

15 mg was taken 30 minutes before exercise up to three times a day.

- Johnson MA, et al. Dihydrocodeine for breathlessness in 'pink puffers'. *BMJ* 1983; **286**: 675–7.

Pain. Dihydrocodeine is used in the management of moderate to severe pain. However, dose-related increase in postoperative pain has been seen¹ in patients given 25 or 50 mg dihydrocodeine tartrate intravenously after dental surgery, and it has been proposed that dihydrocodeine might act as an antagonist in situations where acute pain was accompanied by high opioid activity.² Systematic review of the use of single oral doses of dihydrocodeine has indicated that these are insufficient to provide adequate relief of postoperative pain, and that dihydrocodeine is less effective than ibuprofen.³

- Seymour RA, et al. Dihydrocodeine-induced hyperalgesia in postoperative dental pain. *Lancet* 1982; **i**: 1425–6.
- Henry JA. Dihydrocodeine increases dental pain. *Lancet* 1982; **ii**: 223.
- Edwards JE, et al. Single dose dihydrocodeine for acute postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 26/06/08).

Preparations

BP 2008: Co-dydramol Tablets; Dihydrocodeine Injection; Dihydrocodeine Oral Solution; Dihydrocodeine Tablets.

Proprietary Preparations (details are given in Part 3)

Austral. Paracodin; Rikodeine; **Austria:** Codidol; Dehace; Paracodin; **Belg.:** Codicinton; Paracodine; **Cz.:** DHC Continus; **Fr.:** Dicodin; **Ger.:** DHC; Paracodin; Paracodin N; Remedacen; Tiamon Mono; **Gr.:** Condugesic; **Hong Kong:** DF 118; **Hung.:** DHC; Hydrocodin; **Irl.:** DF 118; DHC Continus; Paracodin; **Ital.:** Paracodina; **Malaysia:** Codesic; **DF 118; NZ:** DHC Continus; **Pol.:** DHC Continus; **Port.:** Didor; **S.Afr.:** DF 118; Paracodin; **Spain:** Contugesic; Paracodina; Tosidrin; **Switz.:** Codicinton; Paracodin; **UK:** DF 118; DHC Continus.

Multi-ingredient: **Arg.:** Lentsusin; **Austral.:** Codox; **Austria:** Paracodin; **Ger.:** Antitussivum Burger N†; Makatussin Tropfen; Paracodin retard†; **Hong Kong:** Codaewon; **Irl.:** Paramol; **Ital.:** Cardiazol-Paracodina; Paracodina; **Jpn.:** Colgen Kowa IB Toumei; **Malaysia:** Dihydrocodeine P; **Switz.:** Escutussin; Makatussin Comp; Paracodin retard†; **UK:** Paramol; Remedene; **USA:** DHC Plus; DiHydro-CP; DiHydro-GP; DiHydro-PE; Duohist DH; Novahistine DH; Pancot; Pancot PD; Pancot-EXP; Panlor; Synalgos-DC.

Preparations

BP 2008: Dipipanone and Cyclizine Tablets.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: **Hong Kong:** Wellconal†; **Irl.:** Diconal†; **S.Afr.:** Wellconal; **UK:** Diconal.

Dipyrrone (BAN, USAN)

Metamizole Sodium (pINN); Aminopyrine-sulphonate Sodium; Analginum; Dipiron; Dipyrone; Dipyrone; Metamisol-natrium; Metamizol; Metamizol sódico; Metamizol sódru sůl monohydrát; Metamizol sódowy; Metamizol Sodum; Métamizole sodique; Metamizolnatrium; Metamizol-nátrium; Metamizolo natrio druská; Metamizolum natriicum; Metamizolum Natrium Monohydricum; Methampyrone; Methylmelubrin; Natrium Novaminsulfonicum; Noramidazophenum; Novamidazofen; Novaminsulfone Sodium; NSC-73205; Sodium Noramidopryne Methanesulphonate; Sulpyrine. Sodium N-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-N-methylaminomethanesulphonate monohydrate.

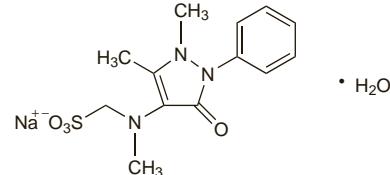
Метамизол Натрий

$C_{13}H_{16}N_3NaO_5S \cdot H_2O = 351.4$.

