For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

IVANODE OD 10

1. Generic Name

Ivabradine Prolonged Release Tablets 10mg

2. Qualitative and quantitative Composition:

Each film coated prolonged release tablet contains:

Ivabradine Hydrochloride

Equivalent to Ivabradine……10mg

Excipients……...q.s.

Colours: Red Oxide of Iron Lake, Yellow Oxide of Iron Lake & Titanium Dioxide I.P.

The excipients used are Hydroxypropyl Methylcellulose Microcrystalline Cellulose, Lactose, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Carbopol , Colloidal Silicon Dioxide, Magnesium Stearate, Polyethylene glycol, Titanium Dioxide, Talcum, Red Oxide of Iron Lake, Yellow Oxide of Iron and Methylene Dichloride.

3. Dosage form and strength

Dosage form: Prolonged Release Tablets

Strength: 10 mg

4. Clinical particulars

4.1 Therapeutic indication

- Treatment of Coronary Artery Disease:
  - i. For The Treatment of Chronic Stable Angina Pectoris in Patients with Normal Sinus Rhythm and who Have a Contraindication or Intolerance for Beta-Blockers.
  - ii. In Combination with Beta Blockers for the Treatment of Chronic Stable Angina Pectoris in Coronary Artery Disease in Patients with Normal Sinus Rhythm Who Are Inadequately Controlled with an Optimal Beta Blocker Dose and Whose Heart Rate Is > 60bpm
- Treatment of Chronic Heart Failure: For Treatment of Chronic Heart Failure in NYHA II to IV Class with Systolic Dysfunction, In Patients in Sinus Rhythm and Whose Heart Rate Is > 75 bpm, In Combination with Standard Therapy Including Beta-Blocker Therapy or When Beta-Blocker Therapy Is Contraindicated or Not Tolerated.

4.2 Posology and method of administration

Posology

As directed by the physician.

Method of administration

IVANODE OD 10 mg tablet should be administered orally. Do not chew the tablet before swallowing.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients

- Resting heart rate below 70 beats per minute prior to treatment
- Cardiogenic shock
- Acute myocardial infarction
- Severe hypotension (< 90/50 mmHg)
- Severe hepatic insufficiency
- Sick sinus syndrome
- Sino-atrial block
- Unstable or acute heart failure
- Pacemaker dependent (heart rate imposed exclusively by the pacemaker)
- Unstable angina
- AV-block of 3rd degree
- Combination with strong cytochrome P450 3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin per os, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone.
- Combination with verapamil or diltiazem which are moderate CYP3A4 inhibitors with heart rate reducing properties.
- Pregnancy, lactation and women of child-bearing potential not using appropriate contraceptive measures.

4.4 Special warnings and precautions for use

Warnings:

Lack of benefit on reported clinical outcomes in patients with symptomatic chronic stable angina pectoris Ivabradine is indicated only for symptomatic treatment of chronic stable angina pectoris because ivabradine has no benefits on cardiovascular outcomes (e.g. myocardial infarction or cardiovascular death).

Measurement of heart rate

Given that the heart rate may fluctuate considerably over time, serial heart rate measurements, ECG or ambulatory 24-hour monitoring should be considered when determining resting heart rate before initiation of ivabradine treatment and in patients on treatment with ivabradine when titration is considered. This also applies to patients with a low heart rate, in particular when heart rate decreases below 50 bpm, or after dose reduction.

Cardiac arrhythmias

Ivabradine is not effective in the treatment or prevention of cardiac arrhythmias and likely loses its efficacy when a tachyarrhythmia occurs (e.g. ventricular or supraventricular tachycardia). Ivabradine is therefore not recommended in patients with atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function.

In patients treated with ivabradine the risk of developing atrial fibrillation is increased. Atrial fibrillation has been more common in patients using concomitantly amiodarone or potent class I anti-arrhythmics. It is recommended to regularly clinically monitor ivabradine treated patients for the occurrence of atrial fibrillation (sustained or paroxysmal), which should also include ECG monitoring if clinically indicated (e.g. in case of exacerbated angina, palpitations, irregular pulse).

