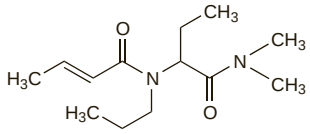
Cropropamide *(BAN, pINN)* ⊗

Cropropamida; Cropropamidum; Kropropamid; Kropropamidi. *N,N*-Dimethyl-2-(*N*-propylcrotonamido)butyramide.

Кропропамид

$C_{13}H_{24}N_2O_2$ = 240.3.

CAS — 633-47-6.



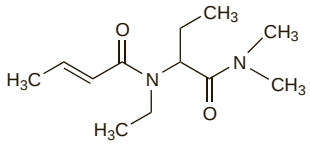
Crotetamide *(BAN, rINN)* ⊗

Crotetamida; Crotétamide; Crotetamidum; Crotethamide. 2-(*N*-Ethylcrotonamido)-*N,N*-dimethylbutyramide.

Кротетамид

$C_{12}H_{22}N_2O_2$ = 226.3.

CAS — 6168-76-9.



Profile

Prethcamide, a mixture of equal parts by weight of cropropamide and crotetamide, has actions similar to those of doxapram (p.2155) and has been used as a respiratory stimulant. Oral doses of 100 mg have been given three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Micoren.

Prolintane Hydrochloride *(BANM, USAN, rINNM)* ⊗

Hidrocloruro de prolintano; Prolintane, Chlorhydrate de; Prolintani Hydrochloridum; SP-732. 1-(α-Propylphenethyl)pyrrolidine hydrochloride.

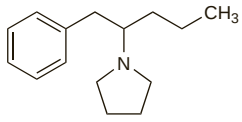
Пролинтана Гидрохлорид

$C_{15}H_{23}N,HCl$ = 253.8.

CAS — 493-92-5 (prolintane); 1211-28-5 (prolintane hydrochloride).

ATC — N06BX14.

ATC Vet — QN06BX14.



(prolintane)

Profile

Prolintane hydrochloride is a mild central stimulant and has properties similar to those of dexamfetamine (p.2153). It has been available mainly in tonic preparations that also contained vitamin supplements. It has also been used in narcolepsy.

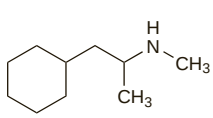
Propylhexedrine *(BAN, rINN)* ⊗

Hexahydrodesoxyephedrine; Propilhexedrina; Propylhexed; Propylhexédrine; Propylhexedrinum. 2-Cyclohexyl-1-methylethyl-(methyl)amine; (±)-*N*-α-Dimethylcyclo-hexaneethylamine.

Пропилгекседрин

$C_{10}H_{21}N$ = 155.3.

CAS — 101-40-6; 3595-11-7 ((±)-propylhexedrine).



Pharmacopoeias. In *US*.

USP 31 (Propylhexedrine). A clear colourless liquid having a characteristic amine-like odour. It slowly volatilises at room temperature and absorbs carbon dioxide from the air. Very slightly soluble in water; soluble 1 in 0.4 of alcohol, 1 in 0.2 of chloroform, and 1 in 0.1 of ether. Its solutions are alkaline to litmus. Store in airtight containers.

Propylhexedrine Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de propilhexedrina; Propylhexédrine, Chlorhydrate de; Propylhexedrini Hydrochloridum.

Пропилгекседрина Гидрохлорид

$C_{10}H_{21}N,HCl$ = 191.7.

CAS — 1007-33-6; 6192-95-6 ((±)-propylhexedrine hydrochloride).

Adverse Effects, Treatment and Precautions

As for Dexamfetamine Sulfate, p.2153.

Nasal inhalation may cause transient burning, stinging, mucosal dryness, and sneezing. Prolonged use can cause rebound congestion, redness, swelling, and rhinitis. Systemic effects such as headache, hypertension, nervousness, and increased heart rate may occur.

