

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ivabradine Zentiva 5 mg film-coated tablets
Ivabradine Zentiva 7.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ivabradine Zentiva 5 mg film-coated tablets

Each film-coated tablet contains 5 mg ivabradine (as hydrochloride).

Ivabradine Zentiva 7.5 mg film-coated tablets

Each film-coated tablet contains 7.5 mg ivabradine (as hydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Ivabradine Zentiva 5 mg film-coated tablets

Round, biconvex white tablets with deep breakline on one side and '5' debossing on other side with diameter 6.5 mm. The tablet can be divided into equal doses.

Ivabradine Zentiva 7.5 mg film-coated tablets

White to off white, round tablets with diameter 7.1 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of chronic stable angina pectoris

Ivabradine is indicated for the symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm and heart rate ≥ 70 beats per minute (bpm). Ivabradine is indicated:

- in adults unable to tolerate or with a contraindication to the use of beta-blockers
- or
- in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose.

Treatment of chronic heart failure

Ivabradine is indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in adult 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 (see section 5.1).

4.2 Posology and method of administration

Posology

Symptomatic treatment of chronic stable angina pectoris

It is recommended that the decision to initiate or titrate treatment takes place with the availability of serial heart rate measurements, ECG or ambulatory 24-hour monitoring.

The starting dose of ivabradine should not exceed 5 mg twice daily in patients aged below 75 years.

After three to four weeks of treatment, if the patient is still symptomatic, if the initial dose is well tolerated and if resting heart rate remains above 60 bpm, the dose may be increased to the next higher dose in patients receiving 2.5 mg twice daily or 5 mg twice daily. The maintenance dose should not exceed 7.5 mg twice daily.

If there is no improvement in symptoms of angina within 3 months after start of treatment, treatment of ivabradine should be discontinued.

In addition, discontinuation of treatment should be considered if there is only limited symptomatic response and when there is no clinically relevant reduction in resting heart rate within three months.

If, during treatment, heart rate decreases below 50 bpm at rest or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension, the dose must be titrated downward including the lowest dose of 2.5 mg twice daily (one half 5 mg tablet twice daily). After dose reduction, heart rate should be monitored (see section 4.4). Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist despite dose reduction.

Treatment of chronic heart failure

The treatment has to be initiated only in patient with stable heart failure.

It is recommended that the treating physician should be experienced in the management of chronic heart failure.

The usual recommended starting dose of ivabradine is 5 mg twice daily. After two weeks of treatment, the dose can be increased to 7.5 mg twice daily if resting heart rate is persistently above 60 bpm or decreased to 2.5 mg twice daily (one half 5 mg tablet twice daily) if resting heart rate is persistently below 50 bpm or in case of symptoms related to bradycardia such as dizziness, fatigue or hypotension. If heart rate is between 50 and 60 bpm, the dose of 5 mg twice daily should be maintained.

If during treatment, heart rate decreases persistently below 50 bpm at rest or the patient experiences symptoms related to bradycardia, the dose must be titrated downward to the next lower dose in patients receiving 7.5 mg twice daily or 5 mg twice daily. If heart rate increases persistently above 60 bpm at rest, the dose can be up titrated to the next upper dose in patients receiving 2.5 mg twice daily or 5 mg twice daily.

Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist (see section 4.4).

Special populations

Elderly

In patients aged 75 years or more, a lower starting dose should be considered (2.5 mg twice daily i.e. one half 5 mg tablet twice daily) before up-titration if necessary.

Renal impairment

No dose adjustment is required in patients with renal insufficiency and creatinine clearance above 15 mL/min (see section 5.2).

No data are available in patients with creatinine clearance below 15 mL/min. Ivabradine should therefore be used with precaution in this population.

Hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment. Caution should be exercised when using ivabradine in patients with moderate hepatic impairment. Ivabradine is contraindicated for use in patients with severe hepatic insufficiency, since it has not been studied in this population and a large increase in systemic exposure is anticipated (see sections 4.3 and 5.2).

Paediatric population

The safety and efficacy of ivabradine in children aged below 18 years have not been established. Currently available data for the treatment of chronic heart failure are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

No data for symptomatic treatment of chronic stable angina pectoris are available.

Method of administration

Tablets must be taken orally twice daily, i.e. once in the morning and once in the evening during meals (see section 5.2). Ivabradine Zentiva 5 mg film-coated tablet can be divided into equal doses. Use a tablet cutter to divide the tablet.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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 (see sections 4.5 and 5.2).

- Combination with verapamil or diltiazem which are moderate CYP3A4 inhibitors with heart rate reducing properties (see section 4.5).
- Pregnancy, lactation and women of childbearing potential not using appropriate contraceptive measures (see section 4.6).