Patients should be informed of signs and symptoms of atrial fibrillation and be advised to contact their physician if these occur.

If atrial fibrillation develops during treatment, the balance of benefits and risks of continued ivabradine treatment should be carefully reconsidered.

Chronic heart failure patients with intraventricular conduction defects (bundle branch block left, bundle branch block right) and ventricular dyssynchrony should be monitored closely.

Use in patients with AV-block of 2nd degree

Ivabradine is not recommended in patients with AV-block of 2nd degree.

Use in patients with a low heart rate

Ivabradine must not be initiated in patients with a pre-treatment resting heart rate below 70 beats per minute.

If, during treatment, resting heart rate decreases persistently below 50 bpm or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension, the dose must be titrated downward or treatment discontinued if heart rate below 50 bpm or symptoms of bradycardia persist.

Combination with calcium channel blockers

Concomitant use of ivabradine with heart rate reducing calcium channel blockers such as verapamil or diltiazem is contraindicated. No safety issue has been raised on the combination of ivabradine with nitrates and dihydropyridine calcium channel blockers such as amlodipine. Additional efficacy of ivabradine in combination with dihydropyridine calcium channel blockers has not been established.

Chronic heart failure

Heart failure must be stable before considering ivabradine treatment. Ivabradine should be used with caution in heart failure patients with NYHA functional classification IV due to limited amount of data in this population.

Stroke

The use of ivabradine is not recommended immediately after a stroke since no reported data is available in these situations.

Visual function

Ivabradine influences retinal function. There is no reported evidence of a toxic effect of long-term ivabradine treatment on the retina . Cessation of treatment should be considered if any unexpected deterioration in visual function occurs. Caution should be exercised in patients with retinitis pigmentosa.

Precautions:

Patients with hypotension

Limited reported data are available in patients with mild to moderate hypotension, and ivabradine should therefore be used with caution in these patients. Ivabradine is contra-indicated in patients with severe hypotension (blood pressure < 90/50 mmHg).

Atrial fibrillation - Cardiac arrhythmias

There is no evidence reported of risk of (excessive) bradycardia on return to sinus rhythm when pharmacological cardioversion is initiated in patients treated with ivabradine. However, in the

absence of extensive data, non-urgent DC-cardioversion should be considered 24 hours after the last dose of ivabradine.

Use in patients with congenital QT syndrome or treated with QT prolonging medicinal products

The use of ivabradine in patients with congenital QT syndrome or treated with QT prolonging medicinal products should be avoided. If the combination appears necessary, close cardiac monitoring is needed.

Heart rate reduction, as caused by ivabradine, may exacerbate QT prolongation, which may give rise to severe arrhythmias, in particular Torsade de pointes.

Hypertensive patients requiring blood pressure treatment modifications.

In the reported SHIFT trial more patients experienced episodes of increased blood pressure while treated with ivabradine (7.1%) compared to patients treated with placebo (6.1%). These episodes occurred most frequently shortly after blood pressure treatment was modified, were transient, and did not affect the treatment effect of ivabradine. When treatment modifications are made in chronic heart failure patients treated with ivabradine blood pressure should be monitored at an appropriate interval.

4.5 Drugs interactions

Pharmacodynamic interactions

Concomitant use not recommended

QT prolonging medicinal products

- Cardiovascular QT prolonging medicinal products (e.g. quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone).

- Non cardiovascular QT prolonging medicinal products (e.g. pimozide, ziprasidone, sertindole, mefloquine, halofantrine, pentamidine, cisapride, intravenous erythromycin).

The concomitant use of cardiovascular and non cardiovascular QT prolonging medicinal products with ivabradine should be avoided since QT prolongation may be exacerbated by heart rate reduction. If the combination appears necessary, close cardiac monitoring is needed.

