Metoprolol *(BAN, USAN, rINN)* ⊗

Métoprolol; Metoprololi; Metoprololum. (±)-1-Isopropylamino-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol.

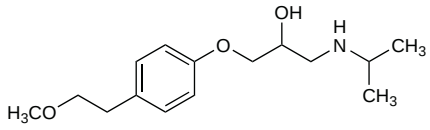
Метопролол

$C_{15}H_{25}NO_3$ = 267.4.

CAS — 54163-88-1; 37350-58-6.

ATC — C07AB02.

ATC Vet — QC07AB02.



Metoprolol Fumarate *(BANM, USAN, rINNM)* ⊗

CGP-2175C; Fumarato de metoprolol; Métoprolol, Fumarate de; Metoprololi Fumaras.

Метопролола Фумарат

$(C_{15}H_{25}NO_3)_2,C_4H_4O_4$ = 650.8.

CAS — 119637-66-0.

ATC — C07AB02.

ATC Vet — QC07AB02.

Pharmacopoeias. In *US.*

USP 31 (Metoprolol Fumarate). A 10% solution in water has a pH of between 5.5 and 6.5. Store in airtight containers. Protect from light.

Metoprolol Succinate *(BANM, USAN, rINNM)* ⊗

Métoprolol, succinate de; Metoprolol Süksinat; Metoprololi succinas; Metoprololio sukcinatas; Metoprololisuksinaatti; Metoprololsuccinat; Metoprolol-sukcinát; Metoprolol-szukcinát; Succinato de metoprolol.

Метопролола Суксинат

$(C_{15}H_{25}NO_3)_2,C_4H_6O_4$ = 652.8.

CAS — 98418-47-4.

ATC — C07AB02.

ATC Vet — QC07AB02.

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

Ph. Eur. 6.2 (Metoprolol Succinate). A white or almost white crystalline powder. Freely soluble in water; soluble in methyl alcohol; slightly soluble in alcohol; very slightly soluble in ethyl acetate. A 2% solution in water has a pH of between 7.0 and 7.6. Protect from light.

USP 31 (Metoprolol Succinate). A white to off-white powder. Freely soluble in water; soluble in methyl alcohol; sparingly soluble in alcohol; slightly soluble in isopropyl alcohol. A 6.5% solution in water has a pH of between 7.0 and 7.6. Store in airtight containers at controlled room temperature.

Metoprolol Tartrate *(BANM, USAN, rINNM)* ⊗

CGP-2175E; H-93/26; Metoprolol tartarát; Metoprolol Tartarat; Métoprolol, tartrate de; Metoprololi tartras; Metoprololio tartratas; Metoprololitartraatti; Metoprolol-tartarát; Metoprololtartrat; Tartrato de metoprolol.

Метопролола Тартрат

$(C_{15}H_{25}NO_3)_2,C_4H_6O_6$ = 684.8.

CAS — 56392-17-7.

ATC — C07AB02.

ATC Vet — QC07AB02.

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

Ph. Eur. 6.2 (Metoprolol Tartrate). A white or almost white crystalline powder or colourless crystals. It exhibits polymorphism. Very soluble in water; freely soluble in alcohol. A 2% solution in water has a pH of between 6.0 and 7.0. Protect from light.

USP 31 (Metoprolol Tartrate). A white crystalline powder. Very soluble in water; freely soluble in alcohol, in chloroform, and in dichloromethane; slightly soluble in acetone; insoluble in ether. A 10% solution in water has a pH of between 6.0 and 7.0. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Stability. Metoprolol tartrate 400 micrograms/mL in glucose 5% or sodium chloride 0.9% was stable for 36 hours when stored at 24° in PVC bags.[1]

1. Belliveau PP, *et al.* Stability of metoprolol tartrate in 5% dextrose injection or 0.9% sodium chloride injection. *Am J Hosp Pharm* 1993; **50:** 950–2.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Breast feeding. Metoprolol is distributed into breast milk and studies[1-3] have shown that the concentration in milk is higher than that in plasma. However, the amount ingested by an infant is likely to be small, and the concentration of metoprolol in infant plasma has been found[3] to be undetectable or very low. No adverse effects have been seen in breast-fed infants whose mothers were given metoprolol and the American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding.

