(p.1165). It is also used to reduce mortality in patients with left ventricular dysfunction after myocardial infarction.

In **hypertension** carvedilol is given in an initial oral dose of 12.5 mg once daily, increased after two days to 25 mg once daily. Alternatively, an initial dose of 6.25 mg is given twice daily, increased after one to two weeks to 12.5 mg twice daily. The dose may be increased further, if necessary, at intervals of at least two weeks, to 50 mg once daily or in divided doses. A dose of 12.5 mg once daily may be adequate for elderly patients.

In **angina pectoris** an initial oral dose of 12.5 mg is given twice daily, increased after two days to 25 mg twice daily.

In **heart failure**, the initial oral dose is 3.125 mg twice daily. It should be taken with food to reduce the risk of hypotension. If tolerated, the dose should be doubled after two weeks to 6.25 mg twice daily and then increased gradually, at intervals of not less than two weeks, to the maximum dose tolerated; this should not exceed 25 mg twice daily in patients with severe heart failure or in those weighing less than 85 kg, or 50 mg twice daily in patients with mild to moderate heart failure weighing more than 85 kg. For doses in children, see below.

In patients with **left ventricular dysfunction after myocardial infarction**, the initial dose is 6.25 mg twice daily, increased after 3 to 10 days, if tolerated, to 12.5 mg twice daily and then to a target dose of 25 mg twice daily. A lower initial dose may be used in symptomatic patients.

A controlled-release preparation containing carvedilol phosphate hemihydrate is available in some countries.

◊ References.

1. Ruffolo RR, *et al.* The pharmacology of carvedilol. *Eur J Clin Pharmacol* 1990; **38:** S82–S88.
2. McTavish D, *et al.* Carvedilol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1993: **45:** 232–58.
3. Morgan T. Clinical pharmacokinetics and pharmacodynamics of carvedilol. *Clin Pharmacokinet* 1994; **26:** 335–46.
4. Louis WJ, *et al.* A risk-benefit assessment of carvedilol in the treatment of cardiovascular disorders. *Drug Safety* 1994; **11:** 86–93.
5. Dunn CJ, *et al.* Carvedilol: a reappraisal of its pharmacological properties and therapeutic use in cardiovascular disorders. *Drugs* 1997; **54:** 161–85.
6. Frishman WH. Carvedilol. *N Engl J Med* 1998; **339:** 1759–65.
7. Keating GM, Jarvis B. Carvedilol: a review of its use in chronic heart failure. *Drugs* 2003; **63:** 1697–1741.
8. Naccarelli GV, Lukas MA. Carvedilol's antiarrhythmic properties: therapeutic implications in patients with left ventricular dysfunction. *Clin Cardiol* 2005; **28:** 165–73.

Administration in children. Carvedilol has been used in children with heart failure, although experience is limited.[1] Beneficial effects have been reported, including improvement in symptoms and ejection fraction, and delaying the need for heart transplantation, and carvedilol appears to be well tolerated. Doses used have varied, with initial oral doses ranging from 10 to 180 micrograms/kg daily and average oral maintenance doses ranging from 200 to 700 micrograms/kg (maximum 50 mg) daily, usually given in two divided doses. However, a randomised study[2] in 161 children and adolescents with heart failure found that carvedilol was not significantly better than placebo: clinical improvement occurred in 56% of those taking carvedilol and 56% of those taking placebo.

In the UK, the *BNFC* recommends that children aged 2 to 18 years with heart failure may be given an initial oral dose of 50 micrograms/kg (maximum 3.125 mg) twice daily, increased as tolerated, by doubling the dose at intervals of at least 2 weeks, to a maintenance dose of 350 micrograms/kg (maximum 25 mg) twice daily.

1. Greenway SC, Benson LN. The use of carvedilol in pediatric heart failure. *Cardiovasc Hematol Disord Drug Targets* 2006; **6:** 35–42.
2. Shaddy RE, *et al.* Carvedilol for children and adolescents with heart failure: a randomized controlled trial. *JAMA* 2007; **298:** 1171–9.

Administration in the elderly. Licensed product information for carvedilol recommends an initial dose of 12.5 mg daily for all adults with hypertension. A study in 16 elderly hypertensive patients (mean age 70 years) given single doses of 12.5 mg and 25 mg found a high incidence of orthostatic hypotension[1] and the authors suggested that a starting dose lower than 12.5 mg may be necessary in elderly patients.

A retrospective study[2] found that standard initial doses for heart failure (see Uses and Administration, above) were well tolerated in elderly patients and that the mean achieved dose was similar in those aged under 70 years and those aged 70 years and older, after adjustment for weight. Adverse effects were more common in the older group, but could generally be managed without stopping carvedilol.