Propylhexedrine is subject to abuse by mouth or intravenously; fatalities due to myocardial infarction, heart failure, or pulmonary hypertension have been reported. Psychosis may occur.

Abuse. References.

1. White L, DiMaio VJM. Intravenous propylhexedrine and sudden death. *N Engl J Med* 1977; **297:** 1071.
2. Anderson RJ, *et al.* Intravenous propylhexedrine (Benzedrex) abuse and sudden death. *Am J Med* 1979; **67:** 15–20.
3. Cameron J, *et al.* Possible association of pulmonary hypertension with an anorectic drug. *Med J Aust* 1984; **140:** 595–7.

Uses and Administration

Propylhexedrine is a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine (p.2154). It has been used as an inhalant for nasal decongestion (p.1548).

Propylhexedrine hydrochloride has been given orally as an anorectic in the treatment of obesity (p.2149) but stimulants are no longer recommended for this indication. The (–)-isomer, levopropylhexedrine hydrochloride, has been used similarly.

Preparations

USP 31: Propylhexedrine Inhalant.

Proprietary Preparations (details are given in Part 3)
USA: Benzedrex.

Multi-ingredient: *S.Afr.:* Reducealin†.

Sibutramine Hydrochloride *(BANM, USAN, rINNM)* ⊗

BTS-54524; Hidrocloruro de sibutramina; Sibutramin Hidroklorür; Sibutramine, Chlorhydrate de; Sibutramini Hydrochloridum. (±)-1-(*p*-Chlorophenyl)-α-isobutyl-*N,N*-dimethylcyclobutanemethylamine hydrochloride monohydrate.

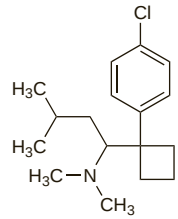
Сибутрамина Гидрохлорид

$C_{17}H_{26}ClN,HCl,H_2O$ = 334.3.

CAS — 106650-56-0 (sibutramine); 84485-00-7 (anhydrous sibutramine hydrochloride); 125494-59-9 (sibutramine hydrochloride monohydrate).

ATC — A08AA10.

ATC Vet — QA08AA10.



(sibutramine)

Adverse Effects

Commonly reported adverse effects of sibutramine are dry mouth, headache, insomnia, and constipation. Diarrhoea, back pain, increased appetite, dizziness, flu-like symptoms, and rhinitis have also occurred. Less frequently reported adverse effects include dyspepsia, nausea, dysmenorrhoea, increased sweating and thirst, oedema, paraesthesia, skin rashes, taste perversion, palpitations, vasodilatation, anxiety, nervousness, drowsiness, and depression. Abnormal bleeding including Henoch-Schönlein purpura and thrombocytopenia, acute interstitial nephritis, glomerulonephritis, emotional lability, seizures, and blurred vision have been reported rarely. Clinically significant increases in heart rate and blood pressure may occur. Sibutramine may decrease salivary flow and therefore increase the risk of dental caries, periodontal disease, or other oral disorders. It may also produce mydriasis. Reversible increases in liver enzymes have been reported.

Precautions

Sibutramine should be avoided in patients with a history of eating disorders such as anorexia nervosa and bulimia nervosa. It is also contra-indicated in patients with uncontrolled or poorly controlled hypertension and should be used with caution in patients with a history of, or with, well-controlled hypertension. Blood pressure and heart rate should be monitored (see below for details). In the event of sustained elevations, the dose should be reduced or treatment discontinued.

Sibutramine should not be used in patients with a history of cerebrovascular disease or cardiovascular disorders such as cardiac arrhythmias, heart failure, peripheral arterial occlusive disease, and coronary artery disease. It should be avoided in patients with severe hepatic or renal impairment; caution has been advised when using sibutramine in those with mild to moderate renal impairment. Sibutramine should also not be used in patients with bipolar disorder, Tourette's syndrome, hyperthyroidism, phaeochromocytoma, benign prostatic hyperplasia, or a history of drug or alcohol abuse. It should be used with caution, if at all, in patients with glaucoma. Sibutramine should also be used with caution in patients with a history of depression, seizures or gallstones (which may be precipitated or exacerbated by weight loss), or a family history of motor or verbal tics.

