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.

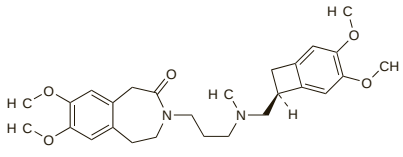
Ивабрадин

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

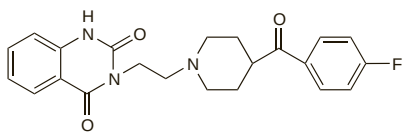
Кетансерин

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