Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Coldadolin; Dolmix; Helopyrin; Nisicur; Seltoc; ***Cz.:*** Cephyl†; ***Ger.:*** Glutisal†; Kolton grippale N†; ***Indon.:*** Farapon; Neo Novapon Plus; ***Jpn:*** Sin Colgen Kowa Kaze; ***Pol.:*** Erka; Etomar; Etopiryna; ***Port.:*** Cephyl; ***Rus.:*** Nextrim Aktiv (Нектрим Актив); ***Switz.:*** Nicaphlogyl†; Seranex sans codeine†.

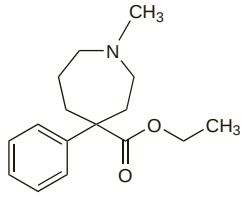
Ethoheptazine Citrate *(BANM, rINNM)*

Citrato de etoheptacina; Éthoheptazine, Citrate d'; Ethoheptazini Citras; Wy-401. Ethyl 1-methyl-4-phenylperhydroazepine-4-carboxylate dihydrogen citrate.

Этогептазина Цитрат

$C_{16}H_{23}NO_2,C_6H_8O_7$ = 453.5.

CAS — 77-15-6 (ethoheptazine); 6700-56-7 (ethoheptazine citrate); 2085-42-9 ((±)-ethoheptazine citrate).



(ethoheptazine)

Profile

Ethoheptazine citrate is an opioid analgesic (p.101) structurally related to pethidine (p.113). It has been used as an analgesic in the short-term treatment of mild to moderate pain, usually with other drugs such as aspirin and meprobamate.

Preparations

Proprietary Preparations (details are given in Part 3)

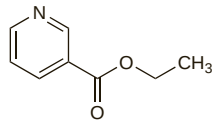
Multi-ingredient: ***India:*** Equagesic; ***S.Afr.:*** Equagesic.

Ethyl Nicotinate

Nicotinato de etilo.

$C_8H_9NO_2$ = 151.2.

CAS — 614-18-6.



Profile

Ethyl nicotinate is used in concentrations of up to 2% in topical rubefacient preparations for the relief of pain in musculoskeletal, joint, and soft-tissue disorders. It has also been used as suppositories in anorectal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Mucotherm.

Multi-ingredient: ***Austria:*** Percucor†; Thermal; ***Belg.:*** Transvane; ***Hung.:*** Nicoflex; ***Irl.:*** Transvasin; ***Norw.:*** Thermal†; ***Switz.:*** Baume Esco Forte; Frixo-Dragon Vert†; Knobel Huile N; Thermocutan†; Ziegella; ***UK:*** PR Heat Spray; Transvasin Heat Rub.

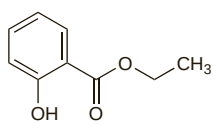
Ethyl Salicylate

Salicilato de etilo. Ethyl 2-hydroxybenzoate.

Этилсалицилат

$C_9H_{10}O_3$ = 166.2.

CAS — 118-61-6.



Profile

Ethyl salicylate is a salicylic acid derivative that is used similarly to methyl salicylate (p.85) in concentrations of up to 5% in topical rubefacient preparations for the relief of pain in musculoskeletal, joint, and soft-tissue disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Deep Heat; Radian-B†; ***Belg.:*** Rado-Salil; ***Israel:*** Deep Heat Spray; ***Ital.:*** Remy; ***Pol.:*** Deep Heat; ***S.Afr.:*** Deep Heat Spray; ***Singapore:*** Deep Heating Spray†; ***Switz.:*** Alginex†; ***UK:*** Deep Heat Spray; Dubam; Numark Muscle Spray; Ralgex.

Ethylmorphine Hydrochloride *(BANM)*

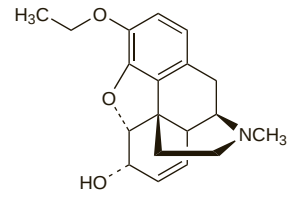
Aethylmorphinae Hydrochloridum; Aethylmorphini Hydrochloridum; Chlorhydrate de Codéthyline; Ethylmorfin-hydrochlorid dihydrát; Éthylmorphine, chlorhydrate d'; Ethylmorphini hydrochloridum; Ethylmorphini Hydrochloridum Dihydricum; Ethylmorphinium Chloride; Etilmorfina, hidrocloruro de; Etilmorfin-hidroklorid; Etilmorfino hidrochloridas; Etylmorfinhydroklorid; Etylomorfiny chlorowodorek; Etyylimorfiinihydrokloridi. 3-*O*-Ethylmorphine hydrochloride dihydrate; 7,8-Didehydro-4,5-epoxy-3-ethoxy-17-methylmorphinan-6-ol hydrochloride dihydrate.

$C_{19}H_{23}NO_3$,HCl,2H_2O = 385.9.

CAS — 76-58-4 (ethylmorphine); 125-30-4 (ethylmorphine hydrochloride).