Concomitant use with precaution

Potassium-depleting diuretics (thiazide diuretics and loop diuretics): hypokalemia can increase the risk of arrhythmia. As ivabradine may cause bradycardia, the resulting combination of hypokalemia and bradycardia is a predisposing factor to the onset of severe arrhythmias, especially in patients with long QT syndrome, whether congenital or substance-induced.

Pharmacokinetic interactions

Cytochrome P450 3A4 (CYP3A4)

Ivabradine is metabolised by CYP3A4 only and it is a very weak inhibitor of this cytochrome. Ivabradine was shown not to influence the metabolism and plasma concentrations of other CYP3A4 substrates (mild, moderate and strong inhibitors). CYP3A4 inhibitors and inducers are liable to interact with ivabradine and influence its metabolism and pharmacokinetics to a clinically significant extent. Drug-drug interaction in reported studies have established that CYP3A4 inhibitors increase ivabradine plasma concentrations, while inducers decrease them. Increased plasma concentrations of ivabradine may be associated with the risk of excessive bradycardia.

Contra-indication of concomitant use

The concomitant use of potent CYP3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin per os, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone is contra-indicated. The potent CYP3A4 inhibitors ketoconazole (200 mg once daily) and josamycin (1 g twice daily) increased ivabradine mean plasma exposure by 7 to 8 fold. Moderate CYP3A4 inhibitors: specific interaction studies in healthy volunteers and patients have shown that the combination of ivabradine with the heart rate reducing agents diltiazem or verapamil resulted in an increase in ivabradine exposure (2 to 3 fold increase in AUC) and an additional heart rate reduction of 5 bpm. The concomitant use of ivabradine with these medicinal products is contraindicated.

Concomitant use not recommended

Grapefruit juice: ivabradine exposure was increased by 2-fold following the co- administration with grapefruit juice. Therefore the intake of grapefruit juice should be avoided.

Concomitant use with precautions

- Moderate CYP3A4 inhibitors: the concomitant use of ivabradine with other moderate CYP3A4 inhibitors (e.g. fluconazole) may be considered at the starting dose of 2.5 mg twice daily and if resting heart rate is above 70 bpm, with monitoring of heart rate.

- CYP3A4 inducers: CYP3A4 inducers (e.g. rifampicin, barbiturates, phenytoin, Hypericum perforatum [St John's Wort]) may decrease ivabradine exposure and activity. The concomitant use of CYP3A4 inducing medicinal products may require an adjustment of the dose of ivabradine. The combination of ivabradine 10 mg twice daily with St John's Wort was shown to reduce ivabradine AUC by half. The intake of St John's Wort should be restricted during the treatment with ivabradine.

Other concomitant use

Specific drug-drug interaction in reported studies have shown no clinically significant effect of the following medicinal products on pharmacokinetics and pharmacodynamics of ivabradine: proton pump inhibitors (omeprazole, lansoprazole), sildenafil, HMG CoA reductase inhibitors (simvastatin), dihydropyridine calcium channel blockers (amlodipine, lacidipine), digoxin and warfarin. In addition there was no clinically significant effect of ivabradine on the pharmacokinetics of simvastatin, amlodipine, lacidipine, on the pharmacokinetics and pharmacodynamics of digoxin, warfarin and on the pharmacodynamics of aspirin.

In reported pivotal phase III clinical trials the following medicinal products were routinely combined with ivabradine with no evidence of safety concerns: angiotensin converting enzyme inhibitors, angiotensin II antagonists, beta-blockers, diuretics, anti- aldosterone agents, short and long acting nitrates, HMG CoA reductase inhibitors, fibrates, proton pump inhibitors, oral antidiabetics, aspirin and other anti- platelet medicinal products.

Paediatric population

In reported studies interaction have only been performed in adults.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Women of childbearing potential

Women of child-bearing potential should use appropriate contraceptive measures during treatment.

Pregnancy

There are no or limited amount of data reported from the use of ivabradine in pregnant women.

The reported studies in animals have shown reproductive toxicity. These studies have shown embryotoxic and teratogenic effects. The potential risk for humans is unknown. Therefore, ivabradine is contra-indicated during pregnancy.

