Orphenadrine Citrate *(BANM, rINNM)*

Citrato de orfenadrina; Mephenamine Citrate; Orfenadriinisitraatti; Orfenadrincitrat; Orfenadrin-citrát; Orfenadrino citratas; Orphenadin Citrate; Orphénadrine, Citrate d'; Orphénadrine, citrate de; Orphenadrini citras. (*RS*)-Dimethyl[2-(2-methylbenzhydryloxy)ethyl]amine dihydrogen citrate.

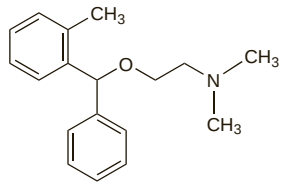
Орфенадрина Цитрат

$C_{18}H_{23}NO,C_6H_8O_7$ = 461.5.

CAS — 83-98-7 (orphenadrine); 4682-36-4 (orphenadrine citrate).

ATC — M03BC01.

ATC Vet — QM03BC01.



(orphenadrine)

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

Ph. Eur. 6.2 (Orphenadrine Citrate). A white or almost white crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. Protect from light.

USP 31 (Orphenadrine Citrate). A white, practically odourless, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; insoluble in chloroform, in ether, and in benzene. Store in airtight containers. Protect from light.

Orphenadrine Hydrochloride *(BANM, rINNM)*

BS-5930; Hidrocloruro de orfenadrina; Mephenamine Hydrochloride; Orfenadriinihydrokloridi; Orfenadrin-hidrokloridi; Orfenadrin-hydrochlorid; Orfenadrinhydroklorid; Orfenadrino hidrochloridas; Orphenadin Hydrochloride; Orphénadrine, Chlorhydrate d'; Orphénadrine, chlorhydrate de; Orphenadrini hydrochloridum. (*RS*)-Dimethyl[2-(2-methylbenzhydryloxy)ethyl]-amine hydrochloride.

Орфенадрина Гидрохлорид

$C_{18}H_{23}NO,HCl$ = 305.8.

CAS — 341-69-5.

ATC — N04AB02.

ATC Vet — QN04AB02.

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

Ph. Eur. 6.2 (Orphenadrine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in alcohol. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. Orphenadrine may cause insomnia.

Abuse. A 23-year-old schizophrenic man, whose treatment included orphenadrine 100 mg three times daily, obtained illicit supplies and increased the dose for euphoric effect.[1] On one occasion he had an epileptic convulsion after a 600-mg dose.

See also under Trihexyphenidyl Hydrochloride, p.820.

1. Shariatmadari ME. Orphenadrine dependence. *BMJ* 1975; **3:** 486.

Overdosage. A report[1] of acute poisoning with orphenadrine after massive overdosage in a schizophrenic patient, who responded to intensive supportive treatment, including large doses of adrenaline, dopamine, and dobutamine to restore blood pressure following asystole. Between 1977 and 1980 twelve deaths due to orphenadrine were recorded by the UK National Poisons Unit.

1. Clarke B, *et al*. Acute poisoning with orphenadrine. *Lancet* 1985; **i:** 1386.

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

Withdrawal. A suspected withdrawal syndrome was reported in a 56-year-old woman who showed slow neurological postoperative recovery after her orphenadrine treatment had been stopped abruptly;[1] her status improved when the drug was restarted.

1. Esler MD, *et al*. Postoperative orphenadrine withdrawal. *Br J Anaesth* 2000; **85:** 497.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220). Orphenadrine is an inhibitor of the cytochrome P450 isoenzyme CYP2B6, which is involved in the metabolism of bupropion to its major metabolite; licensed product information advises that orphenadrine should be used with caution in patients also receiving bupropion.

Chlorpromazine. For the effect of orphenadrine on plasma concentrations of chlorpromazine, see Antiparkinsonian Drugs, p.974.

Dextropropoxyphene. A suggested interaction between orphenadrine and dextropropoxyphene was open to question.[1,2]

1. Pearson RE, Salter FJ. Drug interaction? — orphenadrine with propoxyphene. *N Engl J Med* 1970; **282:** 1215.
2. Puckett WH, Visconti JA. Orphenadrine and propoxyphene (cont.). *N Engl J Med* 1970; **283:** 544.

Pharmacokinetics

Orphenadrine is readily absorbed from the gastrointestinal tract and after intramuscular injection. It is almost completely metabolised to at least 8 metabolites. It is mainly excreted in the urine as metabolites and small amounts of unchanged drug. The half-life of orphenadrine has been reported to be 14 hours (but see below).