4.4 Special warnings and precautions for use

Lack of benefit on 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 (see section 5.1).

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 (see section 4.2).

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 (see section 4.8). 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 bpm (see section 4.3).

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 (see section 4.2).

Combination with calcium channel blockers

Concomitant use of ivabradine with heart rate reducing calcium channel blockers such as verapamil or diltiazem is contraindicated (see sections 4.3 and 4.5). 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 (see section 5.1).

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 data is available in these situations.

Visual function

Ivabradine influences retinal function. There is no evidence of a toxic effect of long-term ivabradine treatment on the retina (see section 5.1). Cessation of treatment should be considered if any unexpected deterioration in visual function occurs. Caution should be exercised in patients with retinitis pigmentosa.

Patients with hypotension

Limited data are available in patients with mild to moderate hypotension, and ivabradine should therefore be used with caution in these patients. Ivabradine is contraindicated in patients with severe hypotension (blood pressure < 90/50 mmHg) (see section 4.3).

Atrial fibrillation – cardiac arrhythmias

There is no evidence 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 (see section 4.5). 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

When treatment modifications are made in chronic heart failure patients treated with ivabradine blood pressure should be monitored at an appropriate interval (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

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 (see section 4.4).

Concomitant use with precaution

Potassium-depleting diuretics (thiazide diuretics and loop diuretics)

Hypokalaemia can increase the risk of arrhythmia. As ivabradine may cause bradycardia, the resulting combination of hypokalaemia 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

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. Interaction 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 (see section 4.4).

Contraindication of concomitant use

Potent CYP3A4 inhibitors

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 contraindicated (see section 4.3). 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 (see section 4.3).

Concomitant use not recommended

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 interaction 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 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

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use appropriate contraceptive measures during treatment (see section 4.3).

Pregnancy

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

Studies in animals have shown reproductive toxicity. These studies have shown embryotoxic and teratogenic effects (see section 5.3). The potential risk for humans is unknown. Therefore, ivabradine is contraindicated during pregnancy (see section 4.3).

Breast-feeding

Animal studies indicate that ivabradine is excreted in milk. Therefore, ivabradine is contraindicated during breast-feeding (see section 4.3). Women that need treatment with ivabradine should stop breast-feeding, and choose for another way of feeding their child.

Fertility

Studies in rats have shown no effect on fertility in males and females (see section 5.3).

4.7 Effects on ability to drive and use machines

Ivabradine has no or negligible influence on the ability to use machines.

A specific 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 (see section 4.8). 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.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions with ivabradine are luminous phenomena (phosphenes) (14.5%) and bradycardia (3.3 %). They 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).

| 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 |

| System organ class | Frequency | Preferred term |
|---|------------------|--|
| 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 st degree block (ECG prolonged PQ interval) Ventricular extrasystoles Atrial fibrillation |
| | Uncommon | Palpitations Supraventricular extrasystoles ECG prolonged QT interval |
| | Very rare | AV 2 nd and 3 rd 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 |
| Renal and urinary disorders | Uncommon | Elevated creatinine in blood |
| General disorders and administration site conditions | Uncommon* | Asthenia, possibly related to bradycardia Fatigue, possibly related to bradycardia |
| | Rare* | Malaise, possibly related to bradycardia |

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

Description of selected adverse reactions

Luminous phenomena (phosphenes)

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

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.

Atrial fibrillation

In the SIGNIFY study atrial fibrillation was observed in 5.3% of patients taking ivabradine compared to 3.8% in the placebo group. In a pooled 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 [1.15 – 1.39].

Increased blood pressure

In the 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.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Symptoms

Overdose may lead to severe and prolonged bradycardia (see section 4.8).

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 Pharmacodynamic properties

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

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 (see section 4.8).

Pharmacodynamic effects

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 (see section 4.8).

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.

Clinical efficacy and safety

The antianginal and anti-ischaemic efficacy of ivabradine was studied in five double-blind randomised trials (three versus placebo, and one each versus atenolol and amlodipine). These trials included a total of 4 111 patients with chronic stable angina pectoris, of whom 2 617 received ivabradine.

Ivabradine 5 mg twice daily was shown to be effective on exercise test parameters within 3 to 4 weeks of treatment. Efficacy was confirmed with 7.5 mg twice daily. In particular, the additional benefit over 5 mg twice daily was established in a reference-controlled study versus atenolol: total exercise duration at trough was increased by about 1 minute after one month of treatment with 5 mg twice daily and further improved by almost 25 seconds after an additional 3-month period with forced titration to 7.5 mg twice daily. In this study, the antianginal and anti-ischaemic benefits of ivabradine were confirmed in patients aged 65 years or more. The efficacy of 5 and 7.5 mg twice daily was consistent across studies on exercise test parameters (total exercise duration, time to limiting angina, time to angina onset and time to 1 mm ST segment depression) and was associated with a decrease of about 70% in the rate of angina attacks. The twice-daily dosing regimen of ivabradine gave uniform efficacy over 24 hours.

