Ivabradine *(rINN)*

Ivabradina; Ivabradinum; S-16257; S-16257-2 (ivabradine hydrochloride). 3-[3-({[(7*S*)-3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}methylamino)propyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-2*H*-3-benzazepin-2-one.

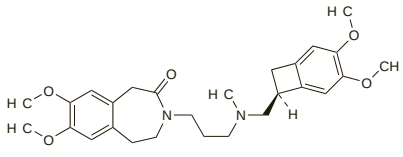
Ивабрадин

$C_{27}H_{36}N_2O_5$ = 468.6.

CAS — 155974-00-8 (ivabradine); 148849-67-6 (ivabradine hydrochloride).

ATC — C01EB17.

ATC Vet — QC01EB17.



Adverse Effects

The most common adverse effects seen with ivabradine are luminous phenomena in the visual field (phosphenes). Other adverse effects include blurred vision, bradycardia, which may be severe, and other cardiac arrhythmias, nausea, constipation, diarrhoea, headache, dizziness, dyspnoea, and muscle cramps. Hyperuricaemia, eosinophilia, and elevated blood-creatinine concentrations have been reported.

◊ Reviews.

1. Savelieva I, Camm AJ. I inhibition with ivabradine: electrophysiological effects and safety. *Drug Safety* 2008; **31:** 95–107.

Precautions

Ivabradine should not be given to patients with resting heart rate below 60 beats/minute, or to patients with cardiogenic shock, severe conduction defects, acute myocardial infarction, or unstable angina. Heart failure should be controlled before ivabradine is started; it has not been studied in severe heart failure. Ivabradine should not be used in patients with congenital QT prolongation. Ivabradine is not recommended in atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function, and regular monitoring for such arrhythmias should be performed. If resting heart rate falls below 50 beats/minute the dose should be reduced; treatment should be stopped if this rate persists.

Ivabradine is contra-indicated in severe hypotension and severe hepatic impairment, and should be used with caution in severe renal impairment.

If unexpected deterioration in visual function occurs, stopping treatment may be considered. Caution should be observed in patients with retinitis pigmentosa.

Studies in *animals* have shown that ivabradine is embryotoxic and teratogenic, and is distributed into breast milk.

Interactions

Ivabradine should not generally be used with drugs that prolong the QT interval.

Ivabradine is metabolised by the cytochrome P450 isoenzyme CYP3A4, and should not be used with potent inhibitors of this enzyme, including azole antifungals such as ketoconazole and itraconazole, macrolide antibacterials such as clarithromycin, HIV-protease inhibitors such as nelfinavir and ritonavir, and nefazodone. Use with the moderate CYP3A4 inhibitors diltiazem and verapamil is also not recommended as the increase in exposure to ivabradine may cause an additional reduction in heart rate. Ivabradine may be used cautiously with other moderate inhibitors, such as fluconazole, at a lower starting dose of 2.5 mg twice daily, with monitoring of the heart rate. Consumption of grapefruit juice should be restricted.

Use with CYP3A4 inducers, such as rifampicin and phenytoin, may require an increase in the dose of ivabradine. St John's wort reduces the exposure to ivabradine by half and its use should be restricted.

Pharmacokinetics

Ivabradine is almost completely absorbed after oral doses but bioavailability is about 40% because of first-pass metabolism. Peak plasma concentrations are achieved after about 1 hour in the fasting state but this is delayed by 1 hour by food and the extent of absorption increased by 20 to 30%. Ivabradine is about 70% bound to plasma proteins.

Ivabradine undergoes extensive metabolism in the liver and gut via the cytochrome P450 isoenzyme CYP3A4 to its main active metabolite *N*-desmethylivabradine (S-18982). This is further metabolised to some degree by CYP3A4. Ivabradine has an elimination half-life of 2 hours. Its metabolites are excreted to a similar extent in the urine and faeces. About 4% of a dose appears in the urine as the parent drug. *Animal* studies indicate that ivabradine is distributed into breast milk.