CAS — 68-89-3 (anhydrous dipyrrone); 5907-38-0 (dipyrrone monohydrate).

ATC — N02BB02.

ATC Vet — QN02BB02.



NOTE Confusingly the term dipyrone sodium also appears to be used synonymously for dipyrone itself. Dipyrone is referred to in some countries by the colloquial name 'Mexican aspirin'. The names noraminophenazonum and novaminsulfon have apparently been applied to dipyrone, but it is not clear whether these are the sodium salt.

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

Ph. Eur. 6.2 (Metamizole Sodium; Dipyrone BP 2008). A white or almost white crystalline powder. Very soluble in water; soluble in alcohol. Protect from light.

Adverse Effects and Precautions

Use of dipyrone is associated with an increased risk of agranulocytosis and with shock.

◊ References

- Levy M. Hypersensitivity to pyrazolones. *Thorax* 2000; **55** (suppl 2): S72–S74.

Effects on the blood. Data collected from 8 population groups in Europe and Israel by the International Agranulocytosis and Aplastic Anemia Study¹ revealed that there was a significant regional variability in the rate-ratio estimate for agranulocytosis and dipyrone (0.9 in Budapest to 33.3 in Barcelona). Although a large relative increase in risk between agranulocytosis and use of dipyrone was found, the incidence was less than some previous reports had suggested.

Blood dyscrasias such as agranulocytosis and granulocytopenia have continued to be reported where dipyrone remains available.^{2–7}

- The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anaemia: a first report of their relation to drug use with special reference to analgesics. *JAMA* 1986; **256**: 1749–57.
- Hedenmalm K, Spiget O. Agranulocytosis and other blood dyscrasias associated with dipyrone (metamizole). *Eur J Clin Pharmacol* 2002; **58**: 265–74.
- Maj S, Lis Y. The incidence of metamizole sodium-induced agranulocytosis in Poland. *J Int Med Res* 2002; **30**: 488–95.
- Maj S, Centkowski P. A prospective study of the incidence of agranulocytosis and aplastic anaemia associated with the oral use of metamizole sodium in Poland. *Med Sci Monit* 2004; **10**: P93–P95.
- Ibanez L, et al. Agranulocytosis associated with dipyrone (metamizole). *Eur J Clin Pharmacol* 2005; **60**: 821–9.
- Hamerchuk N, Cavalcanti AB. Neutropenia, agranulocytosis and dipyrone. *Sao Paulo Med J* 2005; **123**: 247–9.
- Garcia S, et al. Dipyrone-induced granulocytopenia: a case for awareness. *Pharmacotherapy* 2006; **26**: 440–2.

Effects on the skin. Dipyrone has been considered responsible for a case of drug-induced toxic epidermal necrolysis.¹

- Roujeau J-C, et al. Sjögren-like syndrome after drug-induced toxic epidermal necrolysis. *Lancet* 1985; **i**: 609–11.

Hypersensitivity. Cross-sensitivity between aspirin and dipyrone occurred in a patient.¹ Dipyrone produced an exacerbation of dyspnoea, cyanosis, and respiratory arrest.

- Bartoli E, et al. Drug-induced asthma. *Lancet* 1976; **i**: 1357.

Porphyria. Dipyrone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pharmacokinetics

After oral doses dipyrone is rapidly hydrolysed in the gastrointestinal tract to the active metabolite 4-methyl-amino-antipyrine, which after absorption undergoes metabolism to 4-formyl-amino-antipyrine and other metabolites. Dipyrone is also rapidly undetectable in plasma after intravenous doses. None of the metabolites of dipyrone are extensively bound to plasma proteins. Most of a dose is excreted in the urine as metabolites. Dipyrone metabolites are also distributed into breast milk.

◊ References

- Heinemeyer G, et al. The kinetics of metamizol and its metabolites in critical-care patients with acute renal dysfunction. *Eur J Clin Pharmacol* 1993; **45**: 445–50.
- Levy M, et al. Clinical pharmacokinetics of dipyrone and its metabolites. *Clin Pharmacokinet* 1995; **28**: 216–34.
- Zylber-Katz E, et al. Dipyrone metabolism in liver disease. *Clin Pharmacol Ther* 1995; **58**: 198–209.

