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

◊ References.

1. Balfour JA, *et al.* Lornoxicam: a review of its pharmacology and therapeutic potential in the management of painful and inflammatory conditions. *Drugs* 1996; **51:** 639–57.
2. Skjodt NM, Davies NM. Clinical pharmacokinetics of lornoxicam: 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.
4. 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:** 650–5.
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; Lornox; Xefo; ***Chile:*** Acabel†; ***Cz.:*** Xefo; ***Denm.:*** Xefo; ***Ger.:*** Telos; ***Gr.:*** Xefo; ***Hung.:*** Xefo; ***Israel:*** Xefo; ***Ital.:*** Noxon; Taigalor; ***Jpn:*** Lorcam; ***Port.:*** Acabel; Bosporon; ***Rus.:*** Xefocam (Кефокам); ***S.Afr.:*** Xefo; ***Spain:*** Acabel; Bosporon; ***Swed.:*** Xefo; ***Switz.:*** Xefo; ***Thai.:*** Xefo†; ***Turk.:*** Xefo; ***Venez.:*** Acabel.

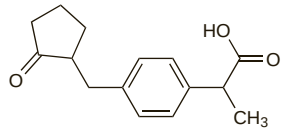
Loxoprofen Sodium *(rINNM)*

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).



(loxoprofen)

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)
Arg.: Oxeno; ***Braz.:*** Loxonin; ***Jpn:*** Lobu; Loxonin; ***Mex.:*** Loxonin; ***Philipp.:*** Loxonin; ***Thai.:*** Loxonin; ***Venez.:*** Loxonin.

Lumiracoxib *(BAN, USAN, rINN)*

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

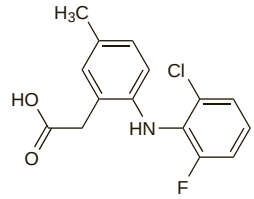
Лумиракоксиб

$C_{15}H_{13}ClFNO_2$ = 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-analysis[2] 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) as a group.

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 meta-analysis 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 study[1] 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 analysis[2] 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.[4] 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 EMEA[7] 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)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Withdrawal 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 17/07/08)
3. 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/Safetywarningsandmessagesformedicines/CON2032098 (accessed 29/08/08)
4. 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)
5. MHRA. Lumiracoxib and liver adverse reactions (issued 16th October, 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2032831 (accessed 29/08/08)
6. MHRA. Lumiracoxib (Prexige): suspension of marketing authorisations (issued 19th November, 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2033073 (accessed 29/08/08)
7. 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.