Dextropropoxyphene *(BAN, pINN)*

Dekstropropoksifeeni; Dextropropoxifen; Dextropropoxifeno; Dextropropoxyphène; Dextropropoxyphenum; Propoxyphene. (+)-(1*S*,2*R*)-1-Benzyl-3-dimethylamino-2-methyl-1-phenylpropyl propionate.

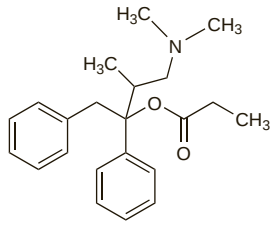
Декстропропоксифен

$C_{22}H_{29}NO_2$ = 339.5.

CAS — 469-62-5.

ATC — N02AC04.

ATC Vet — QN02AC04.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of dextropropoxyphene: Dummies.

Dextropropoxyphene Hydrochloride

(BANM, pINNM)

Dekstropropoksifeenihydrokloridi; Dekstropropoksifeno hidrochloridas; Dextropropoxifén-hidroklorid; Dextropropoxifenhydroklorid; Dextropropoxyfen-hydrochlorid; Dextropropoxyphène, chlorhydrate de; Dextropropoxypheni hydrochloridum; Hidrocloruro de dextropropoxifeno; Propoxyphene Hydrochloride *(USAN)*.

Декстропропоксифена Гидрохлорид

$C_{22}H_{29}NO_2$,HCl = 375.9.

CAS — 1639-60-7.

NOTE. Compounded preparations of dextropropoxyphene hydrochloride may be represented by the following names:

- Co-proxamol (*BAN*)—dextropropoxyphene hydrochloride 1 part and paracetamol 10 parts (w/w).

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

Ph. Eur. 6.2 (Dextropropoxyphene Hydrochloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol. Protect from light.

USP 31 (Propoxyphene Hydrochloride). A white odourless crystalline powder. Freely soluble in water; soluble in alcohol, in acetone, and in chloroform; practically insoluble in ether and in benzene. Store in airtight containers.

Dextropropoxyphene Napsilate *(BANM, pINNM)*

Dextropropoxyphène, Napsilate de; Dextropropoxyphene Napsylate; Dextropropoxypheni Napsilas; Napsilato de dextropropoxifeno; Propoxyphene Napsylate *(USAN)*. Dextropropoxyphene naphthalene-2-sulphonate monohydrate.

Декстропропоксифена Напсилат

$C_{22}H_{29}NO_2$,$C_{10}H_8O_3S$,H_2O = 565.7.

CAS — 17140-78-2 (anhydrous dextropropoxyphene napsilate); 26570-10-5 (dextropropoxyphene napsilate monohydrate).

NOTE. Compounded preparations of dextropropoxyphene napsilate may be represented by the following names:

- Co-proxAPAP (*PEN*)—dextropropoxyphene napsilate and paracetamol.

Pharmacopoeias. In *Br.* and *US*.

BP 2008 (Dextropropoxyphene Napsilate). An odourless or almost odourless white powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in chloroform.

USP 31 (Propoxyphene Napsylate). A white powder having essentially no odour. Very slightly soluble in water; soluble 1 in 15 of alcohol and 1 in 10 of chloroform; soluble in acetone and in methyl alcohol. Store in airtight containers.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Dextropropoxyphene has been subject to abuse (see under Precautions, below).

◊ Reports of dextropropoxyphene dependence and its treatment.

1. Wall R, *et al.* Addiction to Distalgesic (dextropropoxyphene). *BMJ* 1980; **280:** 1213–14.
2. D'Abadie NB, Lenton JD. Propoxyphene dependence: problems in management. *South Med J* 1984; **77:** 299–301.

Adverse Effects

As for Opioid Analgesics in general, p.102.

In the recommended dosage the adverse effects of dextropropoxyphene are less marked than those of morphine. Gastrointestinal effects, dizziness, and drowsiness are the most common. Liver impairment, manifest as abnormal liver function tests and, more rarely, as reversible jaundice, has been reported.

There have been a large number of fatalities from either accidental or intentional overdosage with dextropropoxyphene. Many reports emphasise the rapidity with which death ensues; death within an hour of overdosage is not uncommon, and it can occur within 15 minutes. Overdosage is often complicated by patients also taking other CNS depressants such as alcohol and using mixed preparations such as dextropropoxyphene with paracetamol or aspirin.

Symptoms of overdosage are similar to those of opioid poisoning in general, but in addition patients may experience psychotic reactions. There may be cardiac conduction abnormalities and arrhythmias.

Dextropropoxyphene injections are painful and have a very destructive effect on soft tissues and veins when abused in this way.