In a 889-patients randomised placebo-controlled study, ivabradine given on top of atenolol 50 mg o.d. showed additional efficacy on all ETT parameters at the trough of activity (12 hours after oral intake).

In a 725-patients randomised placebo-controlled study, ivabradine did not show additional efficacy on top of amlodipine 10 mg o.d. at the trough of activity (12 hours after oral intake) while an additional efficacy was shown at peak (3 – 4 hours after oral intake).

In a 1 277-patients randomised placebo-controlled study, ivabradine demonstrated a statistically significant additional efficacy on response to treatment (defined as a decrease of at least 3 angina attacks per week and/or an increase in the time to 1 mm ST segment depression of at least 60 s during a treadmill ETT) on top of amlodipine 5 mg o.d. or nifedipine GITS 30 mg o.d. at the trough of activity (12 hours after oral ivabradine intake) over a 6-week treatment period (OR = 1.3, 95% CI [1.0 – 1.7]; $p = 0.012$). Ivabradine did not show additional efficacy on secondary endpoints of ETT parameters at the trough of activity while an additional efficacy was shown at peak (3 – 4 hours after oral ivabradine intake).

Ivabradine efficacy was fully maintained throughout the 3- or 4-month treatment periods in the efficacy trials. There was no evidence of pharmacological tolerance (loss of efficacy) developing during treatment nor of rebound phenomena after abrupt treatment discontinuation. The antianginal and anti-ischaemic effects of ivabradine were associated with dose-dependent reductions in heart rate and with a significant decrease in rate pressure product (heart rate x systolic blood pressure) at rest and during exercise. The effects on blood pressure and peripheral vascular resistance were minor and not clinically significant.

A sustained reduction of heart rate was demonstrated in patients treated with ivabradine for at least one year ($n = 713$). No influence on glucose or lipid metabolism was observed.

The antianginal and anti-ischaemic efficacy of ivabradine was preserved in diabetic patients ($n = 457$) with a similar safety profile as compared to the overall population.

A large outcome study, BEAUTIFUL, was performed in 10 917 patients with coronary artery disease and left ventricular dysfunction (LVEF < 40%) on top of optimal background therapy with 86.9% of patients receiving beta-blockers. The main efficacy criterion was the composite of cardiovascular death, hospitalisation for acute MI or hospitalisation for new onset or worsening heart failure. The study showed no difference in the rate of the primary composite outcome in the ivabradine group by comparison to the placebo group (relative risk ivabradine: placebo: 1.00, $p = 0.945$).

In a post-hoc subgroup of patients with symptomatic angina at randomisation ($n = 1,507$), no safety signal was identified regarding cardiovascular death, hospitalisation for acute MI or heart failure (ivabradine 12.0% versus placebo 15.5%, $p = 0.05$).

A large outcome study, SIGNIFY, was performed in 19 102 patients with coronary artery disease and without clinical heart failure (LVEF > 40%), on top of optimal background therapy. A therapeutic scheme higher than the approved posology was used (starting dose 7.5 mg twice daily (5 mg twice daily, if age ≥ 75 years) and titration up to 10 mg twice daily.). The main efficacy criterion was the composite of cardiovascular death or non-fatal MI. The study showed no difference in the rate of the primary composite endpoint (PCE) in the ivabradine group by comparison to the placebo group (relative risk ivabradine/placebo 1.08, $p = 0.197$). Bradycardia was reported by 17.9 % of patients in the ivabradine group (2.1% in the placebo group). Verapamil, diltiazem or strong CYP 3A4 inhibitors were received by 7.1% of patients during the study.

A small statistically significant increase in the PCE was observed in a pre-specified subgroup of patients with angina patients in CCS class II or higher at baseline ($n = 12 049$) (annual rates 3.4% versus 2.9%,

relative risk ivabradine/placebo 1.18, $p = 0.018$), but not in the subgroup of the overall angina population in CCS class $\geq I$ ($n = 14\,286$) (relative risk ivabradine/placebo 1.11, $p = 0.110$).

The higher than approved dose used in the study did not fully explain these findings.

The SHIFT study was a large multicentre, international, randomised double-blind placebo controlled outcome trial conducted in 6 505 adult patients with stable chronic CHF (for ≥ 4 weeks), NYHA class II to IV, with a reduced left ventricular ejection fraction ($LVEF \leq 35\%$) and a resting heart rate ≥ 70 bpm. Patients received standard care including beta-blockers (89%), ACE inhibitors and/or angiotensin II antagonists (91%), diuretics (83%), and anti-aldosterone agents (60%). