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

1. 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 seen[1] 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]

1. Seymour RA, *et al.* Dihydrocodeine-induced hyperalgesia in postoperative dental pain. *Lancet* 1982; **i:** 1425–6.
2. Henry JA. Dihydrocodeine increases dental pain. *Lancet* 1982; **ii:** 223.
3. 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.:*** Codicontin; 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.:*** Codicontin; Paracodin; ***UK:*** DF 118; DHC Continus.

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

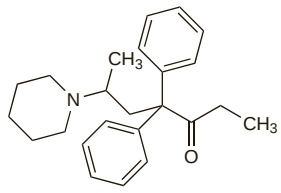
Dipipanone Hydrochloride *(BANM, rINNM)*

Dipipanone, Chlorhydrate de; Dipipanoni Hydrochloridum; Hidrocloruro de dipipanona; Phenylpiperone Hydrochloride; Piperidyl Methadone Hydrochloride; Piperidylamidone Hydrochloride. (±)-4,4-Diphenyl-6-piperidinoheptan-3-one hydrochloride monohydrate.

Дипипанона Гидрохлорид

$C_{24}H_{31}NO,HCl,H_2O$ = 404.0.

CAS — 467-83-4 (dipipanone); 856-87-1 (dipipanone hydrochloride).



(dipipanone)

Pharmacopoeias. In *Br.*

BP 2008 (Dipipanone Hydrochloride). An odourless or almost odourless, white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in acetone; practically insoluble in ether. A 2.5% solution in water has a pH of 4.0 to 6.0.

Profile

Dipipanone hydrochloride is an opioid analgesic (p.101) structurally related to methadone (p.82). Used alone it is reported to be less sedating than morphine. It is used in the treatment of moderate to severe pain.

Dipipanone hydrochloride is usually given in combination preparations with the antiemetic cyclizine hydrochloride to reduce the incidence of nausea and vomiting, but the use of such preparations is not recommended for the management of chronic pain, as the antiemetic is usually only required for the first few days of treatment. The usual oral dose of dipipanone hydrochloride is 10 mg, repeated every 6 hours. The dose may be increased if necessary in increments of 5 mg; it is seldom necessary to exceed a dose of 30 mg. After an oral dose the analgesic effect begins within an hour and lasts about 4 to 6 hours.

Preparations of dipipanone hydrochloride with cyclizine hydrochloride are subject to abuse.

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.

Dipyrone *(BAN, USAN)*

Metamizole Sodium *(pINN)*; Aminopyrine-sulphonate Sodium; Analginum; Dipiron; Dipyron; Dipyroni; Dipyronum; Metamitsolinatrium; Metamizol; Metamizol sódico; Metamizol sodná sůl monohydrát; Metamizol sodowy; Metamizol Sodyum; Métamizole sodique; Metamizolnatrium; Metamizol-nátrium; Metamizolo natrio druska; Metamizolum natricum; Metamizolum Natricum Monohydricum; Methampyrone; Methylmelubrin; Natrium Novaminsulfonicum; Noramidazophenum; Novamidazofen; Novaminsulfone Sodium; NSC-73205; Sodium Noramidopyrine Methanesulphonate; Sulpyrine. Sodium *N*-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-*N*-methylaminomethanesulphonate monohydrate.

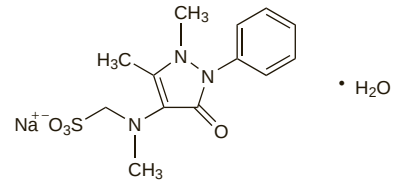
Метамизол Натрий

$C_{13}H_{16}N_3NaO_4S,H_2O$ = 351.4.

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

Pharmacopoeias. 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.
1. 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 Study[1] 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]

1. The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anemia: a first report of their relation to drug use with special reference to analgesics. *JAMA* 1986; **256:** 1749–57.
2. Hedenmalm K, Spigset O. Agranulocytosis and other blood dyscrasias associated with dipyrone (metamizole). *Eur J Clin Pharmacol* 2002; **58:** 265–74.
3. Maj S, Lis Y. The incidence of metamizole sodium-induced agranulocytosis in Poland. *J Int Med Res* 2002; **30:** 488–95.
4. Maj S, Centkowski P. A prospective study of the incidence of agranulocytosis and aplastic anemia associated with the oral use of metamizole sodium in Poland. *Med Sci Monit* 2004; **10:** PI93–PI95.
5. Ibanez L, *et al*. Agranulocytosis associated with dipyrone (metamizol). *Eur J Clin Pharmacol* 2005; **60:** 821–9.
6. Hamerschlak N, Cavalcanti AB. Neutropenia, agranulocytosis and dipyrone. *Sao Paulo Med J* 2005; **123:** 247–9.
7. 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]

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.

1. 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.
1. 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.
2. Levy M, *et al.* Clinical pharmacokinetics of dipyrone and its metabolites. *Clin Pharmacokinet* 1995; **28:** 216–34.
3. 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.: Algiopiret†; Analgina; Dioxadol; Dipigrand; Ditral; Integrobe; Lisalgil; Novacler; Novalgina; Novemina; Unibios Simple; ***Austria:*** Inalgon Neu; Novalgin; Spasmo Inalgon Neu; ***Belg.:*** Analgine; Novalgine; ***Braz.:*** Algirona; Anador; Analgesil; Analgex†; Apiron; Baralgin; Conmel; Difebril; Dipimax; Dipirex†; Dipiron; Dipironax†; Dipix; Diprin; Doralex†; Dorfebril†; Dorilan†; Dornal†; Dorona; Dorpinon; DS500†; Findor†; Magnodor†; Magnopyrol; Maxiliv; Multiralgim†; Nofebrin; Novagreen; Novalgex†; Novalgina; Pirofebran†; Pirogina; Prodopirona; Sifpirona†; Termonal; Termopirona; Termoprin; Toloxin†; Zitalgin†; ***Chile:*** Baralgina M; Conmel; Novalgina†; ***Cz.:*** Novalgin; ***Fr.:*** Novalgine†; ***Ger.:*** Analgin; Berlosin; Metalgin†; Nopain; Novalgin; Novaminsulfon; ***Hong Kong:*** Metilon†; ***Hung.:*** Algopyrin; Algozone; Novalgin; Panalgorin; ***India:*** Novalgin; ***Indon.:*** Antalgin; Antrain; Cornalgin; Foragin; Licogin; Norages; Novalgin; Panstop; Pragesol; Pyronal; Ronalgin; Scanalgin; Unagen; ***Israel:*** Novalgin; Optalgin; Phanalgin; V-Talgin; ***Ital.:*** Novalgina; ***Mex.:*** Alnex; Anaprol; Anapyrol; Apixol†; Avafontan; Avaldrian†; Ayoral Simple†; Carofrit†; Conmel; Dalmasin; Dalsin; Defin; Dimetirol; Dipydol; Dofisan; Dolgan; Dolizol; Dolofur; Domenal; Exalgin†; Exodalina; Fandall; Fardolpin; Farlin; Indigon; Lozima; Mach-2; Macodin; Magnil; Magnol; Magnolonas; Magnopyrol; Magsons; Mayoprina; Mecoten†; Medipirol; Mermid; Messelfenil; Metapirona; Midelin; Minoral; Mizoltec; Modimet; Neo-Melubrina; Neomelin; Neosedal; Paleodina; Pifrol; Piramagno†; Pirandall; Pirasod; Pirinovag; Piromebrina; Poloren†; Precidona; Prodolina; Prolubrin; Pyranol; Pyron; Suprin; Termonil; Utidol; Vegal; ***Neth.:*** Novalgin; ***Pol.:*** Pyrahexal; Pyralgin; Pyralginum; ***Port.:*** Conmel†; Dolocalma; Nolotil; Novalgina†; ***Rus.:*** Analgin (Анальгин); Baralgin M (Баралгин М); ***Spain:*** Algi; Citdolal†; Dolemicin; Lasain; Neo Melubrina; Nolotil; ***Switz.:*** Minalgine; Novalgine; ***Thai.:*** Acodon†; Centagin; Deparon; Genergin; Invoigin; Kno-Paine; Medalgin†; Mezabox; Nivagin; Novalgin; Olangin; ***Turk.:*** Adepiron; Andolor; Baralgin M; Devaljin; Feninox; Geralgine; Kafalgin; Nogesic; Novakom-S; Novalgin; Novo-Plan; Novopyrine; Sebon; Veraljin; ***Urug.:*** Dolanet; ***Venez.:*** Bral; Buscadol†; Combanal†; Combaron†; Conmel; Delsal; Dipamona; Dipidol; Klinomel†; Nimel†; Noval†; Novalcina; Piradro†; Piradrops Simple†; Promel; Rosadol†.

Multi-ingredient: ***Arg.:*** Antispasmina; Apasmo; Apasmo Compuesto; Artifene; Bellatotal; Buscapina Compositum; Calmopirin; Canovex†; Cifespasmo Compuesto; Colobolina D; Craun†; Cronopen Balsamico; D-P†; Dentolina Plus; Dextro + Dipirona; Dextrodip; Dioxadol; Dresan Biotic†; Dresan†; Espasmo Biotenk; Espasmo Dioxadol; Fadagrip; Febrimicina†; Flexicamin A; Gastrolina Compuesta; Gobbicalm; Integrobe Plus; Keptan Compuesto†; Klosidol; Klosidol B1 B6 B12; Lisalgil Compuesto; Luar-G Compositum; Migra Dioxadol; Migral; Migral Compositum; Multin; Novopasmil Compuesto; Paratropina Compuesta; Pasmodina Compuesta; Pasmosedan Compuesto†; Rupe-N Compuesto; Saldeva†; Solacil; Sumal; Tetralgin; Tetralgin Novo; Vicefeno; ***Austria:*** Buscopan Compositum; Spasmium comp; ***Belg.:*** Buscopan Compositum; ***Braz.:*** Algexin; Algice; Aminocid†; Analgin C-R; Analgosedan†; Analverin Composto†; Analverin†; Anapirol†; Baldin-CE†; Banidor†; Bicavine; Binospan; Bioscina Composta†; Bromalgina†; Broncopinol†; Buscopan Composto; Buscoveran Composto; Butilamin; Cafalena†; Cefaldina; Cefaliv; Codeverin†; Dalgex; Dexalgen; Dimex†; Dipirol†; Disbuspan; Doralgex; Doralgina; Dorciflex; Dorflex; Dorcin; Doridina; Dorilen; Doriless; Dorscopena†; Dorsedin; Dorspan; Dorzone; Ductopan†; Enxak; Espasmocron; Espasmodid Composto; Eucaliptan†; Flexalgex; Flexdor; Gripanil†; Gripion†; Gripomatine†; Griponia†; Gripsay; Hioariston; Hiospan Composto; Inib-Dor†; Itaiflex†; Killgrip†; Kindpasm; Lisador; Melpaz†; Migraliv; Migranette; Mionevrix; Miorrelax; Neocopan; Neomigran†; Neosaldina; Neuralgina; Nevralgex; Par; Pasmalgin†; Plenocedan†; Pulmorien†; Relaflex; Rielex; Sedabel†; Sedalene; Sedalex; Sedalgina; Sedalin; Sedol; Spasmotropin; Tensaldin; Tetrapulmo; Theopirina†; Tropinal; Uzara†; Veratropan Composto; ***Chile:*** Bramedil Compuesto; Buscapina Compositum; Cefalmin; Cinabel; Dioran†; Dolcopin; Dolnix; Dolo-Neurobionta†; Dolonase; Fredol; Migragesic; Migranol; Migratam; Neo Butartrol; Nospasmin Compuesto; Piretanyl; Scopanil; Silartrin†; Silrelax†; Sistalgina†; Ultrimin; Viadil Compuesto; Viplan Compuesto; Viproxil Compuesto; ***Cz.:*** Algifen; Algifen Neo; Analgin; Quarelin†; ***Fin.:*** Litalgin; ***Fr.:*** Avafortan†; Cefaline-Pyrazole†; Salgydal a la noramidopyrine†; Visceralgine Forte†; ***Hung.:*** Algopyrin Complex; Quarelin; Ridol†; ***Indon.:*** Analsik; Arsinal; Biomega; Cetalgin; Cetalgin-T; Corsanural; Dactron; Danalgin; Deparon; Dolo Scanneuron; Dolo-Licobion; Foraneural; Goralgin; Hedix; Ikaneuron Plus; Neuralgin RX; Neuro Panstop; Neurobat A; Neurodial; Neurogen; Neurosanbe Plus; Neurotropic Plus; Neuroval; Opineuron; Penagon; Pritagesic; Procolic; Proneuron; Spaslic; Spasmal; Spasminal; Stileran; Supranal; Tropineuron; Unthecol; ***Ital.:*** Soma Complex†; ***Mex.:*** Algosfar; Anadil; Ayoral†; Benfol; Biomesina Compuesta; Bipasmin Compuesto; Bipasmin Compuesto N; Buscapina Compositum; Busconet; Busepan; Busprina; Colepren; Dolnefort; Dolo-Tiaminal; Espasmogress; Hiosinotil Compuesto†; Hiosultrina-F; Korifen; Neo-Brontyl; Neo-Pasmonal; Ortran†; Pasmodil; Pirobutil; Respicil; Retodol Compositum; Selpiran; Serralpina Compuesta; Singril; ***Pol.:*** Gardan P; Scopolan Compositum; Spasmalgon; Tolargin; ***Rus.:*** Analgin-Chinin (Анальгин-Хинин); Antigrippin-ANVI (Антигриппин-АНВИ); Baralgetas (Баралгетас)†; Benalgin (Бенальгин);