

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

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**IVANODE OD 10**

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**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 Methocel K-4M, Microcrystalline Cellulose, Lactose, PVP K-30, Isopropyl Alcohol, Carbopol 71G, Colloidal Silicon Dioxide, Magnesium Stearate, Supercoat White-F, 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**

It is indicated for the treatment of chronic stable angina pectoris in patients with coronary artery disease and treatment of chronic heart failure.

**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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (cannot be estimated from the available data).

<b>System Organ Class</b>	<b>Frequency</b>	<b>Preferred Term</b>
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)
	Common	Blurred vision
	Uncommon*	Diplopia
		Visual impairment
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Common	Bradycardia
		AV 1 <sup>st</sup> degree block (ECG prolonged PQ interval)
		Ventricular extrasystoles
		Atrial fibrillation
	Uncommon	Palpitations, supraventricular extrasystoles
	Very rare	AV 2 <sup>nd</sup> degree block, AV 3 <sup>rd</sup> 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**

Torrent Pharma available at:  
[http://www.torrentpharma.com/index.php/site/info/adverse\\_event\\_reporting](http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting).

By reporting side effects, you can help provide more information on the safety of this medicine.

## 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  $\geq$  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  $0.13 \pm 0.04$  mg/kg bid,  $0.10 \pm 0.04$  mg/kg bid and  $4.1 \pm 2.2$  mg bid in the age subsets [1-3] years, [3-18] years and <40 kg and [3-18] years and  $\geq 40$  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 C<sub>max</sub>) have been observed between elderly ( $\geq 65$  years) or very elderly patients ( $\geq 75$  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 fetuses with cardiac defects in the rat and a small number of fetuses with ectrodactyilia 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<sub>h</sub> currents in the retina, which share extensive homology with the cardiac pacemaker I<sub>f</sub> current.

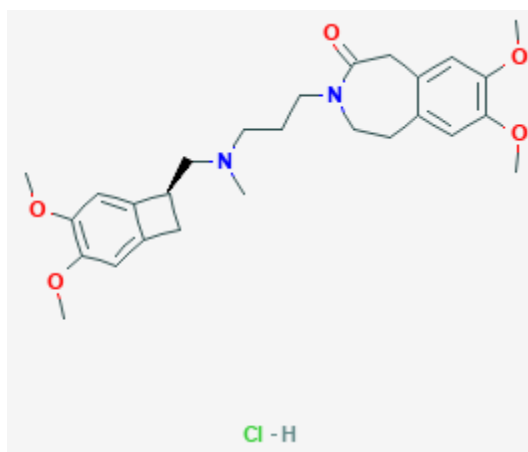
Other long-term repeat dose and carcinogenicity studies revealed no clinically relevant changes. Environmental Risk Assessment (ERA)

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 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 Methocel K-4M, Microcrystalline Cellulose, Lactose, PVP K-30, Isopropyl Alcohol, Carbopol 71G, Colloidal Silicon Dioxide, Magnesium Stearate, Supercoat White-F, 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 Blister strip 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

**Package leaflet: Information for the user**

**IVANODE OD 10**

**Ivabradine Prolonged Release Tablets 10mg**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

## **What is in this leaflet**

What is in this leaflet

- 9.1. What IVANODE OD and what they are used for
- 9.2. What you need to know before you take IVANODE OD
- 9.4. Possible side effects
- 9.5. How to store IVANODE OD Tablets
- 9.6. Contents of the pack and other information

### **9.1 What is IVANODE OD and what it is used for**

IVANODE OD is a heart medicine used to treat:

- Symptomatic stable angina pectoris (which causes chest pain) in adult patients whose heart rate is over or equal to 70 beats per minute. It is used in adult patients who do not tolerate or cannot take heart medicines called beta-blockers. It is also used in combination with beta-blockers in adult patients whose condition is not fully controlled with a beta-blocker.
- Chronic heart failure in adult patients whose heart rate is over or equal to 75 beats per minute. It is used in combination with standard therapy, including beta-blocker therapy or when beta-blockers are contraindicated or not tolerated.

#### About stable angina pectoris (usually referred to as “angina”):

Stable angina is a heart disease which happens when the heart does not receive enough oxygen. It usually appears between 40 and 50 years of age. The most common symptom of angina is chest pain or discomfort. Angina is more likely to happen when the heart beats faster in situations such as exercise, emotion, exposure to the cold or after eating. This increase in heart rate can cause the chest pain in people who suffer from angina.