Uses and Administration

Ivabradine is a selective sinus node I_f inhibitor used in the treatment of angina pectoris in patients unable to take beta blockers. It is given as the hydrochloride, but doses are described in terms of the base; 5.4 mg of ivabradine hydrochloride is equivalent to about 5 mg of ivabradine. It is given orally with food in a usual initial dose of 5 mg twice daily, increased after 3 or 4 weeks if necessary to 7.5 mg twice daily. If the heart rate falls persistently below 50 beats/minute or there are symptoms of bradycardia the dose should be titrated downwards, to as low as 2.5 mg twice daily if necessary. Treatment should be stopped if this low rate or symptoms of bradycardia persist.

In the elderly (75 years or above), a lower initial dose of 2.5 mg twice daily should be considered, before increasing if necessary.

◊ Reviews.

1. DiFrancesco D, Camm JA. Heart rate lowering by specific and selective I current inhibition with ivabradine: a new therapeutic perspective in cardiovascular disease. *Drugs* 2004; **64:** 1757–65.
2. Sulfi S, Timmis AD. Ivabradine—the first selective sinus node I channel inhibitor in the treatment of stable angina. *Int J Clin Pract* 2006; **60:** 222–8.
3. Menown IBA. Ivabradine: a new strategy for management of stable angina. *Br J Hosp Med* 2007; **68:** 321–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Coralan; ***Cz.:*** Corlentor; Procoralan; ***Fr.:*** Corlentor; Procoralan; ***Ger.:*** Procoralan; ***Gr.:*** Procoralan; ***Irl.:*** Procoralan; ***Neth.:*** Corlentor; Procoralan; ***Pol.:*** Procoralan; ***Port.:*** Corlentor; Procoralan; ***Rus.:*** Coraxan (Кораксан); ***UK:*** Procoralan.

Ketanserin *(BAN, USAN, rINN)*

Ketanseriini; Ketanserina; Kétansérine; Ketanserinum; R-41468. 3-{2-[4-(4-Fluorobenzoyl)piperidino]ethyl}quinazoline-2,4(1*H*,3*H*)-dione.

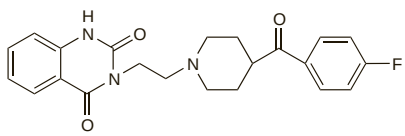
Кетансерин

$C_{22}H_{22}FN_3O_3$ = 395.4.

CAS — 74050-98-9.

ATC — C02KD01.

ATC Vet — QC02KD01; QD03AX90.



Ketanserin Tartrate *(BANM, rINNM)*

Kétansérine, Tartrate de; Ketanserini Tartras; R-49945; Tartrato de ketanserina.

Кетансерина Тартрат

$C_{22}H_{22}FN_3O_3,C_4H_6O_6$ = 545.5.

CAS — 83846-83-7.

ATC — C02KD01.

ATC Vet — QC02KD01.

Adverse Effects and Precautions

Ketanserin has been reported to cause sedation, fatigue, lightheadedness, dizziness, headache, dry mouth, and gastrointestinal disturbances. Oedema has been reported rarely. In patients with predisposing factors such as QT prolongation, chronic use of ketanserin has been associated with ventricular arrhythmias including torsade de pointes; ketanserin should be used with caution in patients taking antiarrhythmics and should not be used in second- or third-degree AV block. Care should be taken to avoid the development of hypokalaemia in patients taking ketanserin, for example if diuretics are also given.

Because ketanserin may cause drowsiness care should be taken in patients who drive or operate machinery.

Ketanserin is reported to be better tolerated in elderly than in younger patients.

Interactions

The hypotensive effects of ketanserin may be enhanced by diuretics and other antihypertensives. Ketanserin should be used with caution in patients taking antiarrhythmics or drugs that cause hypokalaemia since the risk of arrhythmias is increased.

Beta blockers. Profound hypotension occurred in 2 patients one hour after taking ketanserin 40 mg orally.[1] Both patients were also taking a beta blocker which may have exacerbated the reaction.