Breast-feeding

In reported animal studies indicate that ivabradine is excreted in milk. Therefore, ivabradine is contra-indicated during breast-feeding.

Women that need treatment with ivabradine should stop breast-feeding, and choose for another way of feeding their child.

Fertility

In reported studies in rats have shown no effect on fertility in males and females.

4.7 Effects on ability to drive and use machines

A specific reported study to assess the possible influence of ivabradine on driving performance has been performed in healthy volunteers where no alteration of the driving performance was evidenced. However, in post-marketing experience, cases of impaired driving ability due to visual symptoms have been reported. Ivabradine may cause transient luminous phenomena consisting mainly of phosphenes. The possible occurrence of such luminous phenomena should be taken into account when driving or using machines in situations where sudden variations in light intensity may occur, especially when driving at night.

Ivabradine has no influence on the ability to use machines.

4.8 Undesirable effects

Summary of the safety profile

Ivabradine has been studied in clinical trials involving nearly 45,000 participants.

The most common adverse reactions with ivabradine, luminous phenomena (phosphenes) and bradycardia, are dose dependent and related to the pharmacological effect of the medicinal product.

Tabulated list of adverse reactions

The following adverse reactions have been reported during clinical trials and are ranked using the following frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

System Organ Class	Frequency	Preferred Term
Blood and lymphatic system disorders	Uncommon	Eosinophilia
Metabolism and nutrition disorders	Uncommon	Hyperuricaemia
Nervous system disorders	Common	Headache, generally during the first month of treatment
		Dizziness, possibly related to bradycardia
	Uncommon*	Syncope, possibly related to bradycardia
Eye disorders	Very common	Luminous phenomena (phosphenes)

System Organ Class	Frequency	Preferred Term
	Common	Blurred vision
	Uncommon*	Diplopia
		Visual impairment
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Common	Bradycardia
		AV 1st degree block (ECG prolonged PQ interval)
		Ventricular extrasystoles
		Atrial fibrillation
	Uncommon	Palpitations, supraventricular extrasystoles
	Very rare	AV 2nd degree block, AV 3rd degree block
		Sick sinus syndrome
Vascular disorders	Common	Uncontrolled blood pressure
	Uncommon*	Hypotension, possibly related to bradycardia
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea
Gastrointestinal disorders	Uncommon	Nausea
		Constipation
		Diarrhoea
		Abdominal pain*
Skin and subcutaneous tissue disorders	Uncommon*	Angioedema
		Rash
	Rare*	Erythema
		Pruritus
		Urticaria
Musculoskeletal and connective tissue disorders	Uncommon	Muscle spasms
General disorders and administration site conditions	Uncommon*	Asthenia, possibly related to bradycardia
		Fatigue, possibly related to bradycardia
	Rare*	Malaise, possibly related to bradycardia
Investigations	Uncommon	Elevated creatinine in blood
		ECG prolonged QT interval

Frequency calculated from reported clinical trials for adverse events detected from spontaneous report.

Description of adverse reactions

Luminous phenomena (phosphenes) were reported by 14.5% of patients, described as a transient enhanced brightness in a limited area of the visual field. They are usually triggered by sudden variations in light intensity. Phosphenes may also be described as a halo, image decomposition (stroboscopic or kaleidoscopic effects), coloured bright lights, or multiple image (retinal persistency). The onset of phosphenes is generally within the first two months of treatment after which they may occur repeatedly. Phosphenes were generally reported to be of mild to moderate intensity. All phosphenes resolved during or after treatment, of which a majority (77.5%) resolved during treatment. Fewer than 1% of patients changed their daily routine or discontinued the treatment in relation with phosphenes.

Bradycardia was reported by 3.3% of patients particularly within the first 2 to 3 months of treatment initiation. 0.5% of patients experienced a severe bradycardia below or equal to 40 bpm.

