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.: Develanid†; ***Mex.:*** Cedilanid.

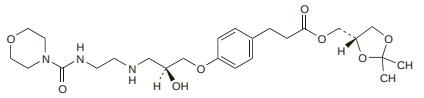
Landiolol Hydrochloride *(rINNM)* ⊗

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

Ландиолола Гидрохлорид

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

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



(landiolol)

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.

Lanoteplase *(USAN, rINN)*

BMS-200980; Lanoteplasa; Lanotéplase; Lanoteplasum; Sun-9216. *N*-[N^2-(*N*-Glycyl-L-alanyl)-L-arginyl]-117-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
Lanoteplase 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 lanoteplase vs accelerated alteplase for the treatment of patients with acute myocardial infarction. *Eur Heart J* 2000; **21:** 2005–13.

Lappaconitine Hydrobromide

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

Лаппаконитина Гидробромид

$C_{32}H_{44}N_2O_8$,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.

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, rINN)*

HBW-023; Lepirudiini; Lepirudina; Lépirudine; Lepirudinum. 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 reported[1] 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 review[2] 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 thrombocytopenia[1] (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.