intramuscular injection, although in rare cases the maximum initial daily dose may be increased to 24 mg.

- 1. Balfour JA, et al. Lornoxicam: a review of its pharmacology therapeutic potential in the management of painful and inflammatory conditions. *Drugs* 1996; **51:** 639–57.

 2. Skjodt NM, Davies NM. Clinical pharmacokinetics of lornoxi-
- cam: a short half-life oxicam. Clin Pharmacokinet 1998; 34: 421-8.
- 3. Frizziero L, et al. Studio a lungo termine su efficacia e sicurezza terapeutica di lornoxicam nell'artrite reumatoide. Minerva Med 2002; 93: 315–20.
- Thienthong S, et al. Treatment of pain after spinal surgery in the recovery room by single dose lornoxicam: a randomized, double blind, placebo-controlled trial. J Med Assoc Thai 2004; 87:
- 5. Zhao H. et al. Application of lornoxicam to patient-controlled analgesia in patients undergoing abdominal surgeries. *Chin Med Sci J* 2005; **20:** 59–62.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Acabel†; Hypodol; Austria: Artok; Lomox; Xefo; Chile: Acabel†;
Cz.: Xefo; Denm.: Xefo; Ger.: Telos; Gr.: Xefo; Hung.: Xefo; Israel: Xefo;
Ital.: Νοχοη; Taigalor; Jpn: Lorcam; Port.: Acabel; Bosporon; Rus.: Xefocam (Κιεφοικαμ); S.Afr.: Xefo; Spain: Acabel; Bosporon; Swed.: Xefo; Switz.: Xefo; Thai.: Xefo†, Turk.: Xefo; Venez.: Acabel.

Loxoprofen Sodium (rINNM)

CS-600 (loxoprofen); Loxoprofène Sodique; Loxoprofeno sódico; Natrii Loxoprofenum. Sodium (±)-p-[(2-oxocyclopentyl)methyl]hydratropate dihydrate.

Натрий Локсопрофен

 $C_{15}H_{17}O_3Na.2H_2O = 304.3.$ CAS — 68767-14-6 (loxoprofen); 80382-23-6 (loxoprofen sodium dihydrate).

Pharmacopoeias. In Jpn.

Profile

Loxoprofen sodium is an NSAID (p.96) given orally for the management of pain and inflammation associated with musculoskeletal and joint disorders or operative procedures. Loxoprofen sodium is given as the dihydrate although doses are expressed in terms of the anhydrous salt. Anhydrous loxoprofen sodium 10 mg is equivalent to about 11.3 mg of loxoprofen sodium dihydrate. A usual oral dose equivalent to 60 mg of the anhydrous form has been given three times daily.

Preparations

Proprietary Preparations (details are given in Part 3) Oxeno; Braz.: Loxonin; Jpn: Lobu; Loxonin; Mex.: Loxonin; **Arg.:** Oxeno; **Braz.:** Loxonin; **Jpn:** Lobu; Loxon **Philipp.:** Loxonin; **Thai.:** Loxonin; **Venez.:** Loxonin.

Lumiracoxib (BAN, USAN, rINN)

Cox-189; Lumiracoxibum. 2-{[(2-Chloro-6-fluorophenyl)amino]-5-methylphenyl}acetic acid.

Лумиракоксиб

 $C_{15}H_{13}CIFNO_2 = 293.7.$ CAS - 220991-20-8. ATC - M01AH06.ATC Vet — QM01AH06.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Hypersensitivity reactions including anaphylaxis and angioedema have occurred in patients receiving lumiracoxib; it should be stopped at the first signs of hypersensitivity.

Lumiracoxib use, particularly at high doses, may cause severe liver toxicity (see Effects on the Liver, below) and its use is contra-indicated in patients with hepatic disease. It should also not be used in those with a history of drug-induced increases in transaminase values greater than 3 times the upper limit of normal (ULN) or in those taking other drugs known to cause clinically significant hepatic toxicity. All patients should have baseline liver function tests before starting lumiracoxib treatment; those in whom transaminases are more than 1.5 times the ULN should not start treatment. Liver function tests should be repeated monthly and lumiracoxib should be stopped in those patients with an increase in transaminases greater than 3 times the ULN; in those with an increase greater than 2 times the ULN, liver function tests should be repeated in 7 days. Patients should be advised to report any symptoms suggestive of liver toxicity such as anorexia, nausea, vomiting, abdominal pain, fatigue, dark urine, and jaundice.