In the reported SIGNIFY -study atrial fibrillation was observed in 5.3% of patients taking ivabradine compared to 3.8% in the placebo group. In a pooled reported analysis of all the Phase II/III double blind controlled clinical trials with a duration of at least 3 months including more than 40,000 patients, the incidence of atrial fibrillation was 4.86% in ivabradine treated patients compared to 4.08% in controls, corresponding to a hazard ratio of 1.26, 95% CI.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

4.9 Overdose

Symptoms

Overdose may lead to severe and prolonged bradycardia.

Management

Severe bradycardia should be treated symptomatically in a specialised environment. In the event of bradycardia with poor haemodynamic tolerance, symptomatic treatment including intravenous beta-stimulating medicinal products such as isoprenaline may be considered. Temporary cardiac electrical pacing may be instituted if required.

5 Pharmacological properties

5.1 Mechanism of Action

Ivabradine is a pure heart rate lowering agent, acting by selective and specific inhibition of the cardiac pacemaker I_f current that controls the spontaneous diastolic depolarisation in the sinus node and regulates heart rate. The cardiac effects are specific to the sinus node with no effect on intra-atrial, atrioventricular or intraventricular conduction times, nor on myocardial contractility or ventricular repolarisation.

Ivabradine can interact also with the retinal current I_h which closely resembles cardiac I_f. It participates in the temporal resolution of the visual system, by curtailing the retinal response to bright light stimuli. Under triggering circumstances (e.g. rapid changes in luminosity), partial inhibition of I_h by ivabradine underlies the luminous phenomena that may be occasionally experienced by patients. Luminous phenomena (phosphenes) are described as a transient enhanced brightness in a limited area of the visual field.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, other cardiac preparations, ATC code: C01EB17

The main pharmacodynamic property of ivabradine in humans is a specific dose dependent reduction in heart rate. Analysis of heart rate reduction with doses up to 20 mg twice daily indicates a trend towards a plateau effect which is consistent with a reduced risk of severe bradycardia below 40 bpm.

At usual recommended doses, heart rate reduction is approximately 10 bpm at rest and during exercise. This leads to a reduction in cardiac workload and myocardial oxygen consumption. Ivabradine does not influence intracardiac conduction, contractility (no negative inotropic effect) or ventricular repolarisation:

-In clinical electrophysiology studies, ivabradine had no effect on atrioventricular or intraventricular conduction times or corrected QT intervals;

- In patients with left ventricular dysfunction (left ventricular ejection fraction (LVEF) between 30 and 45%), ivabradine did not have any deleterious influence on LVEF.

Paediatric population

A reported randomised, double blind, placebo controlled study was performed in 116 paediatric patients (17 aged [6-12] months, 36 aged [1-3] years and 63 aged [3-18] years) with CHF and dilated cardiomyopathy (DCM) on top of optimal background treatment. 74 received ivabradine (ratio 2:1).

The starting dose was 0.02 mg/kg bid in age-subset [6-12] months, 0.05 mg/kg bid in [1-3] years and [3-18] years <40 kg, and 2.5 mg bid in [3-18] years and ≥ 40 kg. The dose was adapted depending on the therapeutic response with maximum doses of 0.2 mg/kg bid, 0.3 mg/kg bid and 15 mg bid respectively. In this study, ivabradine was administered as oral liquid formulation or tablet twice daily. The absence of pharmacokinetic difference between the 2 formulations was shown in an open-label randomised two-period cross-over study in 24 adult healthy volunteers.

A 20% heart rate reduction, without bradycardia, was achieved by 69.9% of patients in the ivabradine group versus 12.2% in the placebo group during the titration period of 2 to 8 weeks (Odds Ratio: E = 17.24, 95% CI [5.91 ; 50.30]).

The mean ivabradine doses allowing to achieve a 20% HRR were 0.13 ± 0.04 mg/kg bid, 0.10 ± 0.04 mg/kg bid and 4.1 ± 2.2 mg bid in the age subsets [1-3] years, [3-18] years and <40 kg and [3-18] years and ≥ 40 kg, respectively.