1. Sandström B, Regårdh C-G. Metoprolol excretion into breast milk. *Br J Clin Pharmacol* 1980; **9:** 518–19.
2. Liedholm H, *et al.* Accumulation of atenolol and metoprolol in human breast milk. *Eur J Clin Pharmacol* 1981; **20:** 229–31.
3. Kulas J, *et al.* Atenolol and metoprolol: a comparison of their excretion into human breast milk. *Acta Obstet Gynecol Scand Suppl* 1984; **118:** 65–9.
4. 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)

Effects on hearing. Loss of hearing in a patient receiving metoprolol appeared to be dose-related;[1] hearing gradually improved over several months once the drug was withdrawn.

1. Fäldt R, *et al.* β Blockers and loss of hearing. *BMJ* 1984; **289:** 1490–2.

Effects on lipid metabolism. Beta blockers may increase serum-triglyceride concentrations. For a report of acute pancreatitis provoked by severe hypertriglyceridaemia in a patient taking atenolol and metoprolol, see p.1227.

Effects on the liver. Acute hepatitis associated with metoprolol has been reported in a 56-year-old woman.[1] The hepatotoxicity could not be explained by deficient oxidation of metoprolol; drug oxidation phenotyping showed she was an extensive metaboliser of debrisoquine and hence metoprolol.

For a discussion of the relationship between polymorphic oxidation of metoprolol and the incidence of adverse effects, see Metabolism, under Pharmacokinetics, below.

1. Larrey D, *et al.* Metoprolol-induced hepatitis: rechallenge and drug oxidation phenotyping. *Ann Intern Med* 1988; **108:** 67–8.

Interactions

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

Antivirals. US licensed product information for *ritonavir* warns that ritonavir may increase concentrations of metoprolol and that the dose of metoprolol may need to be reduced if used together.

Pharmacokinetics

Metoprolol is readily and completely absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism, with a bioavailability of about 50%. Peak plasma concentrations vary widely and occur about 1.5 to 2 hours after a single oral dose. It is moderately lipid-soluble.

Metoprolol is widely distributed; it crosses the blood-brain barrier and the placenta, and is distributed into breast milk. It is about 12% bound to plasma protein. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP2D6, and undergoes oxidative deamination, *O*-dealkylation followed by oxidation, and aliphatic hydroxylation. The metabolites are excreted in the urine with only small amounts of unchanged metoprolol. The rate of metabolism by CYP2D6 is determined by genetic polymorphism; the half-life of metoprolol in fast hydroxylators is stated to be 3 to 4 hours, whereas in poor hydroxylators it is about 7 hours.

The elderly. Several studies[1-3] indicate that age-related physiological changes have negligible effects on the pharmacokinetics of metoprolol.

1. Quarterman CP, *et al.* The effect of age on the pharmacokinetics of metoprolol and its metabolites. *Br J Clin Pharmacol* 1981; **11:** 287–94.
2. Regårdh CG, *et al.* Pharmacokinetics of metoprolol and its metabolite α-OH-metoprolol in healthy, non-smoking, elderly individuals. *Eur J Clin Pharmacol* 1983; **24:** 221–6.
3. Larsson M, *et al.* Pharmacokinetics of metoprolol in healthy, elderly, non-smoking individuals after a single dose and two weeks of treatment. *Eur J Clin Pharmacol* 1984; **27:** 217–22.

Metabolism. Metoprolol is metabolised by the cytochrome P450 isoenzyme CYP2D6 and therefore exhibits a debrisoquine-type genetic polymorphism.[1-3] Poor, intermediate, extensive, and ultrarapid metabolisers of metoprolol have been identified, and studies[4-6] have confirmed that plasma-metoprolol concentrations correlate with metaboliser status. However, the clinical relevance of these differences is less clear. A retrospective study[7] found that the proportion of poor metabolisers among patients who had severe adverse effects was higher than expected, but other studies[8,9] have found no correlation between the incidence of adverse effects and metaboliser status. Controlled studies in patients with hypertension[5] and in healthy subjects[4] have found that there is little or no relationship between plasma concentrations or metaboliser status and either the incidence of adverse effects or the response to therapy.

The subject may be further confused by variations in the phenotype between ethnic groups. Although the incidence of the poor metaboliser phenotype in whites of European origin is reported to be about 9%, a study in 138 Nigerians[10] failed to identify evidence of polymorphic metabolism, and the authors caution against extrapolation of data between different racial groups.

1. Lennard MS, *et al.* Defective metabolism of metoprolol in poor hydroxylators of debrisoquine. *Br J Clin Pharmacol* 1982; **14:** 301–3.
2. Lennard MS, *et al.* Oxidation phenotype—a major determinant of metoprolol metabolism and response. *N Engl J Med* 1982; **307:** 1558–60.
3. McGourty JC, *et al.* Metoprolol metabolism and debrisoquine oxidation polymorphism—population and family studies. *Br J Clin Pharmacol* 1985; **20:** 555–66.
4. Kirchheiner J, *et al.* Impact of the ultrarapid metabolizer genotype of cytochrome P450 2D6 on metoprolol pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 2004; **76:** 302–12.
5. Zineh I, *et al.* Pharmacokinetics and CYP2D6 genotypes do not predict metoprolol adverse events or efficacy in hypertension. *Clin Pharmacol Ther* 2004; **76:** 536–44.
6. Ismail R, Teh LK. The relevance of CYP2D6 genetic polymorphism on chronic metoprolol therapy in cardiovascular patients. *J Clin Pharm Ther* 2006; **31:** 99–109.
7. Wuttke H, *et al.* Increased frequency of cytochrome P450 2D6 poor metabolizers among patients with metoprolol-associated adverse effects. *Clin Pharmacol Ther* 2002; **72:** 429–37.
8. Clark DWJ, *et al.* Adverse effects from metoprolol are not generally associated with oxidation status. *Br J Clin Pharmacol* 1984; **18:** 965–6.
9. Fux R, *et al.* Impact of CYP2D6 genotype on adverse effects during treatment with metoprolol: a prospective clinical study. *Clin Pharmacol Ther* 2005; **78:** 378–87.
10. Iyun AO, *et al.* Metoprolol and debrisoquin metabolism in Nigerians: lack of evidence for polymorphic oxidation. *Clin Pharmacol Ther* 1986; **40:** 387–94.

Pregnancy. The clearance of metoprolol was increased fourfold in 5 pregnant women during the last trimester, compared with that some months after delivery; this was probably due to enhanced hepatic metabolism in the pregnant state.[1]

The disposition of metoprolol was investigated in neonates of mothers treated with metoprolol 50 to 100 mg twice daily.[2] In 15 of the 17 neonates plasma-metoprolol concentrations increased in the first 2 to 5 hours of the postnatal period, then declined over the next 15 hours; 5 of these infants had no detectable metoprolol concentrations in the umbilical plasma. No infant showed signs of beta blockade.

1. Högstedt S, *et al.* Increased oral clearance of metoprolol in pregnancy. *Eur J Clin Pharmacol* 1983; **24:** 217–20.
2. Lundborg P, *et al.* Disposition of metoprolol in the newborn. *Br J Clin Pharmacol* 1981; **12:** 598–600.

Renal impairment. A single dose of a modified-release tablet of metoprolol produced similar plasma-metoprolol concentrations and values for the area under the concentration/time curve in both normal subjects and those with renal impairment.[1] Mean plasma concentrations of the metabolite α-hydroxymetoprolol were increased two to threefold in subjects with renal impairment compared with normal subjects but such a rise was not considered likely to contribute to beta blockade.

1. Lloyd P, *et al.* The effect of impaired renal function on the pharmacokinetics of metoprolol after single administration of a 14/190 metoprolol OROS system. *Am Heart J* 1990; **120:** 478–82.