Lumiracoxib should not be used in patients with ischaemic heart disease, cerebrovascular disease, or peripheral arterial disease. It should be used with caution in patients with significant risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and diabetes mellitus.

Lumiracoxib is also contra-indicated in patients with inflammatory bowel disease, moderate to severe heart failure (NYHA class II to IV), and moderate to severe renal impairment associated with a creatinine clearance of less than 50 mL/minute. Caution is recommended when using lumiracoxib in dehydrated patients; it may be advisable to rehydrate patients before giving lumiracoxib.

Effects on the cardiovascular system. There have been concerns about the adverse cardiovascular effects of selective cyclo-oxygenase-2 (COX-2) inhibitors after the worldwide withdrawal of rofecoxib (see p.121). The cardiovascular safety of lumiracoxib has been assessed in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)1 which involved over 18 000 patients with osteoarthritis. Lumiracoxib 400 mg daily (2 to 4 times the recommended dose) was compared against either naproxen 1 g daily, or ibuprofen 2.4 g daily; low-dose aspirin (100 mg daily or less) was also allowed where indicated. After a planned treatment duration of 1 year, the incidence of myocardial infarction, stroke, or cardiovascular death with lumiracoxib was found to be similar to that for ibuprofen or naproxen. More events were noted in the lumiracoxib versus naproxen subgroup than in the lumiracoxib versus ibuprofen group; however, this difference was not statistically significant and the authors considered that the higher number of patients with a history of vascular risk in the lumiracoxib versus naproxen subgroup could explain this finding. In addition, it was noted that the incidence of heart failure was less frequent with lumiracoxib although, again, this was not significant; however, blood pressure changes from baseline were significantly less likely with lumiracoxib than with ibuprofen or naproxen.

More recently, a meta-analysis2 by the manufacturer (which included the above study along with other published and unpublished clinical studies of lumiracoxib in the treatment of osteoarthritis and rheumatoid arthritis) has also found no evidence that the risk of thrombotic events with lumiracoxib is significantly increased when compared to placebo, to naproxen (1 g daily), or to the NSAIDs diclofenac (150 mg daily), ibuprofen (2.4 g daily), celecoxib (up to 400 mg daily), and rofecoxib (25 mg daily)

For further details on the relative risk of cardiovascular thrombotic events with NSAIDs, see p.97.

For discussion and advice on the use of selective COX-2 inhibitors in patients with cardiovascular or cerebrovascular disease. see under Celecoxib, p.34.

- 1. Farkouh ME, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. *Lancet* 2004; **364**: 675–84.
- 2. Matchaba P, et al. Cardiovascular safety of lumiracoxib: a metaanalysis of all randomized controlled trials ≥1 week and up to 1 year in duration of patients with osteoarthritis and rheumatoid arthritis. Clin Ther 2005; 27: 1196-1214.

Effects on the gastrointestinal tract. It is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of the NSAIDs, and that the selective inhibition of the other isoform, COX-2, by NSAIDs such as lumiracoxib may cause less gastrotoxicity than that seen with the non-selective inhibition of the traditional NSAIDs. However, licensed product information has stated that upper gastrointestinal ulceration and bleeds, in some cases fatal, have occurred with lumiracoxib treatment; consequently it should be used with caution in patients at risk of such events.

Results from controlled studies confirm that NSAIDs selective for COX-2 are associated with a lower incidence of serious gastrointestinal effects. A study¹ in patients with osteoarthritis taking lumiracoxib at supratherapeutic doses (400 mg daily) concluded that there was a lower incidence of definite or probable upper gastrointestinal ulcer complications (bleeding, perforation, or obstruction) after 12 months of treatment when compared with non-selective NSAIDS (ibuprofen 2.4 g daily or naproxen 1 g daily). The incidence of endoscopically-detected ulcers was also less with lumiracoxib than with non-selective NSAIDs. However, the use of low-dose aspirin appeared to nullify any protective gastrointestinal effect of lumiracoxib.

An analysis2 of pooled data from 15 pre-licensing studies in patients with rheumatoid arthritis or osteoarthritis has also concluded that the risk of upper gastrointestinal ulcers and ulcer complications is less with lumiracoxib than with non-selective NSAIDs (diclofenac, naproxen, and ibuprofen).

- 1. Schnitzer TJ, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet* 2004; **364**: 665–74.
- 2. Hawkey CJ, et al. Gastrointestinal tolerability of lumiracoxib in patients with osteoarthritis and rheumatoid arthritis. Clin Gastroenterol Hepatol 2006; 4: 57–66.

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

Effects on the liver. In August 2007, the regulatory authority in Australia withdrew lumiracoxib from the market after reports of hepatotoxicity. 1,2 In the 6 months since marketing, there had been 8 reports of serious adverse liver reactions resulting in 2 deaths and 2 transplantations. There was some concern that prelicensing clinical study data seemed to suggest that those patients who developed elevated liver function tests while on lumiracoxib would recover once the drug was stopped; however, in the 8 Australian cases, some patients did not improve because of the severity of the hepatic damage.

In response to the Australian data, the MHRA in the UK reported that it had received 16 reports of suspected adverse reactions to lumiracoxib;3 of these, one was a case of hepatotoxicity in which the patient recovered after the drug was withdrawn. Worldwide, the MHRA was aware of 11 reports of serious hepatotoxicity including 9 cases of liver failure, 2 deaths, and 3 liver transplants suspected to be at least possibly related to lumiracoxib use. The dose used in most of the cases was higher than the maximum dose of 100 mg daily that is recommended in the UK and other European countries. (Higher maximum daily doses have been licensed in other countries; in Australia, the licensed maximum dose was 400 mg daily for some conditions.) At that time in the UK, new prescribing restrictions on the use of lumiracoxib in osteoarthritis were issued (see Adverse Effects and Precautions, above) while its safety was reviewed by European regulatory authorities. However, lumiracoxib was withdrawn from the Canadian market after Health Canada noted 4 cases of severe hepatotoxicity, including 2 in Canada, associated with the 100-mg dose of lumiracoxib. Following the review of the risks and benefits of lumiracoxib in October 2007, the MHRA reiterated its earlier prescribing restrictions and stated the issue of hepatotoxicity would continue to be monitored. They also advised that, worldwide up until then, there had been 19 cases of severe liver reactions, including 13 of liver failure, 2 deaths, and 3 liver transplants suspected to be possibly related to use of lumiracoxib.5 However, in November 2007, after a further review of worldwide safety data showed an increased number of serious liver reactions with the 100-mg dose which, in some cases, occurred with short-term use, the MHRA suspended the product licence for lumiracoxib.6 Subsequently, the EMEA7 has recommended its withdrawal in the EU

- 1. Australian Therapeutic Goods Administration. Urgent advice regarding management of patients taking lumiracoxib (Prexige) (issued 13th August, 2007). Available at: http://www.tga.gov.au/alerts/prexige.htm (accessed 08/11/07)
- Adverse Drug Reactions Advisory Committee (ADRAC). With-drawal of lumiracoxib in Australia. Aust Adverse Drug React Bull 2008: 27: 6-7. Also available at:
 - http://www.tga.health.gov.au/adr/aadrb/aadr0804.pdf (accessed
- MHRA. New (interim) restrictions on prescription of lumiracoxib, following concerns over liver safety (issued 24th August, 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/ Safetywarningsalertsandrecalls/Safetywarningsandmessag esformedicines/CON2032098 (accessed 29/08/08)
- Health Canada. Withdrawal of market authorisation for Prexige. (issued 4th October, 2007). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2007/2007_141_e.html (accessed 30/10/07)
- MHRA. Lumiracoxib and liver adverse reactions (issued 16th NHRA. Lumiracoxio and river adverse reactions (issued four October, 2007).

 Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessag esformedicines/CON2032831 (accessed 29/08/08)

 MHRA. Lumiracoxio (Prexige): suspension of marketing authorisations (issued 19th November, 2007).
- tiorisatoris (issued 17th 170veninet, 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2033073 (accessed 29/08/08) EMEA. European Medicines Agency recommends withdrawal
- of the marketing authorisations for lumiracoxib-containing medicines (issued 13th December, 2007). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/PR_Lumiracoxib_ 57930107en.pdf (accessed 17/07/08)

Interactions

For interactions associated with NSAIDs in general, see p.99. Lumiracoxib may cause liver toxicity and consequently it should not be used with other drugs known to cause clinically significant hepatotoxicity.

There is the possibility that lumiracoxib may decrease the clearance of drugs that are cytochrome P450 CYP2C9 substrates and caution is advised when it is given with CYP2C9 substrates that have a narrow therapeutic index such as phenytoin and warfarin.

Pharmacokinetics

Lumiracoxib is absorbed from the gastrointestinal tract after oral use with peak plasma concentrations reached in about 2 hours.

Protein binding is at least 98%. Lumiracoxib undergoes extensive hepatic metabolism; several enzymes appear to be involved including glucuronosyltransferase and cytochrome P450 isoenzymes. The main oxidative pathway is mediated by the CYP2C9 isoenzyme; however, this does not appear to be the major pathway. Three major metabolites have been identified: 4'-hydroxylumiracoxib, 5-carboxy-lumiracoxib, and 4'-hydroxy-5-carboxy-lumiracoxib. The 4'-hydroxy metabolite is active as a cyclo-oxygenase-2 (COX-2) inhibitor although it is less potent than lumiracoxib. The plasma half-life of lumiracoxib is about 4 hours. Slightly more of a dose is excreted in the urine (54%) than in the faeces (about 43%); only about 5% of a dose is excreted unchanged.

♦ References.

1. Scott G, et al. Pharmacokinetics of lumiracoxib in plasma and synovial fluid. Clin Pharmacokinet 2004; 43: 467-78

Uses and Administration

Lumiracoxib is an NSAID (p.99) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It has been withdrawn in many countries after reports of hepatotoxicity. In the UK, lumiracoxib was used in the treatment of osteoarthritis of the knee and hip in an oral dose of 100 mg once daily. Higher doses of up to 400 mg daily have been used in some countries but may be associated with an increased risk of hepatotoxicity (see Effects on the Liver, above).

♦ References.

- Lyseng-Williamson KA, Curran MP. Lumiracoxib. Drugs 2004; 64: 2237–46.
- 2. Bannwarth B, Berenbaum F. Clinical pharmacology of lumiracoxib, a second-generation cyclooxygenase 2
 Expert Opin Invest Drugs 2005; 14: 521–33.
- Rordorf CM, et al. Clinical pharmacology of lumiracoxib: a se-lective cyclo-oxygenase-2 inhibitor. Clin Pharmacokinet 2005; 44: 1247-66.
- 4. Schnitzer TJ, et al. Lumiracoxib in the treatment of osteoarthritis, rheumatoid arthritis and acute postoperative dental pain: re sults of three dose-response studies. Curr Med Res Opin 2005;
- 21: 131–61.
 5. Berenbaum F, et al. Efficacy of lumiracoxib in osteoarthritis: a review of nine studies. J Int Med Res 2005; 33: 21–41.
 6. Sheldon E, et al. Efficacy and tolerability of lumiracoxib in the treatment of osteoarthritis of the knee: a 13-week, randomized, double-blind comparison with celecoxib and placebo. Clin Ther 2005: 27: 64-77
- 7. Fleischmann R, et al. Lumiracoxib is effective in the treatment of osteoarthritis of the knee: a prospective randomized 13-week study versus placebo and celecoxib. *Clin Rheumatol* 2006; **25**: 42–53.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Prexige; Austral.: Prexige; Braz.: Prexige; Chile: Prexige; Hung.
Prexige; Indon.: Prexige; NZ: Prexige; Port.: Frexocel†, Hirzia†, UK: Prexige; Port.: Prexide; Prexi

Lysine Aspirin

Acetilsalicilato de lisina; Aspirin DL-Lysine; Lysiiniasetyylisalisylaatti; Lysinacetylsalicylat; Lysine Acetylsalicylate; DL-Lysine Acetylsalicylate; Lysinum Acetylsalicylicum.

Лизин-Аспирин $C_{15}H_{22}N_2O_6 = 326.3.$ CAS — 62952-06-1.

Pharmacopoeias. In Fr.

Adverse Effects, Treatment, and Precautions

As for Aspirin, p.20. Anaphylactic shock has been reported in patients given lysine aspirin by injection.

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

Hypersensitivity. For a suggestion that lysine aspirin might be more suitable than aspirin for the diagnosis of sensitivity to NSAIDs, see under Hypersensitivity on p.21.

Interactions

For interactions associated with aspirin, see p.23.

Uses and Administration

Lysine aspirin has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (see p.23). When given, lysine aspirin dissociates into lysine and aspirin; aspirin is then hydrolysed to salicylic acid. Lysine aspirin 900 mg is equivalent to about 500 mg of aspirin.

Lysine aspirin is used in the treatment of pain, fever, and rheumatic disorders. It is given in oral doses equivalent to 0.5 to 1 g of aspirin, repeated every 4 hours as needed up to a maximum of $3\ g$ of aspirin daily (2 g daily in the elderly) for pain and fever. The dose for rheumatic disorders is equivalent to $3\ to\ 6\ g$ of aspirin daily in 3 or 4 divided doses. Lysine aspirin is also given intramuscularly or intravenously in similar doses; the maximum daily parenteral dose is equivalent to 4 g of aspirin for very severe pain and to 6 g of aspirin for rheumatic disorders.

Lysine aspirin is also used with metoclopramide in the treatment

Lysine aspirin has also been used in the management of thromboembolic disorders

Headache. Some references to the use of lysine aspirin, often with metoclopramide, in the treatment of migraine.

- 1. Tfelt-Hansen P, et al. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. *Lancet* 1995; **346:** 923–6.
- Diener HC. Efficacy and safety of intravenous acetylsalicylic acid lysinate compared to subcutaneous sumatriptan and parenteral placebo in the acute treatment of migraine. A doubleblind, double-dummy, randomized, multicenter, parallel group study. Cephalalgia 1999; 19: 581-8.
- 3. Tfelt-Hansen P. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide (Migpriv) in the treatment of migraine attacks: comparison with placebo and oral sumatriptan. *Funct Neurol* 2000; **15** (suppl 3): 196–201.

Nasal polyps. Two long-term controlled studies suggested that topical (endonasal) lysine aspirin may be effective in preventing the recurrence of nasal polyps after surgical removal (see p.1508) in both aspirin-tolerant and aspirin-sensitive patients. This effect may be attributed to the non-specific anti-inflammatory properties of lysine aspirin. Although no adverse effects were reported in this study, hypersensitivity reactions have been seen after use of salicylates in the presence of nasal polyps (see Hypersensitivity under Adverse Effects of Aspirin, p.21).

In another study2 intranasal lysine aspirin did not show significant clinical benefit in preventing the recurrence of nasal polyps when compared with placebo. However, significant improvement at a microscopic level was noted.

- 1. Nucera E, et al. Effects of lysine-acetylsalicylate (LAS) treatment in nasal polyposis: two controlled long term prospective follow up studies. *Thorax* 2000; **55** (suppl 2): S75–78.
- 2. Parikh AA, Scadding GK. Intranasal lysine-aspirin in aspirinsensitive nasal polyposis: a controlled trial. *Laryngoscope* 2005; **115:** 1385–90.

Proprietary Preparations (details are given in Part 3)

Ags: Aspinia: Coplust; Decitriol; Vectaspini; Begi: Aspegic; Cardegic; Cz.: Aspegic; Dolorosan; Kardegic; Fr.: Aspegic; Cardiosolupsan; Kardegic; Ger.: Aspisolt; Gr.: Aspegic; Chardegic; Mex.: Coraspir; Kardegic; Neth.: Aspegic; Chardegic; Mex.: Aspegic; Chardegic; Mex.: Aspisolt; Gr.: Aspi cacyl instantanee; Aspegic; Kardegic; Venez.: Asalis†.

Multi-ingredient: Belg:: Migpriv; Chile: Dolotol 12; Cz.: Migpriv†, Denm.: Migpriv†; Fin.: Migpriv; Fr.: Aspegic Codeine†; Migpriv; Gr.: Premig, Hung.: Migpriv, Ital.: Migpriv, Migraprim; Mex.: Antigram; Neth.: Migrafin; Norw.: Migpriv; Pol.: Migpriv; Spain: Fluxal†; Swed.: Migpriv; Switz.: Migpriv; UK: Migramax.

Magnesium Salicylate

Salicilato magnésico.

Магния Салицилат

 $C_{14}H_{10}MgO_6, 4H_2O=370.6.$ CAS — 18917-89-0 (anhydrous magnesium salicylate); 18917-95-8 (magnesium salicylate tetrahydrate).

Pharmacopoeias. In Chin. and US.

USP 31 (Magnesium Salicylate). A white, odourless, efflorescent, crystalline powder. Soluble in water and in alcohol; slightly soluble in ether; freely soluble in methyl alcohol. Store in airtight

Adverse Effects, Treatment, and Precautions

As for Aspirin, p.20. Magnesium salicylate should also be used with caution in renal impairment because of the risk of hyper-

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

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

Uses and Administration

Magnesium salicylate has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (see p.23). Anhydrous magnesium salicylate 1 g is equivalent to about 1.2 g of aspirin. It is used in the treatment of pain and fever and has been used in the management of inflammatory conditions such as osteoarthritis, rheumatoid arthritis, and other arthritides. Usual oral

doses of magnesium salicylate, expressed in terms of anhydrous magnesium salicylate, are about 300 to 600 mg every 4 hours for pain or fever.

