and symptoms, delay structural damage, and improve physical function. In both indications, it is given as a subcutaneous injection in a dose of 25 mg twice weekly at intervals of 3 or 4 days. The equivalent weekly dose of 50 mg may also be given either as a single 50-mg injection or as two separate 25-mg injections (given at about the same time). In the UK, NICE recommends, based on guidelines from the British Society of Rheumatology, that treatment be stopped if there is no adequate response after 6 months. Etanercept is also indicated in the treatment of severely active **ankylosing spondylitis**; in the UK, its use is again limited to those who have had an inadequate response to conventional therapy. Doses are similar to those used for rheumatoid arthritis.

Etanercept is also used in the treatment of chronic, moderate to severe plaque **psoriasis**. In the UK, its use is usually limited to patients in whom other systemic treatments are not suitable. The recommended initial dose is 25 mg twice weekly. Alternatively, an initial dose of 50 mg twice weekly at intervals of 3 or 4 days may be given for 12 weeks; the dose should then be reduced to 25 mg twice weekly or 50 mg weekly. Initial doses of 25 or 50 mg once weekly have also been shown to be effective. Treatment should continue until remission is achieved, for up to 24 weeks. Etanercept should be stopped after 12 weeks in patients who show no response.

For details of uses and dosage in children, see below.

Administration in children. Etanercept is used in the treatment of moderately to severely active polyarticular **juvenile idiopathic arthritis**; UK licensed product information limits its use to those who have had an inadequate response to, or who are intolerant of, the disease-modifying antirheumatic drug methotrexate.

In the UK, it is given subcutaneously to children aged 4 years and over in a dose of 400 micrograms/kg (up to a maximum dose of 25 mg) twice weekly at intervals of 3 or 4 days. In the USA, etanercept is licensed for use in children as young as 2 years old. Similar doses are used although they are expressed as 800 micrograms/kg (up to a maximum dose of 50 mg) weekly: doses to be given as 2 separate injections may either be given on the same day or 3 to 4 days apart.

In the UK, NICE recommends, based on guidelines from the British Paediatric Rheumatology Group, that treatment be stopped in children if there is no response after 6 months, or an initial response is not maintained.

For references on the use of etanercept in juvenile idiopathic arthritis, see Rheumatoid Arthritis, below.

Asthma. TNF inhibitors such as etanercept have been investigated in the treatment of refractory asthma (p.1108).[1,2] There is some evidence that only a minority of patients will respond to such therapy, and that the benefits and risks must therefore be carefully assessed.[3]

1. Howarth PH, *et al.* Tumour necrosis factor (TNFα) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax* 2005; **60:** 1012–18.
2. Berry MA, *et al.* Evidence of a role of tumor necrosis factor α in refractory asthma. *N Engl J Med* 2006; **354:** 697–708.
3. Brightling C, *et al.* Targeting TNF-α: a novel therapeutic approach for asthma. *J Allergy Clin Immunol* 2008; **121:** 5–10.

Dementia. A small pilot study[1] and individual case reports[2] have suggested that perispinal injection of etanercept, in doses of 25 to 50 mg weekly, may improve signs of dementia in patients with Alzheimer's disease. However, randomised controlled studies are required to confirm any benefit.

1. Tobinick E, *et al.* TNF-alpha modulation for treatment of Alzheimer's disease: a 6-month pilot study. *MedGenMed* 2006; **8:** 25. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=16926764 (accessed 13/06/08)
2. Tobinick EL, Gross H. Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration. *J Neuroinflammation* 2008; **5:** 2. Available at: http://www.jneuroinflammation.com/content/pdf/1742-2094-5-2.pdf (accessed 13/06/08)

Psoriasis. Etanercept is effective in patients with moderate to severe plaque psoriasis (p.1583).[1-9] It has also been successfully tried in the treatment of erythrodermic psoriasis,[10] and of plaque psoriasis in children and adolescents.[11]

Efficacy may be dose-related; in one study,[1] 25% of patients in the low-dose (25 mg once weekly) group showed at least a 75% improvement compared with 44% in the medium-dose group (25 mg twice weekly) and 59% in the high-dose group (50 mg twice weekly) after 24 weeks of etanercept treatment. However, a later multicentre study[2] in patients with chronic plaque psoriasis found that the therapeutic effect of etanercept was maintained when the dose was reduced after 12 weeks from 50 mg twice weekly to 25 mg twice weekly. An open-label extension[8] of these 2 studies found that efficacy was also sustained when patients who had received etanercept 25 mg twice weekly for at least 24 weeks had their dose altered to 50 mg once weekly.