ATC — R05DA01; S01XA06.

ATC Vet — QR05DA01; QS01XA06.



(ethylmorphine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Ethylmorphine Hydrochloride). A white or almost white crystalline powder. Soluble in water and in alcohol. A 2% solution in water has a pH of 4.3 to 5.7. Protect from light.

Profile

Ethylmorphine hydrochloride is an opioid analgesic (p.101) and has properties similar to those of codeine (p.37). It is used mainly as a cough suppressant. It has also been used for its analgesic and antidiarrhoeal properties. It was formerly given in eye drops as a lymphagogue.

Ethylmorphine free base and the camphorate and camsilate have also been used.

◊ References.

1. Aasmundstad TA, *et al.* Biotransformation and pharmacokinetics of ethylmorphine after a single oral dose. *Br J Clin Pharmacol* 1995; **39:** 611–20.
2. Jonasson B, *et al.* Fatal poisonings where ethylmorphine from antitussive medications contributed to death. *Int J Legal Med* 1999; **112:** 299–302.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dionina; ***Belg.:*** Codethyline; ***Cz.:*** Diolan; ***Fin.:*** Cocillana; ***Fr.:*** Dithiol†; ***UK:*** Collins Elixir.

Multi-ingredient: ***Austria:*** Modiscop; ***Belg.:*** Longbalsem; Saintbois; Tux†; ***Chile:*** Codelasa; ***Fin.:*** Indalgin; ***Fr.:*** Ephydion; Humex†; Tussipax; Vegetoserum; ***Hung.:*** Dolor; ***India:*** Bell Diono Resolvent; Bell Resolvent; ***Ital.:*** Mindol-Merck†; ***Norw.:*** Cosylan; Solvipect comp; ***Port.:*** Bronquiasmol†; Calmarum†; Xarope Antigripal†; ***Spain:*** Demusin; Sedalmerck†; ***Swed.:*** Cocillana-Etyfin; Lepheton; ***Switz.:*** Ipeca†; Phol-Tux; Saintbois; Sano Tuss; ***Turk.:*** Fenokodin; ***Venez.:*** Novacodin.

Etodolac *(BAN, USAN, rINN)*

AY-24236; Etodolaakki; Étodolac; Etodolaco; Etodolacum; Etodolák; Etodolak; Etodolakas; Etodolic Acid. 1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-ylacetic acid.

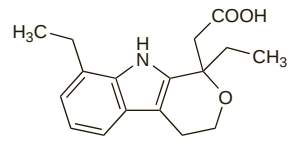
Этодолак

$C_{17}H_{21}NO_3$ = 287.4.

CAS — 41340-25-4.

ATC — M01AB08.

ATC Vet — QM01AB08.



Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Etodolac). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol and in acetone.

USP 31 (Etodolac). Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

The presence of phenolic metabolites of etodolac in the urine may give rise to a false-positive reaction for bilirubin.

Effects on the blood. Agranulocytosis has been reported in a patient receiving etodolac.[1] Coombs-positive haemolytic anaemia due to sensitivity to etodolac metabolites has also been reported.[2]

1. Cramer RL, *et al.* Agranulocytosis associated with etodolac. *Ann Pharmacother* 1994; **28:** 458–60.
2. Cunha PD, *et al.* Immune hemolytic anemia caused by sensitivity to a metabolite of etodolac, a nonsteroidal anti-inflammatory drug. *Transfusion* 2000; **40:** 663–8.

Effects on the gastrointestinal tract. Etodolac is reported to be a preferential inhibitor of cyclo-oxygenase 2 (COX-2) and consequently it may produce less gastric toxicity than the non-selective NSAIDs such as naproxen.[1-3]

1. Taha AS, *et al.* Effect of repeated therapeutic doses of naproxen and etodolac on gastric and duodenal mucosal prostaglandins (PGs) in rheumatoid arthritis (RA). *Gut* 1989; **30:** A751.
2. Bianchi Porro G, *et al.* A double-blind gastroscopic evaluation of the effects of etodolac and naproxen on the gastrointestinal mucosa of rheumatic patients. *J Intern Med* 1991; **229:** 5–8.
3. Weideman RA, *et al.* Risks of clinically significant upper gastrointestinal events with etodolac and naproxen: a historical cohort analysis. *Gastroenterology* 2004; **127:** 1322–8.

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Etodolac is a chiral compound given as the racemate. Peak plasma concentrations of the active (S)-enantiomer and of the inactive (R)-enantiomer are usually obtained within about 2 hours of a dose by mouth but plasma concentrations of the (R)-enantiomer have been reported to greatly exceed those of the (S)-enantiomer. Both enantiomers are highly bound to plasma proteins. Both are also distributed to the synovial fluid, although the difference in their concentrations may not be as marked as the difference in plasma concentrations. The plasma half-life of total etodolac has been reported to be about 7 hours; excretion is mainly in the urine as hydroxylated metabolites and glucuronide conjugates; some may be excreted in the bile.