Uses and Administration

Dipyrone is the sodium sulfonate of aminophenazone (p.19) and has similar properties. Because of the risk of serious adverse effects, in many countries its use is considered justified only in severe pain or fever where no alternative is available or suitable. Dipyrone has been given orally in doses of 0.5 to 4 g daily in divided doses. It has also been given by intramuscular or intravenous injection and rectally as a suppository. A magnesium congener of dipyrone, metamizole magnesium has been used similarly to dipyrone as has the calcium congener metamizole calcium.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Agiopirett; **Alargin:** Dioxadol; Dipigrand; Ditril; Integrabo; Lisalgit; Novacal; Novalgin; Novemina; Unibios Simple; **Austria:** Ialgon Neu; Novalgin; Spasmol Ialgon Neu; **Belg.:** Analigne; Novalgin; **Braz.:** Aligrona; Anadrol; Analges; Analgext; Apiron; Baralgin; Conmet; Difebrin; Dipimax; Dipix; Dipiron; Dipironax†; Dipix; Diprin; Doralex†; Dorfebril; Dorilan†; Dorval; Doron; Dorphin; DS500†; Findor†; Magnodort†; Magnoprot; Maxilin; Multirugam†; Notebrin; Novagreen; Novalge†; Novalgin; Pirofran†; Pirogena; Prodopirona; Sifpirona†; Termonal; Termopirona; Temoprin; Toloxin†; Zitalgin†; **Chile:** Baralina M; Conmet; Novalgin†; **Cz.:** Novalgin; **Fr.:** Novalgin; **Ger.:** Analgin; Berlosin; Metalign†; Novapain; Novalgin; Novaminsulfon; **Hong Kong:** Metilon; **Hung.:** Algopyrin; Algzone; Novalgin; Paragonin; **India:** Novalgin; **Indon.:** Antalgin; Antralin; Coralgan; Foragin; Licogin; Norages; Novalgin; Panstop; Pragol; Pyralon; Novalgin; Scanalgin; Unagen; **Israel:** Novalgin; Optalgan; Phanalgin; V-Talgin; **Ital.:** Novalgin; **Mex.:** Alexn; Anaprol; Anaproxil; Apixon†; Avafontan; Avaldriant; Ayoral Simple†; Carofrit†; Conmet; Dalmasini; Dalsin; Defin; Dimekti; Diproyd; Dofisal; Dolgan; Dolizo†; Dolofr; Domenal; Exalgan†; Exodalina; Fandali; Fardolpin; Farlin; Indigin; Lozima; Mach-2; Macodin; Magnil; Magnol; Magnolonas; Magnopyrox; Magsons; Mayoprina; Mecton†; Medipiro†; Mermid; Messeleni†; Metapirone; Midelin; Minorol; Mizoltec; Moditem; Neo-Melubrina; Neomelin; Neoseda; Paleofina; Pofit; Piramag†; Pirandal; Pirasol; Pirinovag; Piromebrina; Poloren†; Precidona; Prodolina; Prolubring; Pyranol; Pyron; Suprin; Termonil; Utidol; Vega†; **Neth.:** Novalgin; **Pol.:** Pyrahexal; Pyralgin; Pyralginum; **Port.:** Conmet; Docaloma; Nolotil; Novalgin†; **Rus.:** Analgin (Анальгин); Baralgin M (Баралин M); **Span.:** Algir; Cirdol†; Dolemicin; Lasain; Neo Melubrina; Nolotil; **Switz.:** Minalgine; Novalging; **Thail.:** Acodon†; Centagin; Deparon; Gengrin; Invoigin; Kno-Paine; Medalign†; Mezabox; Novalgin; Olan-Gin; **Turk.:** Adepiron; Andolor; Baralgin M; Devaljin; Feninox; Geralgine; Kafalgin; Nogesic; Novakom-S; Novalgin; Novo-Plan; Novopyrine; Sebon; Veraljin; **Urg.:** Dolanet; **Venez.:** Brat; Buscadol†; Combaran†; Comardon†; Conmet; Delsal; Dipamona; Dipidol; Klinomet†; Nime†; Noval†; Novalcina; Piradros; Piradrops Simple†; Promet; Rosadot.

Multi-ingredient: **Arg.:** Antispasmina; Apasmo; Apasmo Compuesto; Artifene; Bellatalo; Buscipana Compositum; Calmoprin; Canovex†; Cifespasmo Compuesto; Colobolina D; Craut†; Cronopen Balsamico; D-P†; Dentolina Plus; Dextro + Dipirona; Dextrodrip; Dioxadol; Dresan Biotic; Dresan†; Espasmo Biotenik; Espasmo Dioxadol; Fadiprin; Febrimicina†; Fleximicina A; Gastrolina Compuesta; Gobicbalm; Integrabo Plus; Keptan Compuesto†; Klosidol; Klosidol BI B6 B12; Lisalgit Compuesto; Luar-G Compositum; Migra Dioxadol; Migral; Migral Compositum; Multin; Novapasmil Composito; Paratropina Compuesta; Pasmofina Composta; Pasmodesan Composto†; Rupe-N Composto; Saldeva; Solaci; Sumal; Tetralgin†; Tetralgin Novo; Vicereno; **Austria:** Buscopan Compositum; Spasmus comp; **Bulg.:** Buscopan Compositum; **Braz.:** Alegrin; Algec; Aminocid†; Analgin C-R; Analgesond†; Analverin Composto†; Analverin†; Aniprinol; Baldwin-CET†; Bandor†; Bicavine; Binospan; Bioscina Composta†; Bromalgin†; Broncopin†; Buscopan Composto; Buscoven Composto; Butilamin†; Cafalena†; Cefalidina; Cefaliv; Codeverin†; Dalges; Dexalen; Dimext; Dipiro†; Dispusan; Doraleg; Doraljina; Dorflex; Dorflex; Dorinc; Dorinda; Dorilon; Dorless; Doroscopina†; Dorsein; Dorspan; Dorsone; Ductopan; Enxal; Espasmocron; Espasmold Composto; Eucalip†; Flexalge; Flexidol; Grianpit†; Gripion†; Gripomatine†; Gripon†; Gripys; Hioparistin; Hiopan Composto; Infb-Dor†; Italflex†; Kiligrif; Kindipasm; Lisador; Melpatz†; Migral; Miganette; Mionevix; Miorelas; Neocar; Neomigran†; Neosalidina; Neurogina; Nevralges; Par; Palsmigin†; Plenocedan†; Pulmorient†; Relatflex; Rielex; Sedabe†; Sedale; Sedalina; Sedalin; Sedol; Sedop; Spasmotropin; Tensaldin; Tetrapulin; Theopirina†; Tropinal; Uzara†; Veratropan Composto; **Chile:** Bremadol Composto; Buscipana Compositum; Cefalim; Cinabel; Diorant; Dolcipin; Dolnix; Dolo-Neurobionta†; Dolonase; Fredol; Migragesic; Migranol; Migratam; Neo Butarot; Nospsin Composto; Piretan†; Scopan; Silartin†; Silre-lax†; Stalagnat†; Ultrimin; Vladil Composto; Viplan Composto; Viproxil Composto; **Cz.:** Aligren; Alfigen Neo; Analgin; Quarelin†; **Fin.:** Litigain; **Fr.:** Avafontan†; Cefaline-Pyrazole†; Salgydal a la noramidopropina; Visceraline Forte†; **Hung.:** Algopyrin Complex; Quarelin; Ridol†; **Indon.:** Analisk; Ársinal; Biomega; Cetalgan; Cetalgan-T; Corsanural; Dactron; Danalgin; Deparon; Dolo Scanneuron; Dolo-Licobion; Foraneural; Goralgin; Hedix; Ikanuron Plus; Neuralgin RX; Neuro Panstop; Neurobat A; Neurodial; Neurogen; Neurosanbe Plus; Neurotropic Plus; Neuroval; Opineuron; Penagon; Prigesic; Procolic; Proneuron; Spasil; Spasmal; Spasminal; Stiller; Supranal; Tropineuron; Untheol; **Ital.:** Soma Complex†; **Mex.:** Agosfar; Anidal; Ayoral†; Benilo; Biomesia Composta; Bipasin Composito; Bipasin Composito N; Buscipana Compositum; Buscon; Busepan; Buspina; Colepren; Dolfent; Dolo-Tiaminal; Espasmogress; Hiosinotil Composto†; Hiosutrina-F; Konfren; Neo-Brontyl; Neo-Pasmonal; Ortran†; Pasmodil; Pirobutrol; Resipicil; Retadol Compositum; Selpiran; Serralpina Composta; Singril; **Pol.:** Gardan; Gerdan; Scopolan Compositum; Spasmalgon; Tolarign; **Rus.:** Analgin-Chinin (Анальгин-Хинин); Antigrippin-ÁNVI (Антигриппин-АНВИ); Baralgetas (Баралгетас); Benalgin (Бенальгин);