Mean LVEF increased from 31.8% to 45.3% at M012 in ivabradine group versus 35.4% to 42.3% in the placebo group. There was an improvement in NYHA class in 37.7% of ivabradine patients versus 25.0% in the placebo group. These improvements were not statistically significant.

The safety profile, over one year, was similar to the one described in adult CHF patients.

The long-term effects of ivabradine on growth, puberty and general development as well as the long-term efficacy of therapy with ivabradine in childhood to reduce cardiovascular morbidity and mortality have not been studied.

The European Medicines Agency has waived the obligation to submit the results of studies with the reference product containing ivabradine in all subsets of the paediatric population for the treatment of angina pectoris.

The European Medicines Agency has waived the obligation to submit the results of studies with the reference product containing ivabradine in children aged 0 to less than 6 months for the treatment of chronic heart failure.

5.3 Pharmacokinetic properties

Under physiological conditions, ivabradine is rapidly released from tablets and is highly water-soluble (> 10 mg/ml). Ivabradine is the S-enantiomer with no bioconversion demonstrated in vivo. The N-desmethylated derivative of ivabradine has been identified as the main active metabolite in humans.

Absorption and bioavailability

Ivabradine is rapidly and almost completely absorbed after oral administration with a peak plasma level reached in about 1 hour under fasting condition. The absolute bioavailability of the film-coated tablets is around 40%, due to first-pass effect in the gut and liver.

Food delayed absorption by approximately 1 hour, and increased plasma exposure by 20 to 30%. The intake of the tablet during meals is recommended in order to decrease intra-individual variability in exposure.

Distribution

Ivabradine is approximately 70% plasma protein bound and the volume of distribution at steady-state is close to 100 l in patients. The maximum plasma concentration following chronic administration at the recommended dose of 5 mg twice daily is 22 ng/ml (CV = 29%). The average plasma concentration is 10 ng/ml (CV = 38%) at steady-state.

Biotransformation

Ivabradine is extensively metabolised by the liver and the gut by oxidation through cytochrome P450 3A4 (CYP3A4) only. The major active metabolite is the N-desmethylated derivative (S 18982) with an exposure about 40% of that of the parent compound. The metabolism of this active metabolite also involves CYP3A4. Ivabradine has low affinity for CYP3A4, shows no clinically relevant CYP3A4 induction or inhibition and is therefore unlikely to modify CYP3A4 substrate metabolism or plasma concentrations. Inversely, potent inhibitors and inducers may substantially affect ivabradine plasma concentrations.

Elimination

Ivabradine is eliminated with a main half-life of 2 hours (70-75% of the AUC) in plasma and an effective half-life of 11 hours. The total clearance is about 400 ml/min and the renal clearance is about 70 ml/min. Excretion of metabolites occurs to a similar extent via faeces and urine. About 4% of an oral dose is excreted unchanged in urine.

Linearity/non linearity

The kinetics of ivabradine is linear over an oral dose range of 0.5-24 mg.

Special populations

- Elderly: no pharmacokinetic differences (AUC and Cmax) have been observed between elderly (≥ 65 years) or very elderly patients (≥ 75 years) and the overall population.

- Renal impairment: the impact of renal impairment (creatinine clearance from 15 to 60 ml/min) on ivabradine pharmacokinetic is minimal, in relation with the low contribution of renal clearance (about 20%) to total elimination for both ivabradine and its main metabolite S 18982.

- Hepatic impairment: in patients with mild hepatic impairment (Child Pugh score up to 7) unbound AUC of ivabradine and the main active metabolite were about 20% higher than in subjects with normal hepatic function. Data are insufficient to draw conclusions in patients with moderate hepatic impairment. No data are available in patients with severe hepatic impairment.

- Paediatric population: The pharmacokinetic profile of ivabradine in paediatric chronic heart failure patients aged 6 months to less than 18 years is similar to the pharmacokinetics described in adults when a titration scheme based on age and weight is applied.

