

Labetalol is used as the hydrochloride in the management of hypertension (p.1171). It is also used to induce hypotension during surgery. Labetalol decreases blood pressure more rapidly than other beta blockers; the full antihypertensive effect may be seen within 1 to 3 hours of an oral dose.

In **hypertension** labetalol hydrochloride is usually given in an initial oral dose of 100 mg twice daily with food, gradually increased if necessary according to response and standing blood pressure, to 200 to 400 mg twice daily; total daily doses of 2.4 g, in two to four divided doses, have occasionally been required. Lower doses may be adequate in elderly patients; an initial dose of 50 to 100 mg twice daily has been recommended, and the usual maintenance dose is 100 to 200 mg twice daily.

For the emergency treatment of hypertension labetalol hydrochloride may be given by slow intravenous injection. In the UK a dose of 50 mg is recommended, given over a period of at least 1 minute; if necessary this dose may be repeated at intervals of 5 minutes until a total of 200 mg has been given. In the USA an initial dose of 20 mg is recommended, given over 2 minutes; subsequent doses of 40 to 80 mg may be given every 10 minutes, if necessary, up to a maximum of 300 mg. Blood pressure should be monitored, and the patient should remain supine during the injection and for 3 hours afterwards, to avoid excessive orthostatic hypotension. After bolus intravenous injection a maximum effect is usually obtained within 5 minutes and usually lasts up to 6 hours, although it may extend as long as 18 hours.

Labetalol hydrochloride has also been given by intravenous infusion in usual doses of 2 mg/minute. Suggested concentrations for intravenous infusions are 1 mg/mL or 2 mg/3 mL of suitable diluent. In hypertension in pregnancy, labetalol infusion may be started at the rate of 20 mg/hour, then doubled every 30 minutes until a satisfactory response is obtained or a dose of 160 mg/hour is reached. In hypertension after myocardial infarction, labetalol infusion may be started at the rate of 15 mg/hour and gradually increased until a satisfactory response is obtained or a dose of 120 mg/hour is reached.

The initial dose in **hypotensive anaesthesia** is 10 to 20 mg intravenously, with increments of 5 to 10 mg if satisfactory hypotension is not achieved after 5 minutes. A higher initial dose may be required in patients who do not receive halothane anaesthesia.

For the use of labetalol in children, see below.

Action. Labetalol has 2 optical centres; it is used as the racemic mixture of the 4 stereoisomers. The *R,R*- isomer is responsible for the beta-blocking activity and has limited alpha-blocking activity; it also has beta-adrenergic mediated peripheral vasodilating activity. The *S,S*-isomer has the most potent alpha-blocking activity. The *S,S*-isomer has some alpha-blocking activity and the *R,S*-isomer does not appear to have either alpha- or beta-adrenergic blocking effect.¹ The pure *R,R*-isomer, dilevalol, was withdrawn from the market because of hepatotoxicity.

- Gold EH, *et al.* Synthesis and comparison of some cardiovascular properties of the stereoisomers of labetalol. *J Med Chem* 1982; **25**: 1363–70.

Administration in children. Labetalol has been used in the management of hypertension in children,¹ although experience is limited. The *BNFC* suggests the following doses:

for **hypertensive emergencies**, labetalol hydrochloride may be given by intravenous infusion as follows:

- neonates: 500 micrograms/kg per hour adjusted at intervals of at least 15 minutes according to response, to a maximum of 4 mg/kg per hour
- 1 month to 12 years: 0.5 to 1 mg/kg per hour adjusted at intervals of at least 15 minutes according to response, to a maximum of 3 mg/kg per hour
- 12 to 18 years: 30 to 120 mg/hour adjusted at intervals of at least 15 minutes according to response

for **hypertension**, labetalol hydrochloride may be given as follows:

- 1 month to 12 years: 1 to 2 mg/kg three or four times daily by mouth or a single intravenous injection in a dose of 250 to 500 micrograms/kg to a maximum of 20 mg
- 12 to 18 years: similar doses to adults (see above) although a lower initial oral dose of 50 to 100 mg twice daily is recommended

- Bunchman TE, *et al.* Intravenously administered labetalol for treatment of hypertension in children. *J Pediatr* 1992; **120**: 140–4.

Preparations

BP 2008: Labetalol Injection; Labetalol Tablets;

USP 31: Labetalol Hydrochloride Injection; Labetalol Hydrochloride Oral Suspension; Labetalol Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Bioscor; **Austral.:** Presolol; **Trandate;** **Austria:** Trandate; **Belg.:** Trandate; **Canad.:** Trandate; **Chile:** Trandate; **Cz.:** Coreton; **Trandate;** **Denm.:** Trandate; **Fin.:** Albetol; **Fr.:** Trandate; **Gr.:** Trandate; **Hong Kong:** Trandate; **Irl.:** Trandate; **Israel:** Trandate; **Ital.:** Ipobal; **Trandate;** **Malaysia:** Tolbetol; **Trandate;** **Neth.:** Trandate; **Norw.:** Trandate; **NZ:** Hybloc; **Trandate;** **Port.:** Trandate; **S.Afr.:** Trandate; **Singapore:** Trandate; **Spain:** Trandate; **Swed.:** Trandate; **Switz.:** Trandate; **UK:** Trandate; **USA:** Normodyne; **Trandate;** **Venez.:** Trandate; **Trandate;**

Multi-ingredient: **Ital.:** Trandur.

Lacidipine (BAN, USAN, rINN)

GR-43659X; GX-1048; Lacidipin; Lacidipino; Lacidipinum; Lasidipiini; Lasidipin. Diethyl 4-[2-[(*tert*-butoxycarbonyl)vinyl]phenyl]-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate.

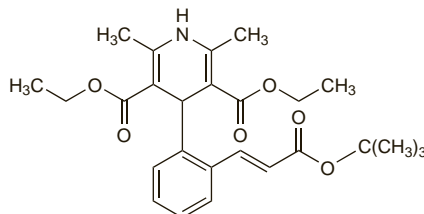
Лацидипин

$C_{26}H_{33}NO_6$ = 455.5.

CAS — 103890-78-4.

ATC — C08CA09.

ATC Vet — QC08CA09.



Pharmacopoeias. In *Br*:

BP 2008 (Lacidipine). A white to pale yellow crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in acetone and in dichloromethane.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1350).

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1352).

Pharmacokinetics

Lacidipine is rapidly but poorly absorbed from the gastrointestinal tract after oral doses and undergoes extensive first-pass metabolism; the bioavailability has been reported to be 2 to 9%, or 18.5% (range 4 to 52%) using a more sensitive assay method. It is more than 95% bound to plasma proteins. Lacidipine is eliminated by metabolism in the liver and metabolites are excreted mainly by the biliary route. About 70% of an oral dose is eliminated in the faeces, the remainder in the urine. The average steady-state terminal elimination half-life of lacidipine is 13 to 19 hours.

Uses and Administration

Lacidipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p.1354). It is used in the treatment of hypertension (p.1171).

The usual initial dose of lacidipine is 2 mg once daily by mouth increased if necessary after 3 to 4 weeks or more to 4 mg daily; a further increase in dose to 6 mg daily may be necessary in some patients.

◊ **Reviews.**

- Lee CR, Bryson HM. Lacidipine: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the treatment of hypertension. *Drugs* 1994; **48**: 274–96.
- Zanchetti A, ed. Cardiovascular advantages of a third generation calcium antagonist: symposium on lacidipine. *Drugs* 1999; **57** (suppl 1): 1–29.
- McCormack PL, Wagstaff AJ. Lacidipine: a review of its use in the management of hypertension. *Drugs* 2003; **63**: 2327–56.

Preparations

BP 2008: Lacidipine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Lacipil; **Midotens; Belg.:** Motens; **Braz.:** Lacipil; **Midotens; Cz.:** Lacipil; **Denm.:** Midotens; **Fr.:** Caldine; **Ger.:** Motens; **Gr.:** Balnox; **Lacipil; Lacitens; Motens; Hong Kong:** Lacipil; **Hung.:** Lacipil; **India:** Sinopil; **Indon.:** Lacipil; **Ital.:** Aponil; **Lacipil; Lacirex; Ladip; Viapres; Malaysia:** Lacipil; **Mex.:** Lacipil; **Midotens; Neth.:** Motens; **Philipp.:** Lacipil; **Pol.:** Lacipil; **Port.:** Lacipil; **Tens; Rus.:** Lacipil (Лаципил); **Singapore:** Lacipil; **Spain:** Lacimen; **Lacipil; Motens; Switz.:** Motens; **Thai.:** Motens; **Turk.:** Lacipil; **UK:** Motens; **Venez.:** Lacipil; **Tens; Trandate;**

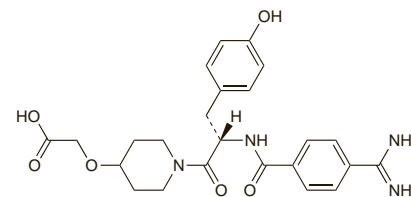
Lamifiban (USAN, rINN)

Lamifibán; Lamifibanum; Ro-44-9883; Ro-44-9883/000. {[1-(*N*-(*p*-Aminobenzoyl)-L-tyrosyl)-4-piperidyl]oxy}acetic acid.

Ламифибан

$C_{24}H_{28}N_4O_6$ = 468.5.

CAS — 144412-49-7 (lamifiban); 243835-65-6 (lamifiban hydrochloride).



Profile

Lamifiban is a glycoprotein IIb/IIIa-receptor antagonist. It has been investigated as an antiplatelet drug given intravenously for the management of thromboembolic disorders, such as unstable angina and myocardial infarction.

◊ **References.**

- Thérault P, *et al.* Platelet membrane receptor glycoprotein IIb/IIIa antagonism in unstable angina: the Canadian Lamifiban Study. *Circulation* 1996; **94**: 899–905.
- The PARAGON Investigators. International, randomized, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. *Circulation* 1998; **97**: 2386–95.
- The PARADIGM Investigators. Combining thrombolysis with the platelet glycoprotein IIb/IIIa inhibitor lamifiban: results of the Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction (PARADIGM) trial. *J Am Coll Cardiol* 1998; **32**: 2003–10.
- Global Organization Network (PARAGON)-B Investigators. Randomized, placebo-controlled trial of titrated intravenous lamifiban for acute coronary syndromes. *Circulation* 2002; **105**: 316–21.

Lanatoside C (BAN, rINN)

Celanide; Celanidum; Lanatosid C; Lanatosidi C; Lanatosido C; Lanatosidum C; Lanatozyd c. 3-[(O-β-D-Glucopyranosyl-(1→4)-O-3-acetyl-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1→4)-O-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1→4)-O-2,6-dideoxy-β-D-ribo-hexopyranosyl)oxy]-12,14-dihydroxy-3β,5β,12β-card-20(22)-enolide.

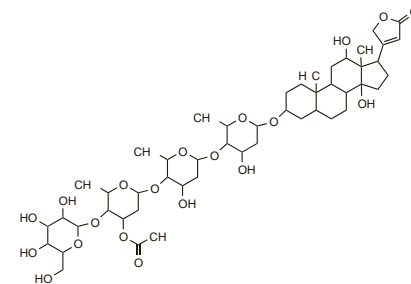
Ланатозид С

$C_{49}H_{76}O_{20}$ = 985.1.

CAS — 17575-22-3.

ATC — C01AA06.

ATC Vet — QC01AA06.



Pharmacopoeias. In *Jpn* and *Pol*.

Profile

Lanatoside C is a cardiac glycoside with positive inotropic activity. It is obtained from digitalis lanata leaf (p.1258). It has general properties similar to those of digoxin (p.1259) and has been used in the treatment of some cardiac arrhythmias and in heart failure. Mixtures of lanatosides A, B, and C have also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Develandit; **Mex.:** Cedilanid.