Half-life. While the mean elimination half-life of orphenadrine in 5 healthy subjects given a single dose of the hydrochloride was found to be 15.5 hours, elimination half-lives of 30.5 and 40 hours were calculated in 2 patients given repeated oral doses.[1]

1. Labout JJM, *et al*. Difference between single and multiple dose pharmacokinetics of orphenadrine hydrochloride in man. *Eur J Clin Pharmacol* 1982; **21:** 343–50.

Uses and Administration

Orphenadrine, which is a congener of diphenhydramine (p.577) without sharing its soporific effect, is a tertiary amine antimuscarinic with actions and uses similar to those of trihexyphenidyl (p.820). It also has weak antihistaminic and local anaesthetic properties. Orphenadrine is used as the hydrochloride and the citrate; doses are expressed in terms of the relevant salt.

Orphenadrine is used as the hydrochloride in the symptomatic treatment of **parkinsonism** (p.791), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. The initial oral dose of orphenadrine hydrochloride is 150 mg daily in divided doses gradually increased by 50 mg every 2 or 3 days according to response; the usual maintenance dose is in the range of 150 to 300 mg daily, but some patients may require a total of up to 400 mg daily. Orphenadrine hydrochloride has also been given intramuscularly.

Orphenadrine is also used as the citrate to relieve pain due to **skeletal muscle spasm**. It is given orally in a dose of 100 mg twice daily or by intramuscular or slow intravenous injection in a dose of 60 mg which has been repeated every 12 hours.

Combinations of orphenadrine with an NSAID, usually diclofenac, or with paracetamol, have been used in the treatment of musculoskeletal and joint disorders.

Hiccup. Orphenadrine citrate has been used in some countries for the treatment of intractable hiccup. For the management of intractable hiccups see under Chlorpromazine, p.976.

Muscle and joint disorders. References to the use of orphenadrine in the management of leg cramps and other painful conditions associated with skeletal muscle spasm,[1,2] and with diclofenac in osteoarthritis and other musculoskeletal disorders.[3,4]

1. Latta D, Turner E. An alternative to quinine in nocturnal leg cramps. *Curr Ther Res* 1989; **45:** 833–7.
2. Hunskaar S, Donnell D. Clinical and pharmacological review of the efficacy of orphenadrine and its combination with paracetamol in painful conditions. *J Int Med Res* 1991; **19:** 71–87.
3. Uitz E, *et al*. Diclofenac/Orphenadrin-Infusionstherapie bei Patienten mit aktivierten Arthrosen. *Wien Med Wochenschr* 1998; **148:** 179–82.
4. Aglas F, *et al*. Ergebnisse einer Anwendungsbeobachtung mit Diclofenac/Orphenadrin-Infusionen bei Patienten mit muskuloskelettalen Krankheiten und Funktionsstorungen. *Acta Med Austriaca* 1998; **25:** 86–90.

Preparations

BP 2008: Orphenadrine Hydrochloride Tablets;
USP 31: Orphenadrine Citrate Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Norflex; ***Belg.:*** Disipal; ***Canad.:*** Norflex; ***Chile:*** Plenactol; ***Denm.:*** Disipal; Lysantin; Norflex†; ***Fin.:*** Norflex; ***Ger.:*** Norflex; ***Gr.:*** Disipal; Norflex; ***India:*** Orphipal; ***Israel:*** Flexin; ***Ital.:*** Disipal; ***Malaysia:*** Norflex; ***Mex.:*** Norflex; ***Norw.:*** Disipal†; ***NZ:*** Disipal; Norflex; ***Port.:*** Norflex†; ***S.Afr.:*** Disipal; Norflex; Phenerine; ***Swed.:*** Disipal†; Norflex; ***Thai.:*** Norflex; Orfenal†; ***UK:*** Biorphen; Disipal; ***USA:*** Banflex; Flexon; Norflex; ***Venez.:*** Norflex.

