Preparations

BP 2008: Acebutolol Capsules; Acebutolol Tablets;
USP 31: Acebutolol Hydrochloride Capsules.

Proprietary Preparations (details are given in Part 3)
Belg.: Sectral; ***Canad.:*** Monitan; Rhotral; Sectral; ***Chile:*** Beloc; Grifobutol; ***Cz.:*** Acecor; Apo-Acebutol; Sectral; ***Denm.:*** Diasectral; ***Fin.:*** Diasectral; Espesil; ***Fr.:*** Sectral; ***Ger.:*** Prent; ***Hong Kong:*** Sectral; ***Irl.:*** Sectral†; ***Israel:*** Sectral; ***Ital.:*** Prent; Sectral; ***Malaysia:*** Sectral†; ***Neth.:*** Sectral; ***NZ:*** ACB; ***Pol.:*** Abutol; Sectral; ***Port.:*** Prent; ***S.Afr.:*** Butobloc; Sectral; ***Singapore:*** ACB†; Sectral; ***Spain:*** Sectral†; ***Switz.:*** Sectral†; ***Turk.:*** Prent; ***UK:*** Sectral; ***USA:*** Sectral; ***Venez.:*** Flebutol†.

Multi-ingredient: ***Belg.:*** Sectrazide; ***Ger.:*** Sali-Prent; Tredalat; ***Indon.:*** Sectrazide; ***Neth.:*** Secadrex†; ***Spain:*** Secadrex†; ***UK:*** Secadrex†.

Acenocoumarol *(BAN, rINN)*

Acénocoumarol; Acenocoumarolum; Acenocumarin; Acenocumarol; Acenokumarol; Asenokumarol; G-23350; Nicoumalone; Nikumalon. (*RS*)-4-Hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl]-coumarin.

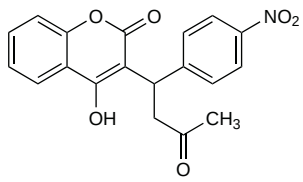
Аценокумарол

$C_{19}H_{15}NO_6$ = 353.3.

CAS — 152-72-7.

ATC — B01AA07.

ATC Vet — QB01AA07.



Pharmacopoeias. In *Br.* and *Pol.*
BP 2008 (Acenocoumarol). An almost white to buff-coloured odourless or almost odourless powder. It exhibits polymorphism. Practically insoluble in water and in ether; slightly soluble in alcohol and in chloroform; dissolves in aqueous solutions of alkali hydroxides.

Adverse Effects, Treatment, and Precautions

As for Warfarin Sodium, p.1425.

Effects on the fetus. In a group of women who received acenocoumarol for anticoagulant prophylaxis of mechanical heart valves during pregnancy,[1] fetal loss occurred in 13 of 61 pregnancies where oral anticoagulation was continued during the first trimester. Apart from 1 case of hydrocephalus no malformations were reported in the remaining neonates.

1. Meschengieser SS, *et al.* Anticoagulation in pregnant women with mechanical heart valve prostheses. *Heart* 1999; **82:** 23–6.

Interactions

The interactions associated with oral anticoagulants are discussed in detail under warfarin (p.1427). Specific references to interactions involving acenocoumarol can be found there under the headings for the following drug groups: analgesics; antiarrhythmics; antibacterials; antidepressants; antifungals; antigout drugs; antihistamines; antineoplastics; antiplatelets; antivirals; diuretics; gastrointestinal drugs; immunosuppressants; lipid regulating drugs; sex hormones; and vaccines.

Pharmacokinetics

Acenocoumarol is readily absorbed from the gastrointestinal tract and is excreted chiefly in the urine mainly as metabolites. It is extensively bound to plasma proteins. Figures reported for elimination half-life vary; UK licensed product information gives a range of 8 to 11 hours. Acenocoumarol crosses the placenta; only small quantities have been detected in breast milk. It is given as a racemic mixture; the *R*-isomer is more potent. The stereo-isomers have different pharmacokinetics. Metabolism of the *S*-isomer is mediated mainly by the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism; other isoenzymes as well are involved in the metabolism of the *R*-isomer.

◊ References.

1. Ufer M. Comparative pharmacokinetics of vitamin K antagonists: warfarin, phenprocoumon and acenocoumarol. *Clin Pharmacokinet* 2005; **44:** 1227–46.