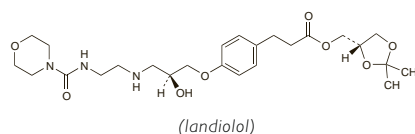
Landirolol Hydrochloride (rNNM) ⊗

Hidrocloruro de landiolol; Landiolol, Chlorhydrate de; Landiolol Hydrochloridum; (ONO-1101). (–)-[(S)-2,2-Dimethyl-1,3-dioxolano-4-yl]methyl p-[(S)-2-hydroxy-3-[[2-(4-morpholinecarboxamido)ethyl]amino]propoxy]hydrocinnamate hydrochloride.

Ландиолола Гидрохлорид

$C_{25}H_{39}N_3O_8 \cdot HCl = 546.1$.

CAS — 133242-30-5 (landiolol); 144481-98-1 (landiolol hydrochloride).



Profile

Landiolol is a short-acting, cardioselective beta blocker given intravenously as the hydrochloride in the management of intra- and postoperative cardiac arrhythmias.

References.

1. Kitamura A, *et al.* Efficacy of an ultrashort-acting beta-adrenoceptor blocker (ONO-1101) in attenuating cardiovascular responses to endotracheal intubation. *Eur J Clin Pharmacol* 1997; **51**: 467–71.
2. Atarashi H, *et al.* Pharmacokinetics of landiolol hydrochloride, a new ultra-short-acting beta-blocker, in patients with cardiac arrhythmias. *Clin Pharmacol Ther* 2000; **68**: 143–50.
3. Mizuno J, *et al.* Age and sex-related differences in dose-dependent hemodynamic response to landiolol hydrochloride during general anesthesia. *Eur J Clin Pharmacol* 2007; **63**: 243–52.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Onoact.

Lanotepase (USAN, rNN)

BMS-200980; Lanotepasa; Lanotéplase; Lanotepasum; Sun-9216. N-[N²-(N-Glycyl-L-alanyl)-L-arginyl]-17-L-glutamine-245-L-methionine-(1-5)-(87-527)-plasminogen activator (human tissue-type protein moiety).

Ланотеплаза

$C_{2184}H_{3323}N_{633}O_{666}S_{29} = 50032.5$.

CAS — 171870-23-8.

Profile

Lanotepase is a thrombolytic that has been investigated in acute myocardial infarction; development was stopped after an unacceptable rate of intracranial haemorrhage was found.

References.

1. The InTIME-II Investigators. Intravenous NPA for the treatment of infarcting myocardium early: InTIME-II, a double-blind comparison of single-bolus lanotepase vs accelerated alteplase for the treatment of patients with acute myocardial infarction. *Eur Heart J* 2000; **21**: 2005–13.

Lappaconitine Hydrobromide

(1 α ,14 α ,16 β)-20-Ethyl-1,14,16-trimethoxyaconitane-4,8,9-triol 4-[2-(acetylaminobenzoate)] hydrobromide.

Лалпаконитина Гидробромида

$C_{32}H_{44}N_2O_8 \cdot HBr = 665.6$.

CAS — 32854-75-4 (lappaconitine); 97792-45-5 (lappaconitine hydrobromide).

Profile

Lappaconitine hydrobromide is an antiarrhythmic drug given orally in a usual dose of 25 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)

Rus.: Allapinin (Аллапинин).

Leech

Blutegel; Hirudo; Sangsue; Sanguessugas; Sanguijuela; Sanguisuga.

Description. *Hirudo medicinalis* is the leech commonly used in medicine and is a fresh-water annelid.

The symbol † denotes a preparation no longer actively marketed

NOTE. The substance described in the *Chin. P.* as Hirudo (Leech) is the dried body of *Whitmania pigra*, *Hirudo nipponica*, or *Whitmania acranulata*.

Profile

Leeches are used for withdrawing blood from congested areas and have been found to be of value in plastic surgery. The buccal secretion of the leech contains the anticoagulant hirudin (p.1305). Once used a leech should not be applied to another patient.