1. Krum H, *et al.* Postural hypotension in elderly patients given carvedilol. *BMJ* 1994; **309:** 775–6.
2. Lawless CE, *et al.* Titration of carvedilol in elderly heart failure patients. *Am J Geriatr Cardiol* 2005; **14:** 230–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Antibloc; Bidecar; Carvedil; Carvel†; Corafen; Coritensil; Corubin; Dilatrend; Duobloc; Filten; Hipoten; Isobloc; Kollosteril; Rodipal; Rudoxil; Veraten; Vicardol; ***Austral.:*** Dilatrend; Kredex; ***Austria:*** Dilatrend; Hybridil; ***Belg.:*** Dimitone; Kredex; ***Braz.:*** Cardilol; Carvedilat; Coreg; Dilatrend†; Divelol; Ictus; Karvil; ***Canad.:*** Coreg; ***Chile:*** Betaplex; Blocar; Dilatrend; Dualten; Lodipres; Novocar†; Off-Ten; ***Cz.:*** Apo-Carve; Atram; Carvedigamma; Carvesan; Carvetrend; Coryol; Dilatrend; Talliton; ***Denm.:*** Carvetone; Dimitone; ***Fin.:*** Cardiol; ***Fr.:*** Kredex; ***Ger.:*** CarLich; Carve; Carve-Q; Carvecard; Carvedigamma; Dilatrend; Dimetil; Querto; ***Gr.:*** Carvedilen; Carvepen; Dilatrend; ***Hong Kong:*** Dilatrend; ***Hung.:*** Carvedigamma; Carvol; Coryol; Dilatrend; Talliton; ***India:*** Carloc; Carvil; Cevas; ***Indon.:*** Carbloxal; Dilbloc; V-Bloc; ***Irl.:*** Biocard; Eucardic; ***Israel:*** Carvedexxon; Dimitone; ***Ital.:*** Carvipress; Colver; Dilatrend; Dilocar; ***Malaysia:*** Caslot; Cavel; Dilatrend; ***Mex.:*** Dilatrend; ***Neth.:*** Eucardic; ***Norw.:*** Kredex; ***NZ:*** Dilatrend; ***Philipp.:*** Dilatrend; ***Pol.:*** Atram; Carvedigamma; Carvetrend; Coryol; Dilatrend; Vivacor; ***Port.:*** Dilbloc; ***Rus.:*** Acridilole (Акридилол); Cardivas (Кардивас); Carvetrend (Карветренд); Carvidil (Карвидил); Coryol (Корионл); Talliton (Таллитон); ***S.Afr.:*** Carloc; Carvetrend; Dilatrend; ***Singapore:*** Dilatrend; ***Spain:*** Coropres; ***Swed.:*** Kredex; ***Switz.:*** Dilatrend; ***Thai.:*** Dilatrend; ***Turk.:*** Dilatrend; ***UK:*** Eucardic; ***USA:*** Coreg; ***Venez.:*** Carbatil; Carvedil; Coventrol; Dilatrend.

Multi-ingredient: ***Arg.:*** Carvedil D; ***Austria:*** Co-Dilatrend; Dilaplus.

Celiprolol Hydrochloride

(BANM, USAN, rINNM) ⊗

Céliprolol, chlorhydrate de; Celiprolol-hydrochlorid; Celiprolol-hydroklorid; Celiprololi hydrochloridum; Celiprololio hidrochloridas; Celiprololu chlorowodorek; Hidrocloruro de celiprolol; Seliprololihydrokloridi. 3-{3-Acetyl-4-[3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl}-1,1-diethylurea hydrochloride.

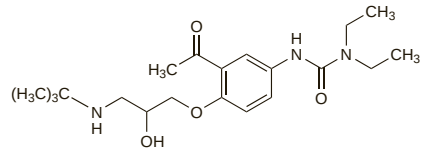
Целипролола Гидрохлорид

$C_{20}H_{33}N_3O_4$,HCl = 416.0.

CAS — 56980-93-9 (celiprolol); 57470-78-7 (celiprolol hydrochloride).

ATC — C07AB08.

ATC Vet — QC07AB08.



(celiprolol)

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

Ph. Eur. 6.2 (Celiprolol Hydrochloride). A white or very slightly yellow, crystalline powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; soluble in alcohol; very slightly soluble in dichloromethane. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Tremor and palpitations associated with intrinsic sympathomimetic activity at $beta_2$ receptors have been reported.

Interactions

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

Pharmacokinetics

Celiprolol is absorbed from the gastrointestinal tract in a non-linear fashion; the percentage of the dose absorbed increases with increasing dose. The plasma elimination half-life is about 5 to 6 hours. Celiprolol crosses the placenta. It has low lipid solubility and is about 25% bound to plasma proteins. Metabolism is minimal and celiprolol is mainly excreted unchanged in the urine and faeces.