Uses and Administration

Metoprolol is a cardioselective beta blocker (p.1225). It is reported to lack intrinsic sympathomimetic activity and to have little or no membrane-stabilising activity.

It is used in the management of hypertension (p.1171), angina pectoris (p.1157), cardiac arrhythmias (p.1160), myocardial infarction (p.1175), and heart failure (p.1165). It is also used in the management of hyperthyroidism (p.2165) and in the prophylactic treatment of migraine (p.616).

Metoprolol is given orally and intravenously as the tartrate. Modified-release tablets usually contain the tartrate or the succinate, but the fumarate has also been used. Doses are usually expressed in terms of the tartrate; 95 mg of metoprolol fumarate or metoprolol succinate is equivalent to about 100 mg of metoprolol tartrate.

The bioavailability of metoprolol is increased if taken with food and it has been recommended that some preparations are taken with or immediately after a meal.

Reduced doses should be given to patients with hepatic impairment.

In **hypertension** metoprolol tartrate is usually given in an initial oral dose of 100 mg daily, as a single dose or in two divided doses. The dose may be increased weekly, according to response; the usual maintenance dose is 100 to 200 mg daily, but up to 400 mg daily may be given.

The usual oral dose for **angina pectoris** is 50 to 100 mg two or three times daily.

In the treatment of **cardiac arrhythmias** the usual oral dose is 50 mg two or three times daily, increased if necessary up to 300 mg daily in divided doses.

For the emergency treatment of cardiac arrhythmias metoprolol tartrate may be given intravenously in an initial dose of up to 5 mg, at a rate of 1 to 2 mg/minute; this may be repeated, if necessary, at intervals of 5 minutes to a total dose of 10 to 15 mg. When acute arrhythmias have been controlled, maintenance therapy may be started 4 to 6 hours after intravenous therapy, at oral doses not exceeding 50 mg three times daily.

Arrhythmias may be prevented on induction of anaesthesia, or controlled during anaesthesia, by the slow intravenous injection of 2 to 4 mg; further injections of 2 mg may be repeated as necessary to a maximum total dose of 10 mg.

Metoprolol is also used as an adjunct in the early management of acute **myocardial infarction.** Treatment should be given within 12 hours of the onset of chest pain; metoprolol tartrate 5 mg should be given intravenously at 2-minute intervals to a total of 15 mg, where tolerated. After 15 minutes, in patients who have received the full intravenous dose, oral treatment should be started; 50 mg is given every 6 hours for 2 days. In patients who have failed to tolerate the full intravenous dose a reduced oral dose should be given as, and when, their condition permits. Subsequent maintenance dosage is 100 mg given twice daily by mouth. In patients who did not receive metoprolol by intravenous injection as part of the early management of myocardial infarction, metoprolol may be started once the clinical condition of the patient stabilises, in a dose of 200 mg daily in 2 or 4 divided doses.

In the management of stable, symptomatic **heart failure** metoprolol succinate may be given as an oral modified-release preparation. The initial dose is the equivalent of metoprolol tartrate 12.5 to 25 mg once daily, increased as tolerated, at intervals of 2 weeks, with a target dose of 200 mg once daily.

As an adjunct in the treatment of **hyperthyroidism** metoprolol tartrate may be given in oral doses of 50 mg four times daily. Doses of 100 to 200 mg are given daily in divided doses for **migraine** prophylaxis.

◊ General references.

1. Plosker GL, Clissold SP. Controlled release metoprolol formulations: a review of their pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension and ischaemic heart disease. *Drugs* 1992; **43:** 382–414.
2. Prakash A, Markham A. Metoprolol: a review of its use in chronic heart failure. *Drugs* 2000; **60:** 647–78.
3. Tangeman HJ, Patterson JH. Extended-release metoprolol succinate in chronic heart failure. *Ann Pharmacother* 2003; **37:** 701–10.