1. Waller PC, *et al*. Profound hypotension after the first dose of ketanserin. *Postgrad Med J* 1987; **63:** 305–7.

Pharmacokinetics

Ketanserin is rapidly absorbed from the gastrointestinal tract but has a bioavailability of about 50% due to first-pass hepatic metabolism. Peak plasma concentrations occur between 30 and 120 minutes after an oral dose. Ketanserin is about 95% bound to plasma proteins. The terminal half-life is stated to be between 13 and 18 hours but some studies report that following multiple doses the half-life is 19 to 29 hours. The metabolite ketanserinol has a terminal half-life of 31 to 35 hours after multiple doses, and it has been suggested that reconversion of ketanserinol to ketanserin may be responsible for the prolonged half-life of the parent compound during chronic use.

About 68% of an oral dose is excreted in urine, and 24% in faeces, mainly as metabolites. Studies in *animals* suggest that ketanserin may cross the placenta and that some is present, with metabolites, in breast milk.

◊ References.

1. Persson B, *et al*. Clinical pharmacokinetics of ketanserin. *Clin Pharmacokinet* 1991; **20:** 263–79.

Uses and Administration

Ketanserin is a serotonin antagonist with a high affinity for peripheral serotonin-2 ($5\text{-}HT_2$) receptors and thus inhibits serotonin-induced vasoconstriction, bronchoconstriction, and platelet aggregation. It also has some $alpha_1$-antagonist and histamine H_1-antagonist properties, but the clinical significance of these is controversial.

Ketanserin is used in the management of hypertension (p.1171) and has also been tried in other conditions (see below).

Ketanserin is given as the tartrate, but doses are usually expressed in terms of the base. Ketanserin tartrate 27.6 mg is equivalent to about 20 mg of ketanserin.

Ketanserin produces a gradual hypotensive effect when given orally, and 2 or 3 months of therapy may be required to produce the maximum reduction in blood pressure. After intravenous injection a fall in blood pressure is generally produced in 1 or 2 minutes and lasts for 30 to 60 minutes.

In **hypertension** the usual initial oral dose is 20 mg twice daily, increasing, if necessary, after 2 to 4 weeks, to 40 mg twice daily. It has also been given by intravenous or intramuscular injection. The dose of ketanserin may need to be reduced, or the dosage intervals increased, in patients with hepatic impairment (see below).

◊ Reviews.

1. Brogden RN, Sorkin EM. Ketanserin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in hypertension and peripheral vascular disease. *Drugs* 1990; **40:** 903–49.

Administration in hepatic impairment. A study[1] in patients with cirrhosis found that the half-life and volume of distribution of ketanserin were decreased but the area under the concentration-time curve was markedly increased; the rate of metabolism was reduced. The results suggested that the dosage should be reduced or the dosage interval increased when ketanserin is given to patients with cirrhosis.

Licensed product information recommends a maximum oral dose of 20 mg twice daily for patients with severe hepatic impairment.

1. Lebrec D, *et al*. Pharmacokinetics of ketanserin in patients with cirrhosis. *Clin Pharmacokinet* 1990; **19:** 160–6.

Administration in renal impairment. Results from a study in 12 patients with chronic renal impairment, of whom 6 required haemodialysis, suggested that no adjustment of a dose of ketanserin 20 mg twice daily was required in patients with renal impairment.[1]

1. Barendregt JNM, *et al*. Ketanserin pharmacokinetics in patients with renal failure. *Br J Clin Pharmacol* 1990; **29:** 715–23.

Peripheral vascular disease. Ketanserin is one of many drugs that have been tried in the management of peripheral vascular disease (p.1178) but results have been contradictory. Subgroup analysis of the multicentre Prevention of Atherosclerotic Complications with Ketanserin Trial (PACK),[1] involving 3899 patients with intermittent claudication, suggested that ketanserin might be of benefit in preventing limb amputation in some patients. Conflicting results have also been reported in patients with Raynaud's syndrome (see Vasospastic Arterial Disorders, p.1188). A systematic review[2] found that ketanserin led to a small improvement in Raynaud's syndrome in patients with systemic sclerosis but that adverse effects increased; the authors concluded that ketanserin was not clinically beneficial in such patients.

Ketanserin has also been tried in other conditions associated with impaired peripheral blood flow: see Wounds and Ulcers, below.

