

Preparations

BP 2008: Etoricoxib Capsules; Etoricoxib Tablets;
USP 31: Etoricoxib Capsules; Etoricoxib Extended-Release Tablets; Etoricoxib Tablets.

Proprietary Preparations (details are given in Part 3)

Austria: Lodine†; **Braz.:** Flancox; **Canada:** Ultradol†; **Denm.:** Todolac; **Fin.:** Lodine; **Fr.:** Lodine; **Gr.:** Eridoxan†; **Lonine:** **Hong Kong:** Lodine; **Indon.:** Lonene; **Israel:** Etopan; **Ital.:** Lodine†; **Jpn:** Hyphen; **Mex.:** Lodine†; **Port.:** Acudor; **Articular:** Dugalga; **Lodine†:** **Metazin†:** **Sodolac:** **Switz.:** Lodine; **Thail.:** Etonox; **Turk.:** Edolar; **Etolin:** **Etol:** **Lodine:** **Tadolac:** **UK:** Eccoxolac; **Etopan:** **Lodine:** **USA:** Lodine†; **Venez.:** Lodine†.

Etofenamate (BAN, USAN, rINN)

B-577; Bay-d-1107; Etofenamaatti; Etofenamát; Etofenamat; Etofenamate; Etofenamate; Etofenamato; Etofenamatum; TV-485; TVX-485; WHR-5020. 2-(2-Hydroxyethoxy)ethyl N-(α,α,α -trifluoro-m-tolyl)anthranilate.

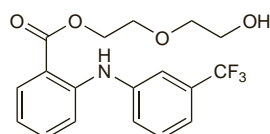
Этофенамат

$C_{18}H_{18}F_3NO_4 = 369.3$.

CAS — 30544-47-9.

ATC — M02AA06.

ATC Vet — QM02AA06.



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

Ph. Eur. 6.2 (Etofenamate). A yellowish viscous liquid. Practically insoluble in water; miscible with alcohol and with ethyl acetate.

Profile

Etofenamate is an NSAID (p.96) that has been applied topically in a concentration of 5 or 10% for the relief of pain and inflammation associated with musculoskeletal, joint, and soft-tissue disorders. It has also been given by deep intramuscular injection in single doses of 1 g.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Bayrogel†; **Contour†:** **Floglo:** **Austria:** Rheumon; **Traumon;** **Belg.:** Flexium; **Braz.:** Bayro; **Chile:** Bayagel; **Bayro†:** **Flogojet;** **Master-Gel†;** **Val-orel;** **Cz.:** Etoget†; **Rheuma Denkt†;** **Rheumon;** **Traumon;** **Ger.:** Algesalona E†; **Rheuma-Gel;** **Rheumon;** **Traumon;** **Gr.:** Cimal†; **Etofenol;** **Fenam†;** **Melferut;** **Pazergicel†;** **Radermin;** **Reumina;** **Roiplon;** **Hong Kong:** Flogoprofen; **Hung.:** Activon Extra; **Rheumon;** **Traumon†;** **Ital.:** Bayro; **Mex.:** Bayro; **Pol.:** Rheumon; **Traumon;** **Port.:** Fenogel; **Reumon;** **Spain:** Aspitopic; **Fl-ogoprofen;** **Zenavan;** **Switz.:** Activon†; **Etofen†:** **Rheumon;** **Traumalix;** **Turk.:** Doline; **Flexo;** **Painex;** **Rheumon;** **Venez.:** Traflan.

Multi-ingredient: **Arg.:** Bayagel; **Austria:** Thermo-Rheumon; **Chile:** Bayro-Thermo†; **Cz.:** Thermo-Rheumon†; **Ger.:** Thermo-Rheumon†; **Gr.:** Thermo-Roiplon; **Hung.:** Thermo-Rheumon†; **Mex.:** Bayro Thermo; **Pol.:** Thermo-Rheumon; **Turk.:** Thermo-Doline; **Thermo-Rheumon;** **Thermoflex;** **Venez.:** Reugel.

Etoricoxib (BAN, USAN, rINN)

Étoricoxib; Etoricoxibum; Etorikoksib; Etorikoksibi; Etorikoxib; L-791456; MK-0663; MK-663. 5-Chloro-6'-methyl-3-[p-(methylsulfonyl)phenyl]-2,3'-bipyridine.

