Moxisylyte is given as the hydrochloride but the dose may be expressed in terms of the base. Moxisylyte hydrochloride 45.2 mg is equivalent to about 40 mg of moxisylyte.

In the management of **peripheral vascular disease**, the usual oral dose is the equivalent of 40 mg of moxisylyte four times daily increased if necessary to 80 mg four times daily. It should be withdrawn if there is no response in 2 weeks.

Moxisylyte has been used locally in the eye to reverse the mydriasis caused by phenylephrine and other sympathomimetics. It has also been used orally in benign prostatic hyperplasia, although such use has been associated with hepatotoxicity; the doses used in prostatic hyperplasia were generally higher than those in peripheral vascular disease.

◊ Reviews.

1. Marquer C, Bressolle F. Moxisylyte: a review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in impotence. *Fundam Clin Pharmacol* 1998; **12:** 377–87.

Preparations

BP 2008: Moxisylyte Tablets.

Proprietary Preparations (details are given in Part 3)
Fr.: Carlytene; Icavex†; ***Irl.:*** Opilon; ***Port.:*** Arlitene†; ***UK:*** Opilon.

Moxonidine *(BAN, USAN, rINN)*

BDF-5895; BDF-5896; BE-5895; LY-326869; Moksonidi; Moksonidiini; Moksonidin; Moksonidinas; Moxonid; Moxonidin; Moxonidina; Moxonidinum; Moxonidum. 4-Chloro-5-(2-imidazolin-2-ylamino)-6-methoxy-2-methylpyrimidine.

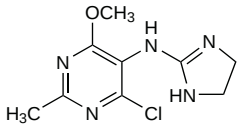
Моксонидин

$C_9H_{12}ClN_5O$ = 241.7.

CAS — 75438-57-2.

ATC — C02AC05.

ATC Vet — QC02AC05.



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

Ph. Eur. 6.2 (Moxonidine). A white or almost white powder. Very slightly soluble in water and in acetonitrile; slightly soluble in dichloromethane; sparingly soluble in methyl alcohol.

Adverse Effects and Treatment

Moxonidine has similar adverse effects to clonidine (p.1247) but causes less sedation. The incidence of dry mouth may also be lower.

Precautions

Moxonidine should not be used in patients with conduction disorders, bradycardia, severe arrhythmias, severe heart failure, severe ischaemic heart disease, severe hepatic or renal impairment, or a history of angioedema. Licensed product information suggests that it should also be avoided in patients with intermittent claudication or Raynaud's disease, Parkinson's disease, epilepsy, glaucoma, and depression. Moxonidine is distributed into breast milk and should not be used during breast feeding.

Although rebound hypertension has not been reported after moxonidine withdrawal it should not be stopped abruptly but should be withdrawn gradually over 2 weeks. As for clonidine (p.1247), if patients are also receiving a beta blocker, this should be stopped several days before moxonidine is withdrawn.

Interactions

The hypotensive effect of moxonidine may be enhanced by other antihypertensives and drugs that cause hypotension. The effect of sedatives and hypnotics, including benzodiazepines, may be enhanced by moxonidine.

Pharmacokinetics

Moxonidine is well absorbed when given orally and has a bioavailability of about 88%. Peak plasma concentrations occur 0.5 to 3 hours after an oral dose. It is excreted almost entirely in the urine as unchanged drug and metabolites; about 50 to 75% of an oral dose is excreted as unchanged drug. The mean plasma elimination half-life is 2 to 3 hours and is prolonged in renal impairment. Moxonidine is about 7% bound to plasma proteins. It is distributed into breast milk.

Uses and Administration

Moxonidine is a centrally acting antihypertensive structurally related to clonidine (p.1247). It appears to act through stimulation of central imidazoline receptors to reduce sympathetic tone, and also has $alpha_2$-adrenoceptor agonist activity. It is used in the treatment of hypertension (p.1171) and has also been investigated for heart failure (but see below).

In the treatment of hypertension, moxonidine is given orally in a usual initial dose of 200 micrograms once daily. The dose may be increased if necessary, after 3 weeks, to 400 micrograms daily as a single dose or in 2 divided doses, and after a further 3 weeks, to a maximum dose of 600 micrograms daily in 2 divided doses. The dose should be reduced in patients with renal impairment (see below).