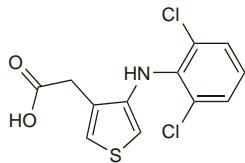
Maxigan (Максиган); Nebalgan (Небалган); Pentalgin-N (Пентаглибин-Н); Revalgin (Ревалигин); Sedal-M (Седал-М); Sedalgan-Neo (Седальгин-Нео); Spasgan (Спазган); Spasmalon (Спазмалон); Spasmalin (Спазмалин); Tempalgin (Темгалгин); Tempanginol (Темпанигинол). **S.Afr.:** Baralgin; Buscopan Compositum; Norifortant; Scopex Com. **Spain:** Biscapina Compositum; Nolotil Compositum. **Tha.:** Butarion; Novapam. **Turk.:** Buscapin Compositum; Butilamina Compuesta; Cotar; Diezol Compuesto; Flemibar; Hioscinol Compuesto; Praxona; Sarfan Compuesto; Sistalcin Compositum.

Eltenac (rINN)

Elténam; Eltenaco; Eltenacum. 4-(2,6-Dichloroanilino)-3-thiopheneacetic acid.

Эльтенак

$C_{12}H_9Cl_2NO_2S = 302.2$.
CAS — 72895-88-6.



Profile

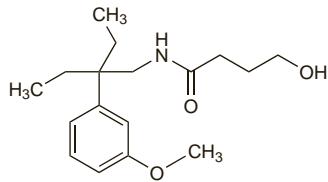
Eltenac is an NSAID (p.96) used in veterinary medicine.

Embutramide (BAN, USAN, rINN)

Embutramida; Embutramidum; Hoe-18-680. N-(β,β-Diethyl-m-methoxyphenethyl)-4-hydroxybutyramide.

Эмбутрамида

$C_{17}H_{27}NO_3 = 293.4$.
CAS — 15687-14-6.



Profile

Embutramide is an opioid analgesic used in veterinary medicine for euthanasia.

Enoxolone (BAN, rINN)

Enoksolonas; Enoksoloni; Enoxolon; Enoxolona; Énoxolone; Enoxolonus; Glycyrhetic Acid; Glycyrrhetic Acid; Kwas glicyryzynowy. 3β-Hydroxy-11-oxo-olean-12-en-30-oic acid.

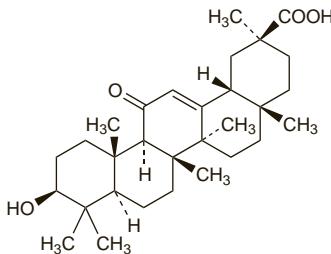
Эноксолона

$C_{30}H_{46}O_4 = 470.7$.

CAS — 471-53-4.

ATC — D03AX10.

ATC Vet — QD03AX10.



NOTE. Do not confuse with glycyrrhetic acid (p.2316).

Pharmacopoeias. In Eur (see p.vii).

Ph. Eur. 6.2 (Enoxolone). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in dehydrated alcohol; sparingly soluble in dichloromethane. Protect from light.

Profile

Enoxolone is a complex triterpene prepared from glycyrrhetic acid (p.2316), a constituent of liquorice (p.1740). Enoxolone is used locally in preparations for the treatment of non-infective in-

flammatory disorders of the skin, mouth, throat, and rectum. Enoxolone potassium (potassium glycyrheticinate) has been used similarly.

Derivatives of enoxolone, including its aluminium salt (p.1729) and carbenoxolone (p.1714) have been used in the treatment of benign peptic ulcer disease and other gastrointestinal disorders.