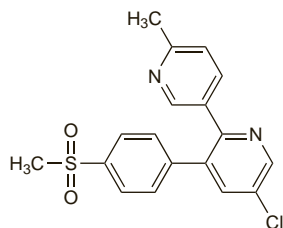
Эторикоксиб

$C_{18}H_{15}ClN_2O_2S = 358.8$.

CAS — 202409-33-4.

ATC — M01AH05.

ATC Vet — QM01AH05.



Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

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

with severe hepatic impairment (Child-Pugh score of 10 or more). Therapy should be stopped if persistently abnormal liver enzyme values are seen.

Etoricoxib should not be used in patients with ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease. It should be used with caution in patients with significant risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and diabetes mellitus. Etoricoxib, particularly at high doses, may be associated with more frequent and severe hypertension compared with other NSAIDs and selective COX-2 inhibitors; blood pressure monitoring during etoricoxib treatment is recommended. Etoricoxib should not be used in patients with hypertension whose blood pressure is not controlled (see also Effects on the Cardiovascular System, below).

Etoricoxib is also contra-indicated in patients with inflammatory bowel disease, moderate to severe heart failure (NYHA class II to IV), and renal impairment associated with a creatinine clearance of less than 30 mL/minute. Caution is recommended when using etoricoxib in dehydrated patients; it may be advisable to rehydrate patients before giving etoricoxib.

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 etoricoxib has been assessed in the MEDAL programme¹ which pooled data from 3 studies involving over 30 000 patients with either osteoarthritis or rheumatoid arthritis. Patients with osteoarthritis were given etoricoxib 60 or 90 mg daily; those with rheumatoid arthritis received 90 mg daily. In all studies, diclofenac 150 mg daily was given as the comparator; low-dose aspirin (100 mg daily or less) was also allowed where indicated. After an average treatment duration of 18 months, the rates of thrombotic events such as myocardial infarction, stroke, and sudden or unexplained death with etoricoxib were similar to those for diclofenac. (It has been suggested that diclofenac itself may increase the risk of some thrombotic events; for further details, see p.97.) The programme also found that the rate of some other non-thrombotic cardiovascular events was increased with etoricoxib: one of the 3 studies showed that there was a non-significant increase in the rate of heart failure with etoricoxib 90 mg daily compared to diclofenac; withdrawals due to oedema were also more frequent with high-dose etoricoxib than with diclofenac or etoricoxib 60 mg daily. In addition, the number of patients stopping treatment because of hypertension was higher with both doses of etoricoxib than with diclofenac. Similar results were seen in the other 2 studies.

In another study² that pooled pre-licensing data, the risk of thrombotic events with etoricoxib, given at a dose of at least 60 mg daily, was also found to be similar to that for placebo treatment, ibuprofen (2.4 g daily), diclofenac (150 mg daily), and naproxen (1 g daily), although there was a trend towards more events with etoricoxib than with naproxen. For details on the relative risk of thrombotic events associated with non-selective NSAIDs, see p.97.

The EMEA's Committee for Medicinal Products for Human Use (CHMP)³ has recommended the inclusion of a warning in the labelling of etoricoxib that it must not be given to patients whose blood pressure is persistently above 140/90 mmHg and inadequately controlled; in addition, high blood pressure should be controlled before starting treatment and monitored for 2 weeks afterwards then regularly thereafter.

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. Cannon CP, *et al.* Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2006; **368**: 1771–81.
2. Curtis SP, *et al.* Pooled analysis of thrombotic cardiovascular events in clinical trials of the COX-2 selective inhibitor etoricoxib. *Curr Med Res Opin* 2006; **22**: 2365–74.
3. EMEA. EMEA recommends strengthening warnings and contraindications for etoricoxib-containing medicines used in the treatment of rheumatoid arthritis and ankylosing spondylitis (issued 26 June 2008). Available at: <http://www.emea.europa.eu/pdfs/human/press/pr/33363608en.pdf> (accessed 16/07/08)

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 etoricoxib may cause less gastrotoxicity than that seen with the non-selective inhibition of the traditional NSAIDs. However, licensed product information states that upper gastrointestinal perforation, ulceration, and bleeds, in some cases fatal, have occurred with etoricoxib treatment; consequently, it should be used with caution in patients with a history of, or at risk

of developing, such events. In addition, etoricoxib should not be used in patients with active gastrointestinal ulceration or bleeding.