Administration in children. Metoprolol has been used in children, although experience is limited. A study[1] in children aged 6 to 16 years with hypertension found that modified-release metoprolol succinate was well tolerated in doses of up to the equivalent of metoprolol tartrate 2 mg/kg daily, although efficacy was not established. US licensed product information nevertheless allows the use of oral doses of metoprolol succinate once daily in children aged 6 to 16 years; the initial dose is the equivalent of metoprolol tartrate 1 mg/kg daily (maximum 50 mg), adjusted according to response to a maximum of 2 mg/kg (not more than 200 mg) daily.

The *BNFC* recommends that for hypertension children aged 1 month to 12 years may be given standard formulations of metoprolol tartrate in an initial dose of 1 mg/kg twice daily orally, increased if necessary to a maximum dose of 8 mg/kg daily in 2 to 4 divided doses. Children over 12 years may be given the adult dose (see above).

1. Batisky DL, *et al.* Efficacy and safety of extended release metoprolol succinate in hypertensive children 6 to 16 years of age: a clinical trial experience. *J Pediatr* 2007; **150:** 134–9.

Preparations

BP 2008: Metoprolol Injection; Metoprolol Tartrate Tablets;
USP 31: Metoprolol Succinate Extended-Release Tablets; Metoprolol Tartrate and Hydrochlorothiazide Tablets; Metoprolol Tartrate Injection; Metoprolol Tartrate Oral Solution; Metoprolol Tartrate Oral Suspension; Metoprolol Tartrate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Beloc†; Belozok; Lopresor; ***Austral.:*** Betaloc; Lopresor; Metohexal; Metolol†; Metrol; Minax; Toprol; ***Austria:*** Beloc; Lanoc; Metohexal; MetoMed; Metopal†; Metostadol; Metotyrol†; Seloken; ***Belg.:*** Lopresor; Selo-Zok; Seloken; Slow-Lopresor; ***Braz.:*** Lopressor; Selo-Zok; Seloken; ***Canad.:*** Betaloc; Lopresor; Novo-Metoprol; Nu-Metop; ***Cz.:*** Betaloc; Corvitol†; Egilok; Emzok; Metohexal†; Vasocardin; ***Denm.:*** Dura-Zok†; Mepronet; Metocar; Metozoc†; Selo-Zok; Seloken; ***Fin.:*** Metblock†; Metoprolin; Metozoc†; Seloken; Seloken ZOC; Selopral; Spesicor; ***Fr.:*** Lopressor; Seloken; Selozok; ***Ger.:*** Azumetop†; Beloc; Beloc-Zok; Jeprolol; Jutabloc; Lopresor; Meprolol; Meto; Meto-Succinat; Meto-Tablinen; Metobeta; Metodoc; Metodura; Metohexal; Metok†; Metomerck†; Metoprogamma; Prelis; Sigaprolol†; ***Gr.:*** Lopresor; ***Hong Kong:*** Betaloc; CP-Metolol; Denex†; Minax; Novo-Metoprol; Sefloc; ***Hung.:*** Betaloc; Egilok; Huma-Metoprol†; Ritmetol†; ***India:*** Betaloc; Metolar; Revelol; Selopres; ***Indon.:*** Cardiosel; Lopresor; Loprolol; Seloken; ***Irl.:*** Betaloc; Lopresor; Metocor; Metop; ***Israel:*** Lopresor; Metopress†; Neobloc; ***Ital.:*** Lopresor; Seloken; ***Jpn:*** Seloken; ***Malaysia:*** Beatrolol†; Betaloc; Betatab†; Denex; ***Mex.:*** Bioprol; Eurolol; Futaline; Kenaprol; Lopresor; Metopresol; Proken M†; Prolaken; Promiced; Prontol; Ritmolol; Selectadril†; Seloken; Sermetrol; Synadrenol†; ***Neth.:*** Lopresor; Selokeen; ***Norw.:*** Metozoc†; Selo-Zok; Seloken; ***NZ:*** Betaloc; Lopresor; Slow-Lopresor; ***Philipp.:*** Betaloc; Betaryx; Betazok; Cardiosel; Cardiostat; Cardiotab; Metocare; Metoprim; Metospec; Metostad; Montebloc; Neobloc; Prolohex; Valvexin; ***Pol.:*** Betaloc; Beto; Metocard; Metohexal; ***Port.:*** Lopresor; ***Rus.:*** Betaloc ZOK (Беталок ЗОК); Corvitol (Корвадил); Egilok (Эгилок); Emzok (Эмзок); Metocard (Метокард); Serdol (Сердол); Vasocardin (Вазокардин); ***S.Afr.:*** Lopresor; ***Singapore:*** Betaloc; Denex; ***Spain:*** Beloken; Lopresor; ***Swed.:*** Seloken; Seloken ZOC; ***Switz.:*** Beloc; Beloc COR†; Beloc-Zok; Lopresor; Metopress; ***Thai.:*** Betaloc; Cardeloc; Cardoxone; Denex†; Melol; Metoblock; Metolol; Minax; Sefloc; ***Turk.:*** Beloc; Lopresor; Problok; ***UK:*** Betaloc; Lopresor; ***USA:*** Lopressor; Toprol; ***Venez.:*** Lopresor.

Multi-ingredient: ***Arg.:*** Diubeloc†; ***Austria:*** Beloc comp; Metoprolol compositum; Seloken retard Plus; Triloc; ***Belg.:*** Logimat; Logroton; Selozide; Zok-Zid; ***Braz.:*** Selopress; ***Cz.:*** Logimax†; ***Denm.:*** Logimax; Zok-Zid; ***Fin.:*** Logimax; Selocomp ZOC; Seloken ZOC/ASA†; ***Fr.:*** Logimax; Logroton; ***Ger.:*** Azumetop HCT†; Belnif; Beloc-Zok comp; Meprolol Comp; Meto comp†; Meto-Isis comp†; meto-thiazid†; Metobeta comp; Metodura comp; Metohexal comp; Metoprolol comp; Metostad Comp; Mobloc; Prelis comp; Treloc; ***Gr.:*** Logimax; ***Hong Kong:*** Betaloc Comp; CP-Metolol Co; Logimax; ***Hung.:*** Logimax; ***India:*** Metolar-H; ***Irl.:*** Co-Betaloc; ***Israel:*** Logimax; ***Ital.:*** Igroton-Lopresor; Selozide†; ***Malaysia:*** Logroton; ***Mex.:*** Logimax; Selopres; ***Neth.:*** Logimax; Selokomb; ***Philipp.:*** Betazide; Logimax; ***Rus.:*** Logimax (Логимакс); ***Spain:*** Higrotensin; Logimax; Selopresin†; ***Swed.:*** Logimax; Seloken ZOC/ASA†; ***Switz.:*** Logimax; Logroton; ***UK:*** Co-Betaloc†; ***USA:*** Lopressor HCT.

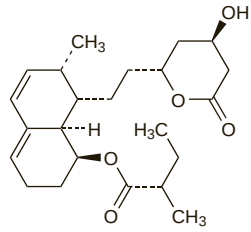
Mevastatin *(rINN)*

Compactin; CS-500; Mevastatina; Mévastatine; Mevastatinum; ML-236B. (1*S*,7*S*,8*S*,8a*R*)-1,2,3,7,8,8a-Hexahydro-7-methyl-8-{2-[(2*R*,4*R*)-tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl]ethyl}-1-naphthyl (*S*)-2-methylbutyrate.

Мевастатин

$C_{23}H_{34}O_5$ = 390.5.

CAS — 73573-88-3.



Profile

Mevastatin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin) (see Simvastatin, p.1390) that has been isolated from *Penicillium citrinum*. It is a lipid regulating drug but is no longer used in clinical practice because of reports of toxicity in *animals*.

Mexiletine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de mexiletina; Kö-1173; Meksiletiinihydrokloridi; Meksiletin Hidroklorür; Meksiletino hidrochloridas; Mexilétine, chlorhydrate de; Mexiletin-hidroklorid; Mexiletin-hydrochlorid; Mexiletinhydroklorid; Mexiletini hydrochloridum. 1-Methyl-2-(2,6-xylyloxy)ethylamine hydrochloride.