◊ Enoxolone is a potent inhibitor of the enzyme 11β-hydroxysteroid dehydrogenase, which inactivates cortisol, and use with hydrocortisone has been shown in *animal* studies to potentiate the activity of hydrocortisone in skin.¹ Whether this also increased the systemic absorption and toxicity of hydrocortisone was unclear.² However, for reference to adverse effects attributed to systemic inhibition of cortisol when enoxolone (glycyrrhetic acid) is produced during metabolism of ingested liquorice, see Effects on Fluid and Electrolyte Homeostasis, p.1740.

A cream containing enoxolone with hyaluronic acid, telmesteine, and a grape extract, has been investigated with apparent benefit in the management of mild to moderate eczema.^{3,4} However, topical application of enoxolone has been associated with contact dermatitis.⁵

1. Teelucksingh S, et al. Potentiation of hydrocortisone activity in skin by glycyrrhetic acid. *Lancet* 1990; **335**: 1060-3.
2. Greaves MW. Potentiation of hydrocortisone activity in skin by glycyrrhetic acid. *Lancet* 1990; **336**: 876.
3. Belloni G, et al. A randomised, double-blind, vehicle-controlled study to evaluate the efficacy and safety of MAS063DP (Atopiclair) in the treatment of mild to moderate atopc dermatitis in adults. *Eur J Dermatol* 2005; **15**: 31-6.
4. Abramovits W, Boguniewicz M. Adult Atopiclair Study Group. A multicenter, randomized, vehicle-controlled clinical study to examine the efficacy and safety of MAS063DP (Atopiclair) in the management of mild to moderate atopc dermatitis in adults. *J Drugs Dermatol* 2006; **5**: 236-44.
5. Tanaka S, et al. Allergic contact dermatitis from enoxolone. *Contact Dermatitis* 2001; **44**: 192.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Demanox. **Fr.:** Arthrodont; Moustidose; PO 12. **S.Afr.:** Arthrodont.

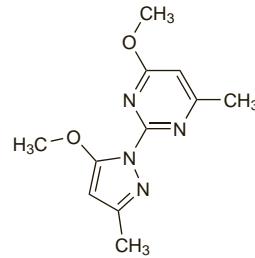
Multi-ingredient: **Arg.:** Anastim con RTH; Empecid Pie; **Chile:** Ginglacer; Ruboril; Sebium AKN; Suavigel; **Fr.:** Apasance; Ergyne; Fluocarl dents sensibles; Hexalyse; Hyseke; Hyseke Solaire; Mousticlogne; Moustidose Bebe-Nourrisson; Night Peel; Novophane; Novophane S; Photoderm Flusht; Photoderm Laser; Pyreflor; Sebium AKN; Sedorhoide; Tiq'Aouta; Vocady; **Hong Kong:** Hexalyse; **Indon.:** Polik; **Israel:** Aptahagone; Apatha-X; Gelclair; **Ital.:** Acnesan; Bactilene Benoden; Gel Gengivale; Biuthymus DS; Eudent con Glysant; Fluocaril; Lenipasta; Lenirosef; Lismucil Gola; Neo-Stomogen; Pastiglie Valda; Pyrex; Skaf 2; Videm; **Mex.:** Angenovag; Periodentyl; **Port.:** Despigmentante; **Rus.:** Hexalyse (Ferkava); **Spain:** Angileptol; Anginovag; Roberfarin; **UK:** Atopiclair; Gelclair; Xclair; **USA:** Atopiclair; Gelclair; **Venez.:** Sebium AKN; Sensibio DS.

Epirizole (USAN, pINN)

DA-398; Epirizol; Épirizole; Epirizolum; Mepirizole. 4-Methoxy-2-(5-methoxy-3-methylpyrazol-1-yl)-6-methylpyrimidine.

Эпиризол

$C_{11}H_{14}N_4O_2 = 234.3$.
CAS — 18694-40-1.



Pharmacopoeias. In Jpn.

Profile

Epirizole is an NSAID (p.96) that has been given in a usual oral dose of 150 to 450 mg daily in divided doses; larger doses of up to 600 mg daily have been used in patients with rheumatoid arthritis.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Mebront; **Jpn.:** Mebron; **Venez.:** Dalex.