1. Leonardi CL, *et al.* Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003; **349:** 2014–22.
2. Papp KA, *et al.* A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol* 2005; **152:** 1304–12.
3. NICE. Etanercept and efalizumab for the treatment of adults with psoriasis: Technology Appraisal Guidance 103 (issued July 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/TA103guidance.pdf (accessed 13/06/08)
4. Boehncke W-H, *et al.* European Dermatology Expert Group. Recommendations for the use of etanercept in psoriasis: a European dermatology expert group consensus. *J Eur Acad Dermatol Venereol* 2006; **20:** 988–98.
5. Woolacott N, *et al.* NHS Health Technology Assessment Programme. Etanercept and efalizumab for the treatment of psoriasis: a systematic review (issued November 2006). Available at: http://www.hta.ac.uk/fullmono/mon1046.pdf (accessed 13/06/08)
6. Tyring S, *et al.* Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Arch Dermatol* 2007; **143:** 719–26.
7. Romero-Maté A, *et al.* Efficacy and safety of etanercept in psoriasis/psoriatic arthritis: an updated review. *Am J Clin Dermatol* 2007; **8:** 143–55.
8. Elewski B, *et al.* Comparison of clinical and pharmacokinetic profiles of etanercept 25 mg twice weekly and 50 mg once weekly in patients with psoriasis. *Br J Dermatol* 2007; **156:** 138–42.
9. Ahmad K, Rogers S. Two years of experience with etanercept in recalcitrant psoriasis. *Br J Dermatol* 2007; **156:** 1010–14.
10. Esposito M, *et al.* Treatment of erythrodermic psoriasis with etanercept. *Br J Dermatol* 2006; **155:** 156–9.
11. Paller AS, *et al.* Etanercept Pediatric Psoriasis Study Group. Etanercept treatment for children and adolescents with plaque psoriasis. *N Engl J Med* 2008; **358:** 241–51.

Rheumatoid arthritis. Some references to the use of etanercept in rheumatoid arthritis (p.11) and juvenile idiopathic arthritis (p.10).

1. Weinblatt ME, *et al.* A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999; **340:** 253–9.
2. Moreland LW, *et al.* Etanercept therapy in rheumatoid arthritis: a randomized, controlled trial. *Ann Intern Med* 1999; **130:** 478–86.
3. Lovell DJ, *et al.* Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med* 2000; **342:** 763–9.
4. Bathon JM, *et al.* A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000; **343:** 1586–93. Correction. *ibid.* 2001; **344:** 76.
5. Johnson CJ, *et al.* Etanercept in juvenile rheumatoid arthritis. *Ann Pharmacother* 2001; **35:** 464–71.
6. Genovese MC, *et al.* Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum* 2002; **46:** 1443–50.
7. NICE. Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis: Technology Appraisal Guidance 35 (issued March 2002). Available at: http://www.nice.org.uk/nicemedia/pdf/JIA-PDF.pdf (accessed 13/06/08)
8. Klareskog L, *et al.* Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004; **363:** 675–81.
9. Genovese MC, *et al.* Longterm safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. *J Rheumatol* 2005; **32:** 1232–42.
10. Bathon JM, *et al.* Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. *J Rheumatol* 2006; **33:** 234–43.
11. van Riel PLCM, *et al.* ADORE (Add Enbrel or Replace Methotrexate) Study Investigators. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. *Ann Rheum Dis* 2006; **65:** 1478–83.
12. Moreland LW, *et al.* Etanercept treatment in adults with established rheumatoid arthritis: 7 years of clinical experience. *J Rheumatol* 2006; **33:** 854–61.
13. van der Heijde D, *et al.* Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum* 2006; **54:** 1063–74.
14. Chen Y-F, *et al.* NHS Health Technology Assessment Programme. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness (issued November 2006). Available at: http://www.hta.ac.uk/fullmono/mon1042.pdf (accessed 13/06/08)
15. Weisman MH, *et al.* A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases. *Rheumatology (Oxford)* 2007; **46:** 1122–5.
16. Dhillon S, *et al.* Etanercept: a review of its use in the management of rheumatoid arthritis. *Drugs* 2007; **67:** 1211–41. Correction. *ibid.*; 1849.
17. van der Heijde D, *et al.* Etanercept Study 400 Investigators. The safety and efficacy of adding etanercept to methotrexate or methotrexate to etanercept in moderately active rheumatoid arthritis patients previously treated with monotherapy. *Ann Rheum Dis* 2008; **67:** 182–8.
18. van der Heijde D, *et al.* Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2007; **56:** 3928–39.
19. NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis: Technology Appraisal Guidance 130 (issued October 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA130guidance.pdf (accessed 13/06/08)
20. Gartlehner G, *et al.* Biologics for the treatment of juvenile idiopathic arthritis: a systematic review and critical analysis of the evidence. *Clin Rheumatol* 2008; **27:** 67–76.