#### About chronic heart failure :

Chronic heart failure is a heart disease which happens when your heart cannot pump enough blood to the rest of your body. The most common symptoms of heart failure are breathlessness, fatigue, tiredness and ankle swelling.

#### How does IVANODE OD work?

IVANODE OD mainly works by reducing the heart rate by a few beats per minute. This lowers the heart’s need for oxygen especially in the situations when an angina attack is more likely to happen. In this way IVANODE OD Accord helps to control and reduce the number of angina attacks.

Furthermore as elevated heart rate adversely affects the heart functioning and vital prognosis in patients with chronic heart failure, the specific heart rate lowering action of vanode OD helps to improve the heart functioning and vital prognosis in these patients.

## 9.2 What you need to know before you take IVANODE OD

### Do not take IVANODE OD

- if you are allergic to IVANODE OD or any of the other ingredients of this medicine.
- if your resting heart rate before treatment is too slow (below 70 beats per minute);
- if you are suffering from cardiogenic shock (a heart condition treated in hospital);
- if you suffer from a heart rhythm disorder;
- if you are having a heart attack;
- if you suffer from very low blood pressure;
- if you suffer from unstable angina (a severe form in which chest pain occurs very frequently and with or without exertion);
- if you have heart failure which has recently become worse;
- if your heartbeat is exclusively imposed by your pacemaker;
- if you suffer from severe liver problems;
- if you are already taking medicines for the treatment of fungal infections (such as ketoconazole, itraconazole), macrolide antibiotics (such as josamycin, clarithromycin, telithromycin or erythromycin given orally), medicines to treat HIV infections (such as nelfinavir, ritonavir) or nefazodone (medicine to treat depression) or diltiazem, verapamil (used for high blood pressure or angina pectoris);
- if you are a woman able to have children and not using reliable contraception;
- if you are pregnant or trying to become pregnant;
- if you are breast-feeding.

### Warnings and precautions

Talk to your doctor or pharmacist before taking IVANODE OD

- if you suffer from heart rhythm disorders (such as irregular heartbeat, palpitation, increase in chest pain) or sustained atrial fibrillation (a type of irregular heartbeat), or an abnormality of electrocardiogram (ECG) called 'long QT syndrome',
  - if you have symptoms such as tiredness, dizziness or shortness of breath (this could mean that your heart is slowing down too much),
  - if you suffer from symptoms of atrial fibrillation (pulse rate at rest unusually high (over 110 beats per minute) or irregular, without any apparent reason, making it difficult to measure),
  - if you have had a recent stroke (cerebral attack),
  - if you suffer from mild to moderate low blood pressure,
  - if you suffer from uncontrolled blood pressure, especially after a change in your antihypertensive treatment,
  - if you suffer from severe heart failure or heart failure with abnormality of ECG called 'bundle branch block',
  - if you suffer from chronic eye retinal disease,
  - if you suffer from moderate liver problems,
  - if you suffer from severe renal problems.
- If any of the above applies to you, talk straight away to your doctor before or while taking IVANODE OD.

## **Children and adolescents**

IVANODE OD is not intended for use in children and adolescents younger than 18 years.

## **Other medicines and IVANODE OD**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Make sure to tell your doctor if you are taking any of the following medicines, as a dose adjustment of IVANODE OD or monitoring should be required:

- fluconazole (an antifungal medicine)
- rifampicin (an antibiotic)
- barbiturates (for difficult sleeping or epilepsy)
- phenytoin (for epilepsy)
- Hypericum perforatum or St John's Wort (herbal treatment for depression)
- QT prolonging medicines to treat either heart rhythm disorders or other conditions :
  - quinidine, disopyramide, ibutilide, sotalol, amiodarone (to treat heart rhythm disorders)
  - bepridil (to treat angina pectoris)
- certain types of medicines to treat anxiety, schizophrenia or other psychoses (such as pimozide, ziprasidone, sertindole)
- anti-malarial medicines (such as mefloquine or halofantrine)
- intravenous erythromycin (an antibiotic)
- pentamidine (an antiparasitic medicine)
- cisapride (against the gastro-oesophageal reflux)
- Some types of diuretics which may cause decrease in blood potassium level, such as furosemide, hydrochlorothiazide, indapamide (used to treat oedema, high blood pressure).

IVANODE OD with food and drink

Avoid grapefruit juice during treatment with IVANODE OD.