Pharmacokinetic/pharmacodynamic (PK/PD) relationship

PK/PD relationship analysis has shown that heart rate decreases almost linearly with increasing ivabradine and S 18982 plasma concentrations for doses of up to 15-20 mg twice daily. At higher doses, the decrease in heart rate is no longer proportional to ivabradine plasma concentrations and tends to reach a plateau. High exposures to ivabradine that may occur when ivabradine is given in combination with strong CYP3A4 inhibitors may result in an excessive decrease in heart rate although this risk is reduced with moderate CYP3A4 inhibitors. The PK/PD relationship of ivabradine in paediatric chronic heart failure patients aged 6 months to less than 18 years is similar to the PK/PD relationship described in adults.

6. Nonclinical properties

Non-clinical data reveal no special hazard for humans based on reported conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. Reproductive toxicity studies showed no effect of ivabradine on fertility in male and female rats. When pregnant animals were treated during organogenesis at exposures close to therapeutic doses, there was a higher incidence of foetuses with cardiac defects in the rat and a small number of foetuses with ectrodactylia in the rabbit.

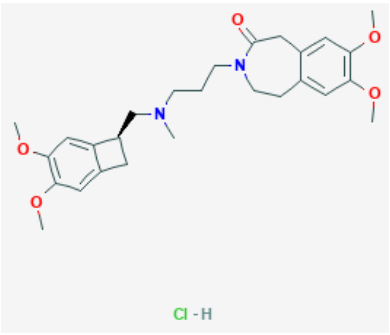
In dogs given ivabradine (doses of 2, 7 or 24 mg/kg/day) for one year, reversible changes in retinal function were observed but were not associated with any damage to ocular structures. These data are consistent with the pharmacological effect of ivabradine related to its interaction with hyperpolarisation-activated I*h* currents in the retina, which share extensive homology with the cardiac pacemaker If current.
Other long-term repeat dose and carcinogenicity studies revealed no clinically relevant changes.
Environmental Risk Assessment (ERA)

The environmental risk assessment of ivabradine has been conducted in accordance to European guidelines on ERA.

Outcomes of these evaluations support the lack of environmental risk of ivabradine and ivabradine does not pose a threat to the environment**.**

7 Description

Ivabradine Hydrochloride is 3-[3-[[(7S)-3,4-dimethoxy-7-bicyclo[4.2.0]octa-1,3,5-trienyl]methyl-methylamino]propyl]-7,8-dimethoxy-2,5-dihydro-1H-3-benzazepin-4-one;hydrochloride having molecular weight of 505.0 g/mol and empirical formula of $C_{27}H_{37}ClN_2O_5$ and the chemical structure is:



Ivabradine Prolonged Release Tablets are brown coloured, round, biconvex, plain on both side, film coated tablets. The excipients used are Hydroxypropyl Methylcellulose, Microcrystalline Cellulose,

Lactose, Polyvinylpyrrolidone, Isopropyl Alcohol, Carbopol 7, Colloidal Silicon Dioxide, Magnesium Stearate, Polyethylene glycol, Titanium Dioxide, Talcum, Red Oxide of Iron Lake, Yellow Oxide of Iron and Methylene Dichloride.

8 Pharmaceutical particulars

8.1 Incompatibilities

Not Applicable

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

IVANODE OD 10 is available in Pack of 10 Tablets.

8.4 Storage and handing instructions

Store at a temperature not exceeding 30°C, Protect from moisture.

Keep out of reach of children.

9 Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10 Details of manufacturer

Manufactured in India by:

Synokem Pharmaceuticals Ltd

Plot No. 56-57, Sector-6A, IIE (SIDCUL),

Ranipur (BHEL), Haridwar – 249403 (Uttarakhand).

11 Details of permission or licence number with date

Mfg Lic No 27/UA/2018 issued on 31.08.2020

12. Date of revision

Feb-2026

MARKETED BY

TORRENT PHARMA

TORRENT PHARMACEUTICALS LTD.

IN/IVANODE OD 10 mg/Feb-26/02/PI