Spondyloarthropathies. References to the use of etanercept in the treatment of ankylosing spondylitis and psoriatic arthritis (p.13).

1. Mease PJ, *et al.* Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet* 2000; **356:** 385–90.
2. Brandt J, *et al.* Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. *Arthritis Rheum* 2003; **48:** 1667–75.
3. Davis JC, *et al.* Enbrel Ankylosing Spondylitis Study Group. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003; **48:** 3230–6.
4. Mease PJ, *et al.* Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004; **50:** 2264–72.
5. Baraliakos X, *et al.* Outcome of patients with active ankylosing spondylitis after two years of therapy with etanercept: clinical and magnetic resonance imaging data. *Arthritis Rheum* 2005; **53:** 856–63.
6. Mease PJ, *et al.* Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. *J Rheumatol* 2006; **33:** 712–21.
7. NICE. Etanercept and infliximab for the treatment of adults with psoriatic arthritis: Technology Appraisal Guidance 104 (issued July 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/TA104guidance.pdf (accessed 13/06/08)
8. Woolacott N, *et al.* NHS Health Technology Assessment Programme. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation (issued September 2006). Available at: http://www.hta.ac.uk/fullmono/mon1031.pdf (accessed 13/06/08)
9. van der Heijde D, *et al.* Etanercept Study 314 Investigators. Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in patients with ankylosing spondylitis. *Ann Rheum Dis* 2006; **65:** 1572–7.
10. Cantini F, *et al.* Switching from infliximab to once-weekly administration of 50 mg etanercept in resistant or intolerant patients with ankylosing spondylitis: results of a fifty-four-week study. *Arthritis Rheum* 2006; **55:** 812–6.
11. Woolacott NF, *et al.* Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review. *Clin Exp Rheumatol* 2006; **24:** 587–93.
12. Braun J, *et al.* Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly and 25 mg twice-weekly. *Rheumatology (Oxford)* 2007; **46:** 999–1004.
13. Romero-Maté A, *et al.* Efficacy and safety of etanercept in psoriasis/psoriatic arthritis: an updated review. *Am J Clin Dermatol* 2007; **8:** 143–55.
14. Frankel EH, *et al.* Etanercept improves psoriatic arthritis patient-reported outcomes: results from EDUCATE. *Cutis* 2007; **79:** 322–6.
15. McLeod C, *et al.* NHS Health Technology Assessment Programme. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. Available at: http://www.hta.ac.uk/fullmono/mon1128.pdf (accessed 13/06/08)
16. Gottlieb AB, *et al.* Use of etanercept for psoriatic arthritis in the dermatology clinic: the Experience Diagnosing, Understanding Care, and Treatment with Etanercept (EDUCATE) study. *J Dermatolog Treat* 2006; **17:** 343–52.
17. Hoy SM, Scott LJ. Etanercept: a review of its use in the management of ankylosing spondylitis and psoriatic arthritis. *Drugs* 2007; **67:** 2609–33.