There have been reports of wound infection from *Aeromonas hydrophila* transmitted by leeches. Prolonged bleeding for up to 10 hours may occur from the site of attachment after removal of the leech.

⊠ Leeches are commonly used in plastic surgery and this has been reviewed.¹

Wound infection by *Aeromonas hydrophila*, an organism normally found in the gut of the leech, is a recognised complication of the use of leeches for decongestion after plastic surgery. Other infecting organisms include *Aeromonas sobria* and *Serratia marcescens*. Infections have caused minor wound drainage, cellulitis, abscess, tissue loss, and sepsis, and a case of meningitis secondary to *Aeromonas* infection has been reported.² The following protocol has been suggested:¹ the site of application should first be cleaned with heparinised saline, and antibacterial prophylaxis with a quinolone and an aminoglycoside given for the duration of application. Patients discharged with open wounds should continue with oral antibacterials until wound closure.

In addition to its anticoagulant properties the buccal secretion of the leech contains anti-inflammatory substances, and leeches have been reported to provide subjective relief of symptoms^{3,4} in osteoarthritis.

1. Whitaker IS, *et al.* Hirudo medicinalis and the plastic surgeon. *Br J Plast Surg* 2004; **57**: 348–53.
2. Ouderkirk JP, *et al.* Aeromonas meningitis complicating medicinal leech therapy. Abstract: *Clin Infect Dis* 2004; **38**: 603. Full version: <http://www.journals.uchicago.edu/doi/full/10.1086/381438> (accessed 19/08/08)
3. Michalsen A, *et al.* Effect of leeches therapy (Hirudo medicinalis) in painful osteoarthritis of the knee: a pilot study. *Ann Rheum Dis* 2001; **60**: 986.
4. Michalsen A, *et al.* Effectiveness of leech therapy in osteoarthritis of the knee: a randomized, controlled trial. *Ann Intern Med* 2003; **139**: 724–30.

Lepirudin (BAN, rNN)

HBW-023; Lepirudiini; Lepirudina; Lépirudine; Lepirudinum. 1-L-Leucine-2-L-threonine-63-desulfohirudin (*Hirudo medicinalis* isoform HV1).

Лепирудин

$C_{287}H_{440}N_{80}O_{111}S_6 = 6979.4$.

CAS — 138068-37-8.

ATC — B01AE02.

ATC Vet — QB01AE02.

Adverse Effects and Precautions

The most frequent adverse effect of the direct thrombin inhibitors is bleeding. Hypersensitivity reactions have been reported. There have been reports of severe anaphylactic reactions, including death, with many occurring on re-exposure. There may be cross-reactivity with other hirudins or hirudin analogues.

Intramuscular injection should be avoided as it may cause local haematoma.

Direct thrombin inhibitors should be used with caution or avoided in patients with hepatic or renal impairment, and in those who are bleeding or at serious risk of bleeding, including those with haemorrhagic blood disorders, recent major bleeding, cerebrovascular disorders, bacterial endocarditis, severe hypertension, or patients who have recently undergone major surgery or puncture of large vessels or organ biopsy.

Hypersensitivity. The EMEA reported¹ in October 2002 that they were aware of 7 cases of severe anaphylactic reactions in patients given lepirudin; in 6 cases this followed re-exposure to the drug, and in 5 cases the patient died. A review² of the manufacturer's safety database identified 9 patients with severe anaphylactic reactions associated with lepirudin; 4 patients died, all of whom had received lepirudin within the previous 1 to 12 weeks. Although the risk of severe anaphylaxis was estimated to be low (0.015% on first exposure and 0.16% on re-exposure),² alternative treatment should be considered before re-exposure to

lepirudin and it should only be used where treatment for an anaphylactic reaction is available.^{1,2}

1. EMEA. EMEA public statement on Refludan (lepirudin)—fatal anaphylactic reactions (issued October 2002). Available at: <http://www.emea.europa.eu/pdfs/human/press/pus/2771702en.pdf> (accessed 16/05/08)
2. Greinacher A, *et al.* Anaphylactic and anaphylactoid reactions associated with lepirudin in patients with heparin-induced thrombocytopenia. *Circulation* 2003; **108**: 2062–5.