Uses and Administration

Acenocoumarol is an oral coumarin anticoagulant with actions similar to those of warfarin (p.1432). It is used in the management of thromboembolic disorders (p.1187). The usual dose is 4 to 12 mg on the first day and 4 to 8 mg on the second day; subsequent maintenance doses range from 1 to 8 mg depending on the response. Acenocoumarol is given in a single dose at the same time every day.

Preparations

BP 2008: Acenocoumarol Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Acenotromb; Antitrom; Azecar; Cumarol; Fortonol; Saxion; Sintrom; ***Austria:*** Sintrom; ***Belg.:*** Sintrom; ***Canad.:*** Sintrom; ***Chile:*** Acenox; Coarol; Isquelium; Neo-Sintrom; ***Fr.:*** Mini-sintrom; Sintrom; ***Gr.:*** Sintrom; ***Hung.:*** Syncumar; ***India:*** Acitrom; ***Israel:*** Sintrom; ***Ital.:*** Sintrom; ***Mex.:*** Sintrom; ***Neth.:*** Sintrom Mitis; ***Pol.:*** Sintrom; Syncumar; ***Port.:*** Sintrom; ***Spain:*** Sintrom; ***Switz.:*** Sintrom; ***UK:*** Sinthrome.

Acetyldigoxin

Acetildigoxina; Acetyldigoxin-beta; Acetyldigoxinum; β-Acetyldigoxinum; Acetyldigoxinum Beta; β-Acetylodigoksyna; Asetyylidigoksiini; Desglucolanatoside C. 3β-[(*O*-3-*O*-Acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,-14-dihydroxy-5β,14β-card-20(22)-enolide (α-acetyldigoxin); 3β-[(*O*-4-*O*-Acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β,14β-card-20(22)-enolide (β-acetyldigoxin).

$C_{43}H_{66}O_{15}$ = 823.0.

CAS — 5511-98-8 (α-acetyldigoxin); 5355-48-6 (β-acetyldigoxin).

ATC — C01AA02.

ATC Vet — QC01AA02.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (β-Acetyldigoxin). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

Profile

Acetyldigoxin is a cardiac glycoside with positive inotropic activity. It has the general properties of digoxin (p.1259) and has been used similarly in the management of some cardiac arrhythmias (p.1160) and in heart failure (p.1165). Usual oral maintenance doses for the β-isomer are 200 to 400 micrograms daily; the α-isomer has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Corotal; Lanatilin; Novodigal; ***Ger.:*** Digostada; Digotab; Digox; Digoxin "Didier"†; Novodigal; Stillacor; ***Ital.:*** Cardioreg†.

Multi-ingredient: ***Austria:*** Digi-Aldopur; Gladixol.

Acipimox *(BAN, rINN)*

Acipimoxum; Asipimoks; Asipimoksi; K-9321. 5-Methylpyrazine-2-carboxylic acid 4-oxide.

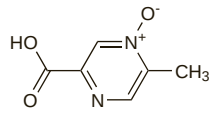
Аципимокс

$C_6H_6N_2O_3$ = 154.1.

CAS — 51037-30-0.

ATC — C10AD06.

ATC Vet — QC10AD06.



Adverse Effects and Precautions

Acipimox may cause peripheral vasodilatation resulting in flushing, itching, and a sensation of heat. Rash and erythema may occur. Gastrointestinal disturbances including heartburn, epigastric pain, nausea, and diarrhoea have been reported, as well as headache, malaise, myalgia, myositis, arthralgia, and dry eye. Urticaria, angioedema, and bronchospasm may occur rarely.

Acipimox is contra-indicated in patients with peptic ulcer disease. It should be used with caution in renal impairment.

Incidence of adverse effects. In a study involving 3009 hyperlipidaemic patients with type 2 diabetes,[1] adverse effects associated with acipimox occurred in 8.8%, resulting in withdrawal in 5.5% of patients. The most frequent adverse effects involved the skin (57.6%), gastrointestinal tract (25.8%), and CNS (9.7%). Labial oedema occurred in 3 cases and an urticarial eruption, collapse, and dyspnoea in another. The incidence of adverse effects was almost twice as high in females as in males, the difference being mainly due to a greater incidence of flushing, pruritus, and skin rashes. The incidence was not affected by age. There was a mean 15.3% reduction in fasting blood-glucose concentrations and an 8.5% reduction in glycosylated haemoglobin during treatment with acipimox.