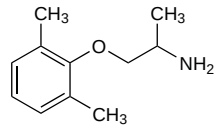
Мексилетина Гидрохлорид

$C_{11}H_{17}NO,HCl$ = 215.7.

CAS — 31828-71-4 (mexiletine); 5370-01-4 (mexiletine hydrochloride).

ATC — C01BB02.

ATC Vet — QC01BB02.



(mexiletine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*
Ph. Eur. 6.2 (Mexiletine Hydrochloride). A white or almost white, crystalline powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; sparingly soluble in dichloromethane. A 10% solution in water has a pH of 4.0 to 5.5.
USP 31 (Mexiletine Hydrochloride). A white powder. Freely soluble in water and in dehydrated alcohol; practically insoluble in ether; slightly soluble in acetonitrile. A 10% solution in water has a pH of between 3.5 and 5.5. Store in airtight containers.

Adverse Effects and Treatment

Mexiletine has a narrow therapeutic ratio; many adverse effects of mexiletine are dose-related and will respond to dosage reduction but may be severe enough to force mexiletine to be stopped and symptomatic and supportive therapy to be given. Toxicity is common with oral or parenteral loading doses when plasma concentrations are high.

The most common adverse effects involve the gastrointestinal tract and CNS. Effects on the gastrointestinal tract include nausea, vomiting, constipation, and diarrhoea; oesophageal ulceration has also been reported. Effects on the nervous system include tremor, confusion, lightheadedness, dizziness, blurred vision and other visual disturbances, sleep disturbances, and speech difficulties. The most frequent cardiovascular effects are hypotension, sinus bradycardia, heart block and AV dissociation, and atrial fibrillation. As with other antiarrhythmics mexiletine may exacerbate arrhythmias. Other adverse effects that have been reported include skin rashes, abnormal liver function tests, thrombocytopenia, positive antinuclear factor titres, and convulsions. The Stevens-Johnson syndrome has been reported rarely.

Incidence of adverse effects. In a study involving 100 patients with ventricular arrhythmias, mexiletine had to be stopped in 49 patients because of intolerable adverse effects.[1] The most common of these affected the gastrointestinal system (27%) and included nausea (10%), vomiting (6%), heartburn (6%), and oesophageal spasm (3%). Intolerable effects on the CNS occurred in 10% of patients and these were most commonly tremor (4%), ataxia (2%), dyskinesia (1%), and tinnitus (1%). When mexiletine was used with another antiarrhythmic, the incidence of intolerable effects was 56%.

Tolerable adverse effects with mexiletine alone were transient and dose-dependent and occurred in 18% of patients. They most often affected the gastrointestinal tract. No irreversible adverse effects were reported and no proarrhythmic effects were seen.

1. Kerin NZ, *et al.* Mexiletine: long-term efficacy and side effects in patients with chronic drug-resistant potentially lethal ventricular arrhythmias. *Arch Intern Med* 1990; **150:** 381–4.

Effects on the lungs. Pulmonary fibrosis has been reported in an elderly patient receiving mexiletine; the manufacturer was aware of 3 other cases.[1]

1. Bero CJ, Rihn TL. Possible association of pulmonary fibrosis with mexiletine. *DICP Ann Pharmacother* 1991; **25:** 1329–31.

Precautions

Mexiletine is contra-indicated in cardiogenic shock and in second- or third-degree AV block (unless the patient has a pacemaker). It should be used with caution in patients with sinus node dysfunction, other conduction disorders, bradycardia, hypotension, heart failure, or hepatic impairment. ECG and blood pressure monitoring should be carried out during treatment.

Absorption of oral mexiletine may be delayed in situations where gastric emptying is slowed, such as acute myocardial infarction.

Breast feeding. Mexiletine is distributed into human breast milk in higher concentrations than in maternal serum. A woman[1] given 200 mg of mexiletine three times daily during the last trimester of pregnancy (see below), went on to breast feed the infant. Concentrations of mexiletine in the maternal milk and serum were found to be 0.6 and 0.3 micrograms/mL respectively on the second day postpartum, and 0.8 and 0.7 micrograms/mL