:*** Ambene (Амбене); ***Thai.:*** Trabit†.

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.

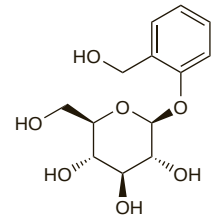
Preparations

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.