Uses and Administration

Celiprolol is a cardioselective beta blocker (p.1225). It is reported to possess intrinsic sympathomimetic activity and direct vasodilator activity. Celiprolol is used as the hydrochloride in the management of hypertension (p.1171) and angina pectoris (p.1157). The usual oral dose of celiprolol hydrochloride is 200 to 400 mg once daily before food. Reduced doses may be required in patients with renal impairment (see below).

◊ References.

1. Milne RJ, Buckley MM-T. Celiprolol: an updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in cardiovascular disease. *Drugs* 1991; **41:** 941–69.
2. Anonymous. Celiprolol: theory and practice. *Lancet* 1991; **338:** 1426–7.
3. Anonymous. Celiprolol—a better beta blocker? *Drug Ther Bull* 1992; **30:** 35–6.
4. Kendall MJ, Rajman I. A risk-benefit assessment of celiprolol in the treatment of cardiovascular disease. *Drug Safety* 1994; **10:** 220–32.
5. Riddell J. Drugs in focus 18: celiprolol. *Prescribers' J* 1996; **36:** 165–8.

Administration in renal impairment. Celiprolol should not be given to patients with a creatinine clearance (CC) of less than 15 mL/minute. Patients with a CC between 15 and 40 mL/minute may be given 100 to 200 mg daily.

Preparations

BP 2008: Celiprolol Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Selectol; ***Belg.:*** Selectol; ***Chile:*** Selectol; ***Cz.:*** Celectol†; Tenoloc; ***Fin.:*** Selectol; ***Fr.:*** Celectol; ***Ger.:*** Celip; Celipro; Celiprogamma; Selectol; ***Gr.:*** Aplonit; Selectol; Versatil; ***Hong Kong:*** Selectol; ***Irl.:*** Selectol; ***Ital.:*** Cordiax; ***Jpn:*** Selectol; ***Neth.:*** Dilanorm; ***NZ:*** Celol; ***Pol.:*** Celipres; ***Spain:*** Cardem; ***Switz.:*** Selectol; ***UK:*** Celectol.

Multi-ingredient: ***Austria:*** Selecturon.

Certoparin Sodium *(BAN, rINN)*

Certoparin; Certoparina sódica; Certoparine Sodique; Certoparinum Natricum.

Цертопарин Натрий

Description. Certoparin sodium is prepared by amyl nitrite degradation of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-*O*-sulfo-2,5-anhydro-D-mannose structure at the reducing end of their chain. The molecular weight of 70% of the components is less than 10 000 and the average molecular weight is about 6000. The degree of sulfation is about 2 to 2.5 per disaccharide unit.

Units

As for Low-molecular-weight Heparins, p.1329.

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p.1329.

Severe bleeding with certoparin may be reduced by the slow intravenous injection of protamine salts; 1 mg of protamine hydrochloride is stated to inhibit the effects of 80 to 120 units of certoparin sodium.

Interactions

As for Low-molecular-weight Heparins, p.1329.

Pharmacokinetics

Certoparin sodium is rapidly and completely absorbed after subcutaneous injection. Peak plasma activity is reached within 2 to 4 hours. The half-life of anti-factor Xa activity is about 4 hours.

Uses and Administration

Certoparin sodium is a low-molecular-weight heparin (p.1329) with anticoagulant activity used for the prevention of postoperative venous thromboembolism (p.1189). It is given by subcutaneous injection in a dose of 3000 units 1 to 2 hours before the procedure, followed by 3000 units daily for 7 to 10 days or until the patient is fully ambulant.

◊ References.

1. Kolb G, *et al.* Reduction of venous thromboembolism following prolonged prophylaxis with the low molecular weight heparin certoparin after endoprothetic joint replacement or osteosynthesis of the lower limb in elderly patients. *Thromb Haemost* 2003; **90:** 1100–5.
2. Riess H, *et al.* Fixed-dose, body weight-independent subcutaneous low molecular weight heparin certoparin compared with adjusted-dose intravenous unfractionated heparin in patients with proximal deep venous thrombosis. *Thromb Haemost* 2003; **90:** 252–9.
3. Diener HC, *et al.* Prophylaxis of thrombotic and embolic events in acute ischemic stroke with the low-molecular-weight heparin certoparin: results of the PROTECT Trial. *Stroke* 2006; **37:** 139–44.
4. Tebbe U, *et al.* AFFECT: a prospective, open-label, multicenter trial to evaluate the feasibility and safety of a short-term treatment with subcutaneous certoparin in patients with persistent non-valvular atrial fibrillation. *Clin Res Cardiol* 2008; **97:** 389–96.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Sandoparin; Troparin; ***Cz.:*** Troparin†; ***Ger.:*** Mono-Embolex; ***Hung.:*** Sandoparin†; ***Switz.:*** Sandoparine; ***UK:*** Alphaparin†.

Multi-ingredient: ***Austria:*** Troparin compositum; ***Ger.:*** Embolex NM†.