Anorectal reactions have followed the prolonged use of suppositories containing dextropropoxyphene; the reactions appear to be dose dependent.

Effects on the blood. A 12-year history of haemolysis and subsequent significant haemolytic anaemia in an elderly woman[1] was associated with chronic, periodic, and occasionally excessive intake of co-proxamol.

1. Fulton JD, McGonigal G. Steroid responsive haemolytic anaemia due to dextropropoxyphene paracetamol combination. *J R Soc Med* 1989; **82:** 228.

Effects on the ears. A report of complete nerve deafness associated with chronic abuse of co-proxamol was made to the UK CSM.[1] The CSM had received 2 other reports of permanent hearing loss attributed to co-proxamol abuse; transient hearing loss had also been reported in 2 patients taking usual doses; 7 further reports described tinnitus.

1. Ramsay BC. Complete nerve deafness after abuse of co-proxamol. *Lancet* 1991; **338:** 446–7.

Effects on the liver. There have been occasional reports of jaundice in patients taking dextropropoxyphene alone but many of the 49 suspected hepatic reactions with dextropropoxyphene reported to the UK CSM by 1985[1] had involved use with paracetamol; clinical features including malaise, jaundice, raised serum transaminases, and sometimes fever, were however generally characteristic of dextropropoxyphene alone. Relapsing jaundice mimicking biliary disease was attributable to the dextropropoxyphene component of co-proxamol in 3 patients,[2] whereas there was no abnormality of liver function in 11 patients on long-term co-proxamol analgesia.[3] Another report of 9 cases found that the hepatotoxicity of dextropropoxyphene mimicked symptoms of large bile duct obstruction, and suggested that such toxicity might be misdiagnosed.[4] A more recent review[5] also concluded that hepatotoxicity with dextropropoxyphene might mimic a biliary tract disease, sometimes with few or no symptoms.

1. CSM. Hepatotoxicity with dextropropoxyphene. *Current Problems 17* 1986. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024424&RevisionSelectionMethod=LatestReleased (accessed 26/06/08)
2. Bassendine MF, *et al.* Dextropropoxyphene induced hepatotoxicity mimicking biliary tract disease. *Gut* 1986; **27:** 444–9.
3. Hutchinson DR, *et al.* Liver function in patients on long-term paracetamol (co-proxamol) analgesia. *J Pharm Pharmacol* 1986; **38:** 242–3.
4. Rosenberg WMC, *et al.* Dextropropoxyphene induced hepatotoxicity: a report of nine cases. *J Hepatol* 1993; **19:** 470–4.
5. Bergeron L, *et al.* Dextropropoxyphène et atteintes hépatiques: à propos de 4 cas et revue de littèrature. *Therapie* 2002; **57:** 464–72.

Effects on the lungs. Hypersensitivity pneumonitis and skin rash has been reported in a patient taking co-proxamol.[1] No such reaction occurred when the patient was subsequently given paracetamol alone.

1. Matusiewicz SP, *et al.* Hypersensitivity pneumonitis associated with co-proxamol (paracetamol + dextropropoxyphene) therapy. *Postgrad Med J* 1999; **75:** 475–6.

Hypoglycaemia. Hypoglycaemia has occasionally been reported with the use of dextropropoxyphene.[1-6]

1. Wiederholt IC, *et al.* Recurrent episodes of hypoglycemia induced by propoxyphene. *Neurology* 1967; **17:** 703–4.
2. Almirall J, *et al.* Propoxyphene-induced hypoglycemia in a patient with chronic renal failure. *Nephron* 1989; **53:** 273–5.
3. Laurent M, *et al.* Hypoglycémie sous dextropropoxyphène chez des grands vieillards: 7 cas. *Presse Med* 1991; **20:** 1628.
4. Lowenstein W, *et al.* Hypoglycémie au dextropropoxyphène: une urgence chez le toxicomane. *Presse Med* 1993; **22:** 133.
5. Santos Gil I, *et al.* Hipoglucemia secundaria a ingestión de dextropropoxifeno en un paciente adicto a drogas. *Med Clin (Barc)* 1998; **110:** 475–6.
6. Shah P, *et al.* Propoxyphene-induced hypoglycemia in renal failure. *Endocr Pract* 2006; **12:** 170–3.