Vasculitic syndromes. For a preliminary report on the use of etanercept in Takayasu's arteritis, see p.1514.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Enbrel; ***Austral.:*** Enbrel; ***Belg.:*** Enbrel; ***Braz.:*** Enbrel; ***Canad.:*** Enbrel; ***Chile:*** Enbrel; ***Cz.:*** Enbrel; ***Denm.:*** Enbrel; ***Fin.:*** Enbrel; ***Fr.:*** Enbrel; ***Ger.:*** Enbrel; ***Gr.:*** Enbrel; ***Hong Kong:*** Enbrel; ***India:*** Enbrel; ***Indon.:*** Enbrel; ***Irl.:*** Enbrel; ***Israel:*** Enbrel; ***Ital.:*** Enbrel; ***Malaysia:*** Enbrel; ***Mex.:*** Enbrel; ***Neth.:*** Enbrel; ***Norw.:*** Enbrel; ***NZ:*** Enbrel; ***Philipp.:*** Enbrel; ***Pol.:*** Enbrel; ***Port.:*** Enbrel; ***S.Afr.:*** Enbrel; ***Singapore:*** Enbrel; ***Spain:*** Enbrel; ***Swed.:*** Enbrel; ***Switz.:*** Enbrel; ***Thai.:*** Enbrel; ***Turk.:*** Enbrel; ***UK:*** Enbrel; ***USA:*** Enbrel; ***Venez.:*** Enbrel.

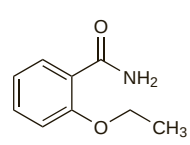
Multi-ingredient: ***Hung.:*** Enbrel.

Ethenzamide *(BAN, rINN)*

Aethoxybenzamidum; Etentsamidi; Etenzamid; Etenzamida; Etenzamide; Éthenzamide; Ethenzamidum; Ethoxybenzamide; Ethylsalicylamide; HP-209. 2-Ethoxybenzamide.

Этензамид

$C_9H_{11}NO_2$ = 165.2.
CAS — 938-73-8.
ATC — N02BA07.
ATC Vet — QN02BA07.



Pharmacopoeias. In *Jpn.*

Profile

Ethenzamide is a salicylic acid derivative (see Aspirin, p.20) given by mouth in painful and inflammatory conditions and to reduce fever.

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†.

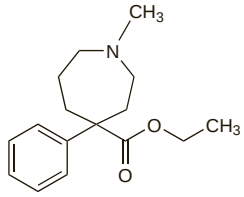
Ethoheptazine Citrate *(BANM, rINNM)*

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)

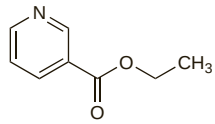
Multi-ingredient: ***India:*** Equagesic; ***S.Afr.:*** Equagesic.

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.

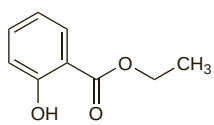
Ethyl Salicylate

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)*

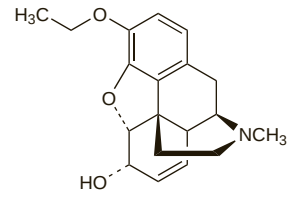
Aethylmorphinae Hydrochloridum; Aethylmorphini Hydrochloridum; Chlorhydrate de Codéthyline; Ethylmorfin-hydrochlorid dihydrát; Éthylmorphine, chlorhydrate d'; Ethylmorphini hydrochloridum; Ethylmorphini Hydrochloridum Dihydricum; Ethylmorphinium Chloride; Etilmorfina, hidrocloruro de; Etilmorfin-hidroklorid; 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.

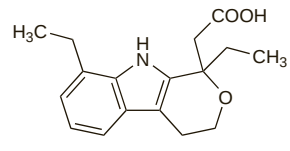
Этодолак

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