◊ References.

1. Brocks DR, *et al.* Stereoselective disposition of etodolac enantiomers in synovial fluid. *J Clin Pharmacol* 1991; **31:** 741–6.
2. Brocks DR, *et al.* The stereoselective pharmacokinetics of etodolac in young and elderly subjects, and after cholecystectomy. *J Clin Pharmacol* 1992; **32:** 982–9.
3. Brocks DR, Jamali F. Etodolac clinical pharmacokinetics. *Clin Pharmacokinet* 1994; **26:** 259–74.
4. Boni J, *et al.* Pharmacokinetic and pharmacodynamic action of etodolac in patients after oral surgery. *J Clin Pharmacol* 1999; **39:** 729–37.
5. Boni JP, *et al.* Pharmacokinetics of etodolac in patients with stable juvenile rheumatoid arthritis. *Clin Ther* 1999; **21:** 1715–24.

Uses and Administration

Etodolac, a pyrano-indoleacetic acid derivative, is an NSAID (p.99) reported to be a preferential inhibitor of cyclo-oxygenase 2 (COX-2). It is used for rheumatoid arthritis, including juvenile idiopathic arthritis, and osteoarthritis and for the treatment of acute pain.

For the treatment of rheumatoid arthritis and osteoarthritis, the recommended oral dose is initially 600 to 1000 mg daily in divided doses adjusted according to response; single daily doses of up to 600 mg may also be given. Modified-release preparations are available for once-daily use in these conditions. For doses in children, see below.

For the treatment of acute pain, the recommended dose is 200 to 400 mg every 6 to 8 hours to a maximum of 1 g daily.

Administration in children. In the USA modified-release preparations of etodolac may be given for the oral treatment of juvenile idiopathic arthritis in children aged 6 to 16 years. Doses are given once daily according to body-weight as follows:

- 20 to 30 kg: 400 mg
- 31 to 45 kg: 600 mg
- 46 to 60 kg: 800 mg
- over 60 kg: 1 g

Preparations

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

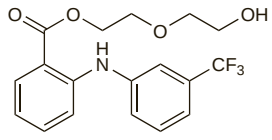
Proprietary Preparations (details are given in Part 3)
Austria: Lodine†; ***Braz.:*** Flancox; ***Canad.:*** Ultradol†; ***Denm.:*** Todolac; ***Fin.:*** Lodine; ***Fr.:*** Lodine; ***Gr.:*** Ecridoxan†; Lonine; ***Hong Kong:*** Lodine; ***Indon.:*** Lonene; ***Israel:*** Etopan; ***Ital.:*** Lodine†; ***Jpn:*** Hypen; ***Mex.:*** Lodine†; ***Port.:*** Acudor; Articulan; Dualgan; Lodine†; Lodot†; Metazin†; Sodolac; ***Switz.:*** Lodine; ***Thai.:*** Etonox; ***Turk.:*** Edolar; Etodin; Etol; Lodine; Tadolak; ***UK:*** Eccoxolac; Etopan; Lodine; ***USA:*** Lodine†; ***Venez.:*** Lodine†.

Etofenamate *(BAN, USAN, rINN)*

B-577; Bay-d-1107; Etofenamaatti; Etofenamát; Etofenamat; Etofenamatas; Étofénamate; Etofenamato; Etofenamatum; TV-485; TVX-485; WHR-5020. 2-(2-Hydroxyethoxy)ethyl *N*-(ααα-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†; Flogol; ***Austria:*** Rheumon; Traumon; ***Belg.:*** Flexium; ***Braz.:*** Bayro; ***Chile:*** Bayagel; Bayro†; Flogojet; Master-Gel†; Valorel; ***Cz.:*** Etogel†; Rheuma Denk†; 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; Flogoprofen; Zenavan; ***Switz.:*** Activon†; Etofen†; Rheumon; Traumalix; ***Turk.:*** Doline; Flexo; Painex; Rheumon; ***Venez.:*** Traflan.

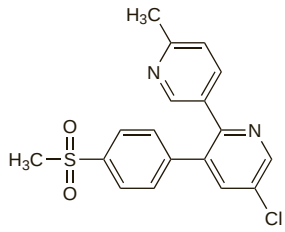
Multi-ingredient: ***Arg.:*** Bayagel; ***Austria:*** Thermo-Rheumon; ***Chile:*** Bayro-Therm†; ***Cz.:*** Thermo-Rheumon†; ***Ger.:*** Thermo-Rheumon†; ***Gr.:*** Thermo-Roiplon; ***Hung.:*** Thermo-Rheumon†; ***Mex.:*** Bayro Termo; ***Pol.:*** Thermo-Rheumon; ***Turk.:*** Thermo-Doline; Thermo-Rheumon; 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 programme[1] 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 study[2] 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 26th 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 study[1] 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 analysis[2] 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.