1. Prevention of Atherosclerotic Complications with Ketanserin Trial Group. Prevention of atherosclerotic complications: controlled trial of ketanserin. *BMJ* 1989; **298:** 424–30. Correction. *ibid.*: 644.
2. Pope JE, *et al.* Ketanserin for Raynaud's phenomenon in progressive systemic sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 26/09/05).

Shivering. Numerous drugs, including ketanserin, have been tried for the treatment of postoperative shivering (p.1779). Ketanserin 10 mg given intravenously has stopped shivering after general anaesthesia.[1,2]

1. Joris J, *et al.* Clonidine and ketanserin both are effective treatment for postanesthetic shivering. *Anesthesiology* 1993; **79:** 532–9.
2. Crisinel D, *et al.* Efficacité de la kétansérine sur le frisson postanesthésique. *Ann Fr Anesth Reanim* 1997; **16:** 120–5.

Wounds and ulcers. Several controlled studies[1-5] have noted improved healing of decubitus, venous, and ischaemic ulcers (see Wounds and Ulcers, p.1585) after topical use of ketanserin 2%. However, when applied topically to surgical wounds no improvement was found and it was suggested that ketanserin is only of benefit where blood supply is compromised.[6]

1. Tytgat H, van Asch H. Topical ketanserin in the treatment of decubitus ulcers: a double-blind study with 2% ketanserin ointment against placebo. *Adv Therapy* 1988; **5:** 143–52.
2. Roelens P. Double-blind placebo-controlled study with topical 2% ketanserin ointment in the treatment of venous ulcers. *Dermatologica* 1989; **178:** 98–102.
3. Janssen PAJ, *et al.* Use of topical ketanserin in the treatment of skin ulcers: a double-blind study. *J Am Acad Dermatol* 1989; **21:** 85–90.
4. Martinez-de Jesus FR, *et al.* Randomized single-blind trial of topical ketanserin for healing acceleration of diabetic foot ulcers. *Arch Med Res* 1997; **28:** 95–9.
5. Salazar JJ, *et al.* Use of topical ketanserin for the treatment of ulcers in leprosy patients. *Indian J Lepr* 2001; **73:** 103–10.
6. Lawrence CM, *et al.* The effect of ketanserin on healing of fresh surgical wounds. *Br J Dermatol* 1995; **132:** 580–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Serefrex†; ***Belg.:*** Sufrexal; ***Ital.:*** Serepress; ***Mex.:*** Sufrexal; ***Neth.:*** Ketensin; ***Port.:*** Sufrexal†; ***Thai.:*** Sufrexal†.

Multi-ingredient: *Mex.:* Sufrexal P.

Labetalol Hydrochloride

(BANM, USAN, rINNM) ⊗

AH-5158A; Hidrocloruro de labetalol; Ibidomide Hydrochloride; Labétalol, chlorhydrate de; Labetalol hydrochlorid; Labetalol-hidroklorid; Labetalolhydroklorid; Labetaloli hydrochloridum; Labetalolihydrokloridi; Labetalolio hidrocloridas; Sch-15719W. 5-[1-Hydroxy-2-(1-methyl-3-phenylpropylamino)ethyl]salicylamide hydrochloride.

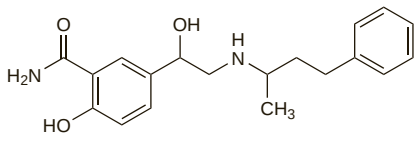
Лабеталола Гидрохлорид

$C_{19}H_{24}N_2O_3,HCl$ = 364.9.

CAS — 36894-69-6 (labetalol); 32780-64-6 (labetalol hydrochloride).

ATC — C07AG01.

ATC Vet — QC07AG01.



(labetalol)

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

Ph. Eur. 6.2 (Labetalol Hydrochloride). A white or almost white powder. Sparingly soluble in water and in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 4.0 to 5.0.

USP 31 (Labetalol Hydrochloride). A white to off-white powder. Soluble in water and in alcohol; insoluble in chloroform and in ether. A 1% solution in water has a pH of 4.0 to 5.0. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Labetalol hydrochloride is compatible with standard intravenous solutions such as glucose 5% and sodium chloride 0.9%. However, precipitation has been reported when labetalol hydrochloride is added to sodium bicarbonate injection 5%.[1] The precipitate is probably labetalol base.[2]

Immediate formation of a precipitate has also been reported when labetalol (generally 5 mg/mL in glucose 5%) was mixed with other drugs including ceftriaxone,[3] furosemide,[4] heparin,[5] insulin,[5] proton pump inhibitors such as pantoprazole,[6] and thiopental.[4] There has also been a report of immediate haze after admixture of labetalol hydrochloride (800 micrograms/mL) with warfarin sodium.[7]

1. Yuen P-HC, *et al.* Compatibility and stability of labetalol hydrochloride in commonly used intravenous solutions. *Am J Hosp Pharm* 1983; **40:** 1007–9.
2. Alam AS. Identification of labetalol precipitate. *Am J Hosp Pharm* 1984; **41:** 74.
3. Leader WG, Jones JM. Incompatibility between ceftriaxone sodium and labetalol hydrochloride. *Am J Health-Syst Pharm* 1996; **53:** 2639.
4. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
5. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1048–51.
6. Péré H, *et al.* Compatibilité du pantoprazole injectable lors d'administration en Y. *Pharmactuel* 2004; **37:** 193–6.
7. Bahal SM, *et al.* Visual compatibility of warfarin sodium injection with selected medications and solutions. *Am J Health-Syst Pharm* 1997; **54:** 2599–2600.

Adverse Effects

The adverse effects associated with beta blockers are described on p.1226. Labetalol also has alpha-blocking activity, which contributes to its adverse effects and these effects may predominate. Orthostatic hypotension may be a problem with high doses or at the start of treatment. Other effects associated with alpha blockade include dizziness, scalp tingling, and nasal congestion. Male sexual function may be impaired to a greater extent than with beta blockade alone. Muscle weakness, tremor, urinary retention, hepatitis, and jaundice have also been reported.

Effects on the liver. By 1990, the FDA had received 11 reports of hepatocellular damage associated with labetalol therapy.[1] Three patients died. Liver function should be monitored and labetalol stopped in patients who develop liver function abnormalities. The *R,R*-isomer of labetalol, dilevalol, was withdrawn from the market because of hepatotoxicity.[2]

1. Clark JA, *et al.* Labetalol hepatotoxicity. *Ann Intern Med* 1990; **113:** 210–13.
2. Harvengt C. Labetalol hepatotoxicity. *Ann Intern Med* 1991; **114:** 341.

Hypersensitivity. Hypersensitivity reactions associated with labetalol may manifest as fever.[1,2] Anaphylactoid reaction to labetalol has also been reported.[3]

1. D'Arcy PF. Drug reactions and interactions: drug fever with labetalol. *Int Pharm J* 1987; **1:** 43–4.
2. Stricker BH, *et al.* Fever induced by labetalol. *JAMA* 1986; **256:** 619–20.
3. Ferree CE. Apparent anaphylaxis from labetalol. *Ann Intern Med* 1986; **104:** 729–30.

Overdosage. Acute oliguric renal failure developed after a short period of moderate hypotension in a patient who ingested labetalol 16 g. Renal function subsequently recovered.[1] Renal failure has also been reported[2] after ingestion of labetalol 6 g. The patient recovered after treatment with glucagon, isoprenaline, and dialysis. Another patient[3] developed circulatory collapse and impaired consciousness after being given labetalol 800 mg orally for hypertensive crisis; glucagon and sympathomimetics were given to restore blood pressure, but amrinone infusion was also needed to improve cardiac output and mental state.

1. Smit AJ, *et al.* Acute renal failure after overdose of labetalol. *BMJ* 1986; **293:** 1142–3.
2. Korzets A, *et al.* Acute renal failure associated with a labetalol overdose. *Postgrad Med J* 1990; **66:** 66–7.
3. Kollef MH. Labetalol overdose successfully treated with amrinone and alpha-adrenergic receptor agonists. *Chest* 1994; **105:** 626–7.

Precautions

As for Beta Blockers, p.1227.

Because labetalol causes orthostatic hypotension it is recommended that injections are given to patients when they are lying down and that patients should remain lying down for the next 3 hours.

