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.

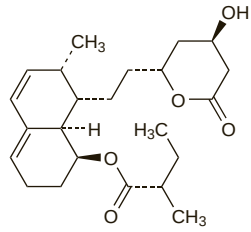
Mevastatin *(rINN)*

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.

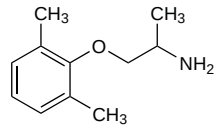
Мексилетина Гидрохлорид

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