◊ References.

1. Chrisp P, Faulds D. Moxonidine: a review of its pharmacology, and therapeutic use in essential hypertension. *Drugs* 1992; **44:** 993–1012.
2. Schachter M, *et al.* Safety and tolerability of moxonidine in the treatment of hypertension. *Drug Safety* 1998; **19:** 191–203.
3. Bousquet P, Feldman J. Drugs acting on imidazoline receptors: a review of their pharmacology, their use in blood pressure control and their potential interest in cardioprotection. *Drugs* 1999; **58:** 799–812.
4. Schachter M. Moxonidine. *Prescribers' J* 1999; **39:** 113–17.
5. Fenton C, *et al.* Moxonidine: a review of its use in essential hypertension. *Drugs* 2006; **66:** 477–96.

Administration in renal impairment. UK licensed product information states that in patients with moderate renal impairment (GFR 30 to 60 mL/minute) single doses of moxonidine should not exceed 200 micrograms and the daily dose should not exceed 400 micrograms; moxonidine should not be given in severe impairment (GFR less than 30 mL/minute).

Heart failure. Heart failure is usually treated with diuretics, ACE inhibitors, and beta blockers (see p.1165). Beta blockers are thought to act by suppressing the sympathetic nervous system, which is activated in heart failure. Centrally-acting antihypertensives such as moxonidine also suppress sympathetic activation and might therefore have a role in heart failure. A study[1] in patients with heart failure found that moxonidine reduced plasma-noradrenaline concentrations and increased left ventricular ejection fraction, but also led to an increase in adverse effects. A further study[2] was stopped early due to increased mortality in the group receiving moxonidine.

1. Swedberg K, *et al.* Effects of sustained-release moxonidine, an imidazoline agonist, on plasma norepinephrine in patients with chronic heart failure. *Circulation* 2002; **105:** 1797–1803.
2. Cohn JN, *et al.* Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON). *Eur J Heart Fail* 2003; **5:** 659–67.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Physiotens; ***Austria:*** Monox; Moxin; Normoxin; ***Belg.:*** Gilutens†; Moxon; ***Braz.:*** Cynt; ***Cz.:*** Cynt; Moxogamma; Moxostad; Physiotens; ***Denm.:*** Moxonat; Physiotens; ***Fin.:*** Physiotens; ***Fr.:*** Physiotens; ***Ger.:*** Cynt; Moxobeta; Moxocard; moxodura; Moxogamma; Physiotens; ***Gr.:*** Cynt; Fisiotens; ***Hong Kong:*** Physiotens; ***Hung.:*** Cynt; Moxogamma; Moxostad; Physiotens; ***Indon.:*** Physiotens; ***Ital.:*** Fisiotens; ***Malaysia:*** Physiotens; ***Neth.:*** Moxamar; Moxaviv; Moxoham; Moxonur; Moxotel; Moxovasc; Normatens; Ratiomox; ***Norw.:*** Physiotens; ***Philipp.:*** Physiotens; ***Pol.:*** Moxogamma; Physiotens; ***Port.:*** Moxon; ***Rus.:*** Cynt (Цинт)†; Physiotens (Физиотенз); ***S.Afr.:*** Physiotens; ***Singapore:*** Physiotens†; ***Spain:*** Moxon; ***Swed.:*** Physiotens; ***Switz.:*** Physiotens; ***Turk.:*** Cynt; ***UK:*** Physiotens.

Nadolol *(BAN, USAN, rINN)* ⊗

Nadololi; Nadololis; Nadololum; SQ-11725. (2*R*,3*S*)-5-(3-*tert*-Butylamino-2-hydroxypropoxy)-1,2,3,4-tetrahydronaphthalene-2,3-diol.

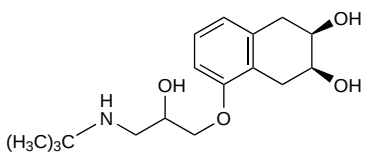
Надолол

$C_{17}H_{27}NO_4$ = 309.4.

CAS — 42200-33-9.

ATC — C07AA12.

ATC Vet — QC07AA12.



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

Ph. Eur. 6.2 (Nadolol). A white or almost white crystalline powder. Slightly soluble in water; freely soluble in alcohol; practically insoluble in acetone.

USP 31 (Nadolol). A white or off-white, practically odourless, crystalline powder. Soluble in water at pH 2; slightly soluble in water at pH 7 to 10; freely soluble in alcohol and in methyl alcohol; insoluble in acetone, in ether, in petroleum spirit, in trichloroethane, and in benzene; slightly soluble in chloroform, in dichloromethane, and in isopropyl alcohol.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Breast feeding. Nadolol is distributed into breast milk and concentrations in milk are higher than those in maternal plasma. In a study[1] in 12 normotensive women given nadolol 80 mg daily by mouth for 5 days, the mean nadolol concentration in milk for the 24 hours after the last dose was 357 nanograms/mL; the equivalent mean serum-nadolol concentration was only 77 nanograms/mL. It was calculated that a 5-kg infant would therefore ingest about 2 to 7% of an equivalent adult dose. No adverse effects have been seen in breast-fed infants whose mothers were given nadolol and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Devlin RG, *et al.* Nadolol in human serum and breast milk. *Br J Clin Pharmacol* 1981; **12:** 393–6.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Hypersensitivity. Hypersensitivity pneumonitis was associated with nadolol in a patient given the drug for migraine.[1] Symptoms improved when nadolol was withdrawn.

1. Levy MB, *et al.* Nadolol and hypersensitivity pneumonitis. *Ann Intern Med* 1986; **105:** 806–7.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Nadolol is incompletely absorbed from the gastrointestinal tract to give peak plasma concentrations about 3 or 4 hours after a dose. It has low lipid solubility. Nadolol is widely distributed and concentrations found in breast milk have been higher than those in serum. It is only about 30% bound to plasma proteins. It does not appear to be metabolised and is excreted mainly in the urine. The plasma half-life has been reported as ranging from about 12 to 24 hours. Nadolol is reported to be dialysable.

◊ In 4 patients with mild hypertension given nadolol 2 mg orally or intravenously, the elimination half-life from plasma was an average of 10 to 12 hours (a range of 5.9 to 12.2 hours after intravenous doses, and a range of 9.6 to 14.2 hours after oral doses). Calculations based on urinary excretion and plasma concentration data suggested that about 33% was absorbed after oral dosage. There was evidence of biliary as well as urinary excretion since after intravenous dosage about 73% was excreted in urine and 23% in faeces. Nadolol did not appear to be metabolised.[1] In a similar study of therapeutic oral doses, terminal half-lives ranging from 14 to 17 hours were reported for nadolol 80 mg given as a single dose and the same dose daily in a multiple dosage regimen.[2]

1. Dreyfuss J, *et al.* Metabolic studies in patients with nadolol: oral and intravenous administration. *J Clin Pharmacol* 1977; **17:** 300–7.
2. Dreyfuss J, *et al.* Pharmacokinetics of nadolol, a beta-receptor antagonist: administration of therapeutic single- and multiple-dosage regimens to hypertensive patients. *J Clin Pharmacol* 1979; **19:** 712–20.

Children. The pharmacokinetics of nadolol given intravenously and orally were studied in six children aged 3 months to 14 years.[1] The elimination half-lives for the two oldest children aged 10 and 14 years were 7.3 and 15.7 hours, respectively. These values are similar to those reported for adults whereas in the children 22 months of age or younger, shorter half-lives of 3.2 to 4.3 hours were found. The shorter half-lives were probably a result of a reduction in the total apparent volume of distribution of nadolol in the youngest children. Elimination rates were similar after either intravenous or oral dosage.

1. Mehta AV, *et al.* Pharmacokinetics of nadolol in children with supraventricular tachycardia. *J Clin Pharmacol* 1992; **32:** 1023–7.

Uses and Administration

Nadolol is a non-cardioselective beta blocker (p.1225). It is reported to lack intrinsic sympathomimetic and