Labetalol should be withdrawn from patients who develop signs of hepatic impairment.

Breast feeding. Labetalol is distributed into breast milk, although it has been suggested[1] that the proportion of a maternal dose likely to be ingested by the infant is very low. In a study[2] in 25 patients, the mean concentration of labetalol in breast milk was less than in maternal plasma in patients given doses between 330 and 800 mg daily, although in 1 patient given 1200 mg daily a higher concentration was found in breast milk. In another study,[3] the concentration of drug in milk exceeded maternal plasma concentration in 2 of 3 mothers, and in 1 infant the plasma-labetalol concentration was similar to that of the mother. However, no adverse effects have been seen in breast-feeding infants whose mothers were given labetalol, and the American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding.

1. Atkinson H, Begg EJ. Concentrations of beta-blocking drugs in human milk. *J Pediatr* 1990; **116:** 156.
2. Michael CA. Use of labetalol in the treatment of severe hypertension during pregnancy. *Br J Clin Pharmacol* 1979; **8** (suppl 2): 211S–215S.
3. Lunell NO, *et al.* Transfer of labetalol into amniotic fluid and breast milk in lactating women. *Eur J Clin Pharmacol* 1985; **28:** 597–9.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Interactions

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

Pharmacokinetics

Labetalol is readily absorbed from the gastrointestinal tract, but is subject to considerable first-pass metabolism. Bioavailability varies widely between patients and may be increased in the presence of food. Peak plasma concentrations occur about 1 to 2 hours after an oral dose. Labetalol has low lipid solubility and only very small amounts appear to cross the blood-brain barrier in *animals*. It is about 50% protein bound. Labetalol crosses the placenta and is distributed into breast milk (see above). Labetalol is metabolised mainly in the liver, the metabolites being excreted in the urine with only small amounts of unchanged labetalol; its major metabolite has not been found to have significant alpha- or beta-blocking effects. Excretion also occurs in the faeces via the bile. The elimination half-life at steady state is reported to be about 6 to 8 hours. On intravenous infusion, the elimination half-life is about 5.5 hours. Labetalol is not removed by dialysis.

The elderly. Analysis[1] of data from 4 single-dose studies and 3 multidose studies indicated that age did not appear to be a significant factor in oral clearance in elderly patients receiving labetalol for long-term management of hypertension.

1. Rocci ML, *et al.* Effects of age on the elimination of labetalol. *Clin Pharmacokinet* 1989; **17:** 452–7.

Pregnancy. The concentration of labetalol has been found to be lower in amniotic fluid[1] and fetal plasma[2] than in maternal plasma. A ratio of infant to maternal drug concentration of 0.2 to 0.8 has been reported[2] based on concentration in infant cord blood at delivery [time since last maternal dose not stated]. In another study,[3] however, higher concentrations were found in cord plasma than in maternal plasma at delivery when infants were delivered 12 to 24 hours after the last maternal dose.

The half-life of labetalol was reported as 24 hours in a neonate of 37 weeks' gestation whose mother had received labetalol 600 mg daily for 11 weeks prior to delivery.[4]

1. Lunell NO, *et al.* Transfer of labetalol into amniotic fluid and breast milk in lactating women. *Eur J Clin Pharmacol* 1985; **28:** 597–9.
2. Michael CA. Use of labetalol in the treatment of severe hypertension during pregnancy. *Br J Clin Pharmacol* 1979; **8** (suppl 2): 211S–215S.
3. Boulton DW, *et al.* Transplacental distribution of labetalol stereoisomers at delivery. *Br J Clin Pharmacol* 1999; **47:** 573–4.
4. Haraldsson A, Geven W. Half-life of maternal labetalol in a premature infant. *Pharm Weekbl (Sci)* 1989; **11:** 229–31.

Uses and Administration

Labetalol is a non-cardioselective beta blocker (p.1225). It is reported to possess some intrinsic sympathomimetic and membrane-stabilising activity. In addition, it has selective $alpha_1$-blocking properties which decrease peripheral vascular resistance. The ratio of alpha- to beta-blocking activity has been estimated to be about 1:3 after oral doses and 1:7 after intravenous doses.