Overdosage. There have been several reviews or retrospective studies of acute self-poisoning with dextropropoxyphene.[1-4] At a symposium on the safety and efficacy of dextropropoxyphene[5] many of the participants dealt with the problems of dextropropoxyphene overdosage, often in conjunction with paracetamol and sometimes with alcohol. Profound and even fatal CNS depression can develop rapidly as a result of the dextropropoxyphene content and in many cases death has occurred within an hour;[6] it was suggested that as few as 15 to 20 tablets of co-proxamol may be fatal.[7,8] Analysis of suicides involving drugs in England and Wales between 1997 and 1999 revealed that the odds of dying after overdose with co-proxamol were 2.3 times that for tricyclic antidepressant overdose, and 28.1 times greater than for paracetamol.[9] Another analysis of suicides due to poisoning in 3 areas of the UK between 2000 and 2001 identified 123 cases of fatal overdose with co-proxamol;[10] those who also consumed alcohol had generally taken fewer co-proxamol tablets than those who had not, emphasising the increased toxicity of the combination.

An analysis of overdosage involving combination analgesic preparations prescribed in Scotland between 2000 and 2002 also found that overdoses with co-proxamol were 10 times more likely to be fatal when compared with co-dydramol or co-codamol.[11] In the USA[12] the incidence of dextropropoxyphene-associated deaths reached a peak in 1977 and then fell at a rate that was not matched by a decline in prescribing.

It is not clear whether the metabolite, nordextropropoxyphene, plays an important role in fatalities.[12] However, nordextropropoxyphene, like dextropropoxyphene, is considered to have local anaesthetic activity and the membrane stabilising activity of dextropropoxyphene has been implicated as a major factor responsible for its severe cardiac depressant effect.[13]

In January 2005, the UK CSM found the risk of toxicity of co-proxamol in overdose to be unacceptable;[14] consequently, co-proxamol has been gradually withdrawn from the UK market. Fixed-dose combinations of dextropropoxyphene and paracetamol have also been withdrawn in several other countries including Sweden and Switzerland.

1. Young RJ. Dextropropoxyphene overdosage: pharmacological considerations and clinical management. *Drugs* 1983; **26:** 70–9.
2. Madsen PS, *et al.* Acute propoxyphene self-poisoning in 222 consecutive patients. *Acta Anaesthesiol Scand* 1984; **28:** 661–5.
3. Segest E. Poisoning with dextropropoxyphene in Denmark. *Hum Toxicol* 1987; **6:** 203–7.
4. Jonasson U, *et al.* Correlation between prescription of various dextropropoxyphene preparations and their involvement in fatal poisonings. *Forensic Sci Int* 1999; **103:** 125–32.
5. Bowen D, *et al.* (ed). Distalgesic; safety and efficacy. *Hum Toxicol* 1984; **3** (suppl): 1S–238S.
6. Proudfoot AT. Clinical features and management of Distalgesic overdose. *Hum Toxicol* 1984; **3** (suppl): 85S–94S.
7. Whittington RM. Dextropropoxyphene deaths: coroner's report. *Hum Toxicol* 1984; **3** (suppl): 175S–185S.
8. Young RJ, Lawson AAH. Distalgesic poisoning—cause for concern. *BMJ* 1980; **280:** 1045–7.
9. Hawton K, *et al.* Co-proxamol and suicide: a study of national mortality statistics and local non-fatal self-poisonings. *BMJ* 2003; **326:** 1006–8.
10. Hawton K, *et al.* A multicentre study of coproxamol poisoning suicides based on coroners' records in England. *Br J Clin Pharmacol* 2005; **59:** 207–12.
11. Afshari R, *et al.* Co-proxamol overdose is associated with a 10-fold excess mortality compared with other paracetamol combination analgesics. *Br J Clin Pharmacol* 2005; **60:** 444–7.
12. Finkle BS. Self-poisoning with dextropropoxyphene and dextropropoxyphene compounds: the USA experience. *Hum Toxicol* 1984; **3** (suppl): 115S–34S.
13. Henry JA, Cassidy SL. Membrane stabilising activity: a major cause of fatal poisoning. *Lancet* 1986; **i:** 1414–17.
14. MHRA. Withdrawal of co-proxamol products and interim updated prescribing information. Message from Professor G Duff, Chairman of CSM (issued 31st January, 2005). Available at: http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con019461.pdf (accessed 28/08/08)

Treatment of Adverse Effects

As for Opioid Analgesics in general, p.102.

Rapid treatment of overdosage with naloxone and assisted respiration is essential. Cardiac effects may not be reversed by naloxone. Gastric lavage and activated charcoal may be of value within 1 hour of ingestion, but dialysis is of little use.

Convulsions may require control with an anticonvulsant, bearing in mind that the CNS depressant effects of dextropropoxyphene can be exacerbated (see also Interactions, below). Stimulants should not be used because of the risk of inducing convulsions.

Patients taking overdoses of dextropropoxyphene with paracetamol will also require treatment for paracetamol poisoning (p.108). Mixtures of dextropropoxyphene and aspirin may be involved; the treatment of aspirin poisoning is described on p.20.