Interactions

Use of direct thrombin inhibitors with thrombolytics, oral anticoagulants, or drugs that affect platelet function may increase the risk of bleeding.

Pharmacokinetics

Lepirudin is metabolised and excreted by the kidney. About 45% of an intravenous dose is detected in the urine and about 35% is excreted unchanged. The terminal elimination half-life of lepirudin is about 1.3 hours. In patients with severe renal impairment the half-life may be prolonged to about 2 days.

Breast feeding. Three hours after injection, plasma concentrations of hirudin in a woman receiving lepirudin 50 mg subcutaneously twice daily were 0.5 to 1 microgram/mL, but no hirudin was detected in the breast milk.

1. Lindhoff-Last E, *et al.* Hirudin treatment in a breastfeeding woman. *Lancet* 2000; **355**: 467–8.

Uses and Administration

Lepirudin is a recombinant hirudin (p.1305) that is a direct inhibitor of thrombin. It is used as an anticoagulant in the management of thromboembolic disorders (p.1187) in patients with heparin-induced thrombocytopenia. It has been investigated in arterial thromboembolic disorders such as myocardial infarction and unstable angina.

In the management of thromboembolism in patients with heparin-induced thrombocytopenia lepirudin is given in an initial dose of 400 micrograms/kg by slow intravenous injection. This is followed by a maintenance dose of 150 micrograms/kg per hour by continuous intravenous infusion, adjusted according to response, usually for 2 to 10 days. Response should be monitored according to the activated partial thromboplastin time (APTT) ratio to achieve a target of 1.5 to 2.5. Doses must not exceed those based on a patient weight of 110 kg and in general an infusion rate of 210 micrograms/kg per hour should not be exceeded.

Doses of lepirudin should be reduced in patients with renal impairment, and infusions should be avoided in those on haemodialysis (see below).

Administration in renal impairment. Doses of lepirudin should be reduced in patients with renal impairment. The initial dose is reduced to 200 micrograms/kg, and the maintenance infusion rate is reduced according to creatinine clearance (CC):

- CC 45 to 60 mL/minute: infusion rate 50% of normal rate
- CC 30 to 44 mL/minute: 30% of normal rate
- CC 15 to 29 mL/minute: 15% of normal rate
- CC below 15 mL/minute: infusion of lepirudin should be avoided, although in haemodialysis patients or cases of acute renal failure further intravenous bolus doses of 100 micrograms/kg may be used on alternate days, according to response

Heparin-induced thrombocytopenia. Lepirudin is effective for the management of thromboembolism in patients with heparin-induced thrombocytopenia¹ (see Effects on the Blood under Adverse Effects of Heparin p.1302). Bleeding is the main complication during treatment, particularly with usual doses (see Uses and Administration, above) and in patients with renal impairment,² and use of lower doses has been suggested.^{1,2}

1. Lubenow N, *et al.* HIT Investigators Group. Lepirudin in patients with heparin-induced thrombocytopenia—results of the third prospective study (HAT-3) and a combined analysis of HAT-1, HAT-2, and HAT-3. *J Thromb Haemost* 2005; **3**: 2428–36.
2. Tardy B, *et al.* GEHT-HIT Study Group. Predictive factors for thrombosis and major bleeding in an observational study in 181 patients with heparin-induced thrombocytopenia treated with lepirudin. *Blood* 2006; **108**: 1492–6.

Ischaemic heart disease. Recombinant hirudins have been investigated as alternatives to heparin in the management of acute ST-elevation myocardial infarction (p.1175) and in non-ST elevation myocardial infarction and unstable angina (see Angina Pectoris, p.1157), and have been used as adjuncts to medical or interventional treatment. Overall they appear to have some benefit over heparin,¹ but their precise role in each situation remains to be confirmed.

The symbol ⊗ denotes a substance whose use may be restricted in certain sports (see p.vii)