Results from controlled studies have suggested that NSAIDs selective for COX-2 were associated with a lower incidence of serious gastrointestinal effects. In a study¹ of the pooled data from 3 randomised clinical studies, etoricoxib (in doses of 60 or 90 mg daily) was associated with significantly less frequent upper gastrointestinal clinical events than diclofenac (150 mg daily). The result was attributed to the lower rate of uncomplicated ulcers with etoricoxib compared with diclofenac; there was no difference in the rate of complicated gastrointestinal events between the 2 drugs. The lower rate of uncomplicated events with etoricoxib compared with diclofenac was not affected by treatment with low-dose aspirin or proton pump inhibitors. An analysis² by the manufacturer, of pooled data from 10 randomised clinical studies, found that etoricoxib (in daily doses of 60, 90, or 120 mg) was associated with a lower combined risk of upper gastrointestinal perforations and bleeding, and symptomatic gastroduodenal ulcers when compared with non-selective NSAIDs (diclofenac 150 mg daily, ibuprofen 2.4 g daily, or naproxen 1 g daily) as a group. This reduced risk was seen even in patients with known risk factors for such complications such as the elderly and those with a history of gastrointestinal reactions.

1. Laine L, *et al.* Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2007; **369**: 465–73.
2. Ramey DR, *et al.* The incidence of upper gastrointestinal adverse events in clinical trials of etoricoxib vs. non-selective NSAIDs: an updated combined analysis. *Curr Med Res Opin* 2005; **21**: 715–22.

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

Interactions

The metabolism of etoricoxib is mediated by the cytochrome P450 isoenzyme CYP3A4. Use with other drugs that inhibit or induce this isoenzyme may result in changes in plasma concentration of etoricoxib. In addition, *in vitro* studies suggest that several other isoenzymes may also mediate the main metabolic pathway of etoricoxib. Rifampicin, a potent inducer of CYP isoenzymes, has produced decreased plasma concentrations of etoricoxib.

Etoricoxib is an inhibitor of human sulfotransferase activity and has been shown to increase the plasma concentration of ethinylestradiol. Interactions with other drugs, such as oral salbutamol and minoxidil, also metabolised by this enzyme may be a possibility and licensed product information advises care with such combinations.

For interactions associated with NSAIDs in general, see p.99.

Pharmacokinetics

Etoricoxib is well absorbed from the gastrointestinal tract after oral doses. Peak plasma concentrations are reached in about 1 hour in fasted adults; food delays absorption by about 2 hours, although it has no effect on the extent of absorption. Plasma protein binding is about 92%. At steady state the half-life of etoricoxib is about 22 hours. Etoricoxib is extensively metabolised with less than 2% of a dose recovered in the urine as the parent drug. The major route of metabolism is via cytochrome P450 isoenzymes including CYP3A4 to form the 6'-hydroxymethyl derivative of etoricoxib, which is then oxidised to the 6'-carboxylic acid derivative, the major metabolite. Both are inactive or only weak cyclo-oxygenase-2 (COX-2) inhibitors. Excretion is mainly via the urine (70%) with only 20% of a dose appearing in the faeces. Studies in *animals* suggest that etoricoxib may cross the placenta and that some is distributed into breast milk.

References

1. Agrawal NGB, *et al.* Single- and multiple-dose pharmacokinetics of etoricoxib, a selective inhibitor of cyclooxygenase-2, in man. *J Clin Pharmacol* 2003; **43**: 268–76.
2. Agrawal NGB, *et al.* Pharmacokinetics of etoricoxib in patients with hepatic impairment. *J Clin Pharmacol* 2003; **43**: 1136–48.
3. Agrawal NGB, *et al.* Pharmacokinetics of etoricoxib in patients with renal impairment. *J Clin Pharmacol* 2004; **44**: 48–58.

The symbol † denotes a preparation no longer actively marketed