1. Lavezzari M, *et al.* Results of a phase IV study carried out with acipimox in type II diabetic patients with concomitant hyperlipoproteinaemia. *J Int Med Res* 1989; **17:** 373–80.

Pharmacokinetics

Acipimox is rapidly and completely absorbed from the gastrointestinal tract and peak plasma concentrations occur within 2 hours. It does not bind to plasma proteins and the plasma half-life is about 2 hours. It is not significantly metabolised and is excreted in the urine, largely unchanged.

Uses and Administration

Acipimox is a lipid regulating drug related to nicotinic acid (p.1957). It is used to reduce cholesterol and triglycerides in the management of hyperlipidaemias (see Action, below), including type IIa, IIb, or IV hyperlipoproteinaemias.

Acipimox is given orally in a usual dose of 250 mg two or three times daily, taken with meals. Doses of up to 1200 mg daily have been used. The dose should be adjusted in renal impairment (see below).

Action. Acipimox is used in the management of hyperlipidaemias (p.1169); it is a derivative of nicotinic acid and has similar effects on plasma lipoproteins but is better tolerated.[1] Its primary action is inhibition of lipolysis, leading to a reduction in circulating free fatty acids and consequently a reduction in very-low-density lipoprotein (VLDL) production in the liver. This results in a reduction of triglycerides, particularly in patients with hypertriglyceridaemia;[2] there may also be a decrease in low-density lipoprotein (LDL)-cholesterol and total cholesterol, and an increase in high-density lipoprotein (HDL)-cholesterol. Similar effects have been reported in patients with mixed hyperlipoproteinaemias, although the reduction of triglycerides and LDL-cholesterol was not significant.[3]

Reduction of free fatty acids by acipimox has a number of other physiological effects that have been utilised. Insulin secretion and sensitivity may be modified, and acipimox has been tried in type 2 diabetes mellitus; it improves plasma lipids and may also reduce blood-glucose concentrations,[4] and has been of benefit in patients with type A insulin resistance.[5] Beneficial effects have also been reported[6] in patients with HIV-associated lipodystrophy and insulin resistance. Growth hormone secretion is stimulated in obese subjects, and acipimox has been used in the investigation of growth hormone disorders.[7] There is also an increase in glucose uptake by the heart, and acipimox has been used to enhance myocardial imaging in ^{18}F-fluorodeoxyglucose positron-emission tomography.[8]

1. Tornvall P, Walldius G. A comparison between nicotinic acid and acipimox in hypertriglyceridaemia—effects on serum lipids, lipoproteins, glucose tolerance and tolerability. *J Intern Med* 1991; **230:** 415–21.
2. Ball MJ, *et al.* Acipimox in the treatment of patients with hyperlipidaemia: a double blind trial. *Eur J Clin Pharmacol* 1986; **31:** 201–4.
3. Otto C, *et al.* Effects of acipimox on haemorheology and plasma lipoproteins in patients with mixed hyperlipoproteinaemia. *Br J Clin Pharmacol* 1998; **46:** 473–8.
4. Lavezzari M, *et al.* Results of a phase IV study carried out with acipimox in type II diabetic patients with concomitant hyperlipoproteinaemia. *J Int Med Res* 1989; **17:** 373–80.
5. Kumar S, *et al.* Suppression of non-esterified fatty acids to treat type A insulin resistance syndrome. *Lancet* 1994; **343:** 1073–4.
6. Hadigan C, *et al.* Inhibition of lipolysis improves insulin sensitivity in protease inhibitor-treated HIV-infected men with fat redistribution. *Am J Clin Nutr* 2003; **77:** 490–4.
7. Cordido F, *et al.* Effect of acute pharmacological reduction of plasma free fatty acids on growth hormone (GH) releasing hormone-induced GH secretion in obese adults with and without hypopituitarism. *J Clin Endocrinol Metab* 1998; **83:** 4350–4.
8. Knuuti MJ, *et al.* Enhancement of myocardial [fluorine-18]fluorodeoxyglucose uptake by a nicotinic acid derivative. *J Nucl Med* 1994; **35:** 989–98.

Administration in renal impairment. Acipimox is contra-indicated in patients with a creatinine clearance below 30 mL/minute. In patients with creatinine clearance between 30 and 60 mL/minute, the interval between doses should be increased.