Preparations

USP 31: Magnesium Salicylate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Rati Salil E†; Canad.: Herbogesic; USA: Backache Maximum Strength Relief; Bayer Select Maximum Strength Backache; Doans; Magan; Mobidin; Momentum Muscular Backache Formula; MST; Novasal; Nuprin Backache†.

Multi-ingredient: Cz.: Cholagol; Hung.: Cholagol; Rus.: Cholagol (Xonaron); USA: Cafgesic Forte; Combiflex ES; Durabac Forte; Extra Strength Doans PM; Mobigesic; Painaid BRF Back Relief Formula; Tetra-Mag.

Meclofenamic Acid (BAN, USAN, rINN)

Acide Méclofénamique; Ácido meclofenámico; Acidum Meclofenamicum; CI-583; INF-4668. N-(2,6-Dichloro-mtolyl)anthranilic acid.

Меклофенамовая Кислота $C_{14}H_{11}CI_2NO_2 = 296.1.$ CAS — 644-62-2. ATC - M01AG04; M02AA18. ATC Vet - QM01AG04; QM02AA18.

Pharmacopoeias. In BP(Vet).

BP(Vet) 2008 (Meclofenamic Acid). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in chloroform; sparingly soluble in ether; soluble in dimethylformamide and in 1M sodium hydroxide.

Meclofenamate Sodium (BANM, USAN, rINNM)

Méclofénamate de Sodium: Meclofenamato sódico: Natrii Meclofenamas.

Натрий Меклофенамат $C_{14}H_{10}Cl_2NNaO_2,H_2O = 336.1.$ CAS — 6385-02-0.

Pharmacopoeias. In US.

USP 31 (Meclofenamate Sodium). A white to creamy white. odourless to almost odourless, crystalline powder. Freely soluble in water, the solution sometimes being somewhat turbid due to partial hydrolysis and absorption of carbon dioxide; the solution is clear above pH 15. Slightly soluble in chloroform; practically insoluble in ether; soluble in methyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions As for NSAIDs in general, p.96.

Incidence of adverse effects. The commonest adverse effect in 2500 patients given meclofenamate sodium was gastrointestinal disturbance. Diarrhoea occurred in 11.2% of patients in double-blind studies and 32.8% of patients in long-term studies (up to 3 years). Ulcers were detected in 22 patients during therapy and skin rashes occurred in 4% of patients. Transient increases in serum aminotransferases and BUN occurred in some patients.

Preston SN. Safety of sodium meclofenamate (MeclomenTM). Curr Ther Res 1978; 23 (suppl 4S): S107–12.

Effects on the blood. Case reports of agranulocytosis1 and thrombocytopenia² associated with meclofenamate therapy.

- 1. Wishner AJ, Milburn PB. Meclofenamate sodium-induced agranulocytosis and suppression of erythropoiesis. J Am Acad Dermatol 1985; 13: 1052–3.
- 2. Rodriguez J. Thrombocytopenia associated with meclofenamate. Drug Intell Clin Pharm 1981; 15: 999.

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Meclofenamate sodium is readily absorbed when given orally. Peak plasma concentrations occur about 0.5 to 2 hours after ingestion. Meclofenamate is over 99% bound to plasma proteins. The plasma elimination half-life of meclofenamate sodium is about 2 to 4 hours. It is metabolised by oxidation, hydroxylation, dehalogenation, and conjugation with glucuronic acid and excreted in urine mainly as glucuronide conjugates of the metabolites. About 20 to 30% is recovered in the faeces. One of the metabolites, a 3-hydroxymethyl compound, is reported to be active although to a lesser extent than the parent drug.

♦ References.

1. Koup JR, et al. A single and multiple dose pharmacokinetic and metabolism study of meclofenamate sodium. *Biopharm Drug Dispos* 1990; **11:** 1–15.

Uses and Administration

Meclofenamic acid, an anthranilic acid derivative similar to mefenamic acid (below), is an NSAID (p.99). It is given orally as the sodium salt in musculoskeletal and joint disorders such as