## **Pregnancy, breast-feeding and fertility**

### *Pregnancy and Breastfeeding*

Do not take IVANODE OD if you are pregnant or are planning to have a baby (see "Do not take IVANODE OD").

If you are pregnant and have taken IVANODE OD, talk to your doctor.

Do not take IVANODE OD if you are able to become pregnant unless you use reliable contraceptive measures (see "Do not take IVANODE OD").

Do not take IVANODE OD if you are breast-feeding (see "Do not take IVANODE OD"). Talk to your doctor if you are breast-feeding or intending to breastfeed as breastfeeding should be discontinued if you take IVANODE OD.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

### **Driving and using machines**

IVANODE OD may cause temporary luminous visual phenomena (a temporary brightness in the field of vision, see “Possible side effects”). If this happens to you, be careful when driving or using machines at times when there could be sudden changes in light intensity, especially when driving at night.

### **IVANODE OD contains lactose**

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

## **9.3 How to take IVANODE OD**

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.  
IVANODE OD should be taken during meals.

### **If you take more IVANODE OD than you should:**

A large dose of IVANODE OD could make you feel breathless or tired because your heart slows down too much. If this happens, contact your doctor immediately. Duration of use.

### **If you forget to take IVANODE OD**

If you forget to take a dose of IVANODE OD, take the next dose at the usual time. Do not take a double dose to make up for the forgotten dose.

The calendar printed on the blister containing the tablets should help you remember when you last took a tablet of IVANODE OD.

### **If you stop taking IVANODE OD**

As the treatment for angina or chronic heart failure is usually life-long, you should discuss with your doctor before stopping this medicinal product.

If you think that the effect of IVANODE OD is too strong or too weak, talk to your doctor or pharmacist.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## **9.4 Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. The frequency of possible side effects listed below is defined using the following convention:

**Very common:** may affect more than 1 in 10 people

**Common:** may affect up to 1 in 10 people

**Uncommon:** may affect up to 1 in 100 people

**Rare:** may affect up to 1 in 1,000 people

**Very rare:** may affect up to 1 in 10,000 people

**Not known:** frequency cannot be estimated from the available data

The most common adverse reactions with this medicine are dose dependent and related to its mode of action:

Very common:

Luminous visual phenomena (brief moments of increased brightness, most often caused by sudden changes in light intensity). They can also be described as a halo, coloured flashes, image decomposition or multiple images. They generally occur within the first two months of treatment after which they may occur repeatedly and resolve during or after treatment

Common:

Modification in the heart functioning (the symptoms are a slowing down of the heart rate). They particularly occur within the first 2 to 3 months of treatment initiation.

Other side effects have also been reported:

Irregular rapid contraction of the heart, abnormal perception of heartbeat, uncontrolled blood pressure, headache, dizziness and blurred vision (cloudy vision).

Uncommon:

Palpitations and cardiac extra beats, feeling sick (nausea), constipation, diarrhoea, abdominal pain, spinning sensation (vertigo), difficulty breathing (dyspnoea), muscle spasms, changes in laboratory parameters : high blood levels of uric acid, an excess of eosinophils (a type of white blood cell) and elevated creatinine in blood (a breakdown product of muscle), skin rash, angioedema (such as swollen face, tongue or throat, difficulty in breathing or swallowing), low blood pressure, fainting, feeling of tiredness, feeling of weakness, abnormal ECG heart tracing, double vision, impaired vision.

Rare:

Urticaria, itching, skin reddening, feeling unwell.

Very rare:

Irregular heart beats

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: [http://www.torrentpharma.com/Index.php/site/info/adverse\\_event\\_reporting](http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting).

By reporting side effects, you can help provide more information on the safety of this medicine.

## **9.5 How to store IVANODE OD**

- Store at a temperature not exceeding 30°C, Protect from moisture.
- Keep out of reach of children.

## **9.6 Contents of the pack and other information**

The active substance is Ivabradine Hydrochloride.

The other excipients used are Methocel K-4M, Microcrystalline Cellulose, Lactose, PVP K-30, Isopropyl Alcohol, Carbopol 71G, Colloidal Silicon Dioxide, Magnesium Stearate, Supercoat White-F, Titanium Dioxide, Talcum, Red Oxide of Iron Lake, Yellow Oxide of Iron and Methylene Dichloride

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

**IVANODE OD 10** is available in Blister strip of 10 tablets.



**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**

Not Applicable

**MARKETED BY**

TORRENT PHARMACEUTICALS LTD.

**IN/IVANODE OD 10 mg/Nov-21/01/PI**