Etanercept (BAN, USAN, rINN)

Étanercept; Etanerceptum; Etanercept; Etanercepti; rh-TNFRFc; TNR-001. A dimer of I-235 tumour necrosis factor receptor (human) fusion protein with 236-467-immunoglobulin G1 (human γ1-chain Fc fragment).

Этанерцепт

$CAS = 185243-69-0$.
ATC — L04AB01.
ATC Vet — QL04AB01.

Adverse Effects and Precautions

As for Infliximab, p.69.

Mild to moderate injection site reactions with symptoms of erythema, itching, pain, or swelling are common with etanercept. Other common reactions include headache, dizziness, asthenia, nausea and vomiting, abdominal pain, dyspepsia, and allergic reactions. Antibodies to etanercept may develop.

Etanercept should be used with caution in patients with heart failure.

◊ References.

1. Sánchez Carazo JL, et al. Safety of etanercept in psoriasis: a critical review. *Drug Safety* 2006; **29**: 675-85.

Wegener's granulomatosis. The addition of etanercept to standard therapy (including cyclophosphamide or methotrexate and corticosteroids) was not shown to be effective in patients with Wegener's granulomatosis and was associated with an increased incidence of various non-cutaneous malignancies.¹ Licensed product information recommends that etanercept should not be added to therapy in patients with Wegener's granulomatosis.

1. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med* 2005; **352**: 351-61.

Interactions

As for Infliximab, p.71. The use of etanercept with sulfasalazine has resulted in decreased white blood cell counts; however, the clinical significance of this is unknown. For an increased incidence of malignancy when etanercept was added to standard immunosuppressive therapy in patients with Wegener's granulomatosis, see above.

Pharmacokinetics

After a single subcutaneous dose of etanercept, UK licensed product information states that the mean half-life is about 70 hours, and the time to peak serum concentration 48 hours. In contrast, US information gives the half-life as 102 hours and the time to peak concentration as about 70 hours, although with a considerable range. Repeated dosing was noted to result in a two- to sevenfold increase in serum levels of etanercept in some patients.

◊ References.

1. Korth-Bradley JM, et al. The pharmacokinetics of etanercept in healthy volunteers. *Ann Pharmacother* 2000; **34**: 161-4.
2. Zhou H. Clinical pharmacokinetics of etanercept: a fully humanized soluble recombinant tumor necrosis factor receptor fusion protein. *J Clin Pharmacol* 2005; **45**: 490-7.
3. Yin D-S, et al. Population pharmacokinetic analysis and simulation of the time-concentration profile of etanercept in pediatric patients with juvenile rheumatoid arthritis. *J Clin Pharmacol* 2005; **45**: 246-56.
4. Don BR, et al. The pharmacokinetics of etanercept in patients with end-stage renal disease on haemodialysis. *J Pharm Pharmacol* 2005; **57**: 1407-13.
5. Sullivan JT, et al. Bioequivalence of liquid and reconstituted lyophilized etanercept subcutaneous injections. *J Clin Pharmacol* 2006; **46**: 654-61.
6. Nestorov I, et al. Pharmacokinetics of subcutaneously administered etanercept in subjects with psoriasis. *Br J Clin Pharmacol* 2006; **62**: 435-45.
7. 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.

Uses and Administration

Etanercept is a recombinant version of soluble human tumour necrosis factor (TNF) receptor that binds specifically to tumour necrosis factor (p.783) and blocks its interaction with endogenous cell-surface TNF receptors. This interaction prevents the important effect of TNF in the inflammatory processes of rheumatoid arthritis; elevated TNF levels are also found in psoriatic plaques, in the synovium of patients with psoriatic arthritis, and in the serum and synovium of patients with ankylosing spondylitis.

Etanercept is used in the treatment of moderately to severely active **rheumatoid arthritis** and active and progressive **psoriatic arthritis**. In the UK, it is licensed for use in patients who have had an inadequate response to standard disease-modifying antirheumatic drugs although, in severe rheumatoid arthritis, it may be used in patients not previously treated with methotrexate. In the USA, it is licensed to treat early rheumatoid arthritis or psoriatic arthritis, to reduce the signs