Any centrally-acting drug such as sibutramine may impair the ability to perform tasks requiring judgement or motor or cognitive skills; if affected, patients should not drive or operate machinery.

Bleeding disorders. Because other drugs that inhibit reuptake of serotonin have occasionally been associated with bleeding disorders and other effects on the blood (see under Fluoxetine, p.392) UK licensed product information for sibutramine recommends that it should be used with caution in patients predisposed to bleeding disorders and in those taking other drugs known to affect haemostasis or platelet function.

Cardiovascular monitoring. Sibutramine may cause clinically significant increases in blood pressure and heart rate and monitoring is recommended in the product information for all patients during treatment. In the first 3 months, blood pressure and heart rate should be checked every 2 weeks; this may be reduced to every month for the next 3 months, and at least every 3 months thereafter. Treatment should be stopped if resting heart rate increases by 10 beats/minute or more, or blood pressure by 10 mmHg or more, at two consecutive visits. In patients with previously well-controlled hypertension, treatment should be stopped if their blood pressure exceeds 145/90 mmHg at two consecutive visits.

Interactions

Sibutramine should not be given with, or within at least 2 weeks of stopping an MAOI; at least 2 weeks should elapse between discontinuation of sibutramine and starting therapy with an MAOI. There is a risk of the serotonin syndrome (p.416) developing if sibutramine is used with other serotonergic drugs such as SSRIs, sumatriptan, lithium, pethidine, fentanyl, dextromethorphan, and pentazocine. Caution is advised when sibutramine is given with other drugs that may increase heart rate or blood pressure such as ephedrine, phenylpropanolamine, and pseudoephedrine. It should not be used with other centrally acting anorectics. Alcohol should be avoided.

Inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole and erythromycin, may increase plasma concentrations of sibutramine. Conversely, inducers of this isoenzyme, such as rifampicin, phenytoin, carbamazepine, and phenobarbital, may reduce plasma concentrations of sibutramine.

Antibacterials. A study in 12 obese subjects indicated that addition of *erythromycin* to sibutramine therapy resulted in little significant alteration in sibutramine pharmacokinetics beyond a modest increase in maximum plasma concentration of one of the active metabolites.[1] A small increase in the QT interval was not considered clinically meaningful.

1. Hinson JL, *et al.* Steady-state interaction study of sibutramine (Meridia™) and erythromycin in uncomplicated obese subjects. *Pharm Res* 1996; **13** (suppl): S116.

Antifungals. A study in 12 obese subjects given sibutramine found that *ketoconazole* moderately increased steady-state plasma concentrations of sibutramine and its active metabolites.[1] There was a significant increase in heart rate but no clinically relevant change in the QT interval.

1. Hinson JL, *et al.* Steady-state interaction study of sibutramine (Meridia™) and ketoconazole in uncomplicated obese subjects. *Pharm Res* 1996; **13** (suppl): S116.

Pharmacokinetics

Sibutramine is well absorbed from the gastrointestinal tract; peak plasma concentrations appear after 1.2 hours (parent drug) and 3 to 4 hours (metabolites). It undergoes extensive first-pass hepatic metabolism, mediated mainly by the cytochrome P450 isoenzyme CYP3A4. Demethylation produces mono- and di-desmethylsibutramine (both of which are pharmacologically active) and is followed by hydroxylation and conjugation to inactive metabolites. Protein binding is 97%. Plasma-elimination half-life is 14 to 16 hours. Elimination is mainly in the urine as inactive metabolites, and partly in the faeces.

◊ References.

1. Hind ID, *et al.* Sibutramine pharmacokinetics in young and elderly healthy subjects. *Eur J Clin Pharmacol* 1999; **54:** 847–9.