Multi-ingredient: ***Arg.:*** Belmalen; Doloctaprin Plus†; Flogodisten; Metaflex Plus†; Mio Aldoron; Mio-Virobron; ***Austral.:*** Norgesic; ***Austria:*** Neodolpasse; Norgesic; ***Braz.:*** Anapirol†; Banidor†; Dalgex; Doralgex; Dorciflex; Dorflex; Doricin; Dorzone; Flexalgex; Flexdor; Itaiflex†; Miorrelax; Nevralgex; Relaflex; Rielex; Sedalex; Theopirina†; ***Canad.:*** Norgesic; ***Chile:*** Norgesic; ***Cz.:*** Neodolpasse; ***Fin.:*** Dolan; Norgesic; ***Ger.:*** Norgesic N†; ***Gr.:*** Norgesic; ***Hong Kong:*** Norgesic; ***Hung.:*** Neodolpasse; ***Irl.:*** Norgesic†; ***Israel:*** Muscol; Norgesic; ***Malaysia:*** Anarex; Norgesic; Orphenadol; Suniton; ***Mex.:*** Norflex Plus; ***NZ:*** Norgesic; ***Philipp.:*** Norgesic; ***Port.:*** Norgesic†; ***S.Afr.:*** Besemax; Besenol; Norflex Co; ***Singapore:*** Anarex; Camgesic; Norgesic; Norphen; Orphenadol; ***Swed.:*** Norgesic; ***Thai.:*** Cenasic; Conlax†; Dorpane; Med-Myolax†; Medgesic; Muscol†; Myodrine; Myoflex; Myosic; Myospa; Nabesac; Neosec; Norgesic; Norgic; Norphen; Nuosic; Nurasic; Orano; Orflex; Orpar; Orphengesic; Parina; Poli-Relaxane; Polydol; Pormus; Relar; Rena; ***UAE:*** Muscadol; ***USA:*** Norgesic; Orphengesic; ***Venez.:*** Norgesic.

Pergolide Mesilate *(BANM, rINNM)*

LY-127809; Mesilato de pergolida; Pergolid Mesilat; Pergolid mesylát; Pergolide, mésilate de; Pergolide Mesylate *(USAN)*; Pergolidi mesilas; Pergolidimesilaatti; Pergolidmesilat; Pergolid-mezilát; Pergolido mesilatas. 8β-Methylthiomethyl-6-propylergoline methanesulphonate; Methyl (8*R*,10*R*)-6-propylergolin-8-ylmethyl sulphide methanesulphonate.

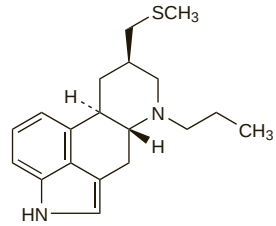
Перголида Мезилат

$C_{19}H_{26}N_2S,CH_4O_3S$ = 410.6.

CAS — 66104-22-1 (pergolide); 66104-23-2 (pergolide mesilate).

ATC — N04BC02.

ATC Vet — QN04BC02.



(pergolide)

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

Ph. Eur. 6.2 (Pergolide Mesilate). A white or almost white crystalline powder. Slightly soluble in water, in alcohol, and in dichloromethane; very slightly soluble in acetone; sparingly soluble in methyl alcohol. Protect from light.

USP 31 (Pergolide Mesylate). A white to off-white powder. Slightly soluble in water, in dehydrated alcohol, and in chloroform; very slightly soluble in acetone; practically insoluble in ether; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Bromocriptine, p.798.

An increased incidence of uterine neoplasms has been reported in *rodents* given high doses of pergolide mesilate.

Effects on mental function. For reports of daytime somnolence occurring in patients receiving dopamine agonists including pergolide, see under Adverse Effects of Levodopa, p.805.

Fibrosis. For reports of fibrotic reactions occurring in patients with Parkinson's disease receiving ergot derivative dopamine agonists including pergolide, see under Adverse Effects of Bromocriptine, p.799.

In Australia,[1] Canada,[2], and Europe[3] regulatory authorities recommended that patients undergo a cardiovascular evaluation before starting treatment with pergolide; periodic clinical monitoring for development of valvular disease or fibrosis is also recommended. Doses of pergolide above 3 mg daily are not recommended by the EMEA.[3] Furthermore, use is restricted to patients who are intolerant of, or who fail to respond to, non-ergot drug treatment and it is contra-indicated in patients with a history of fibrotic disorders or in those with anatomical evidence of cardiac valvulopathy.[4] In 2007, based on further evidence from 2 studies,[5,6] pergolide was withdrawn from the market in the USA[7] and Canada.[8]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Cardiac valvulopathy with pergolide. *Aust Adverse Drug React Bull* 2004; **23:** 14. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0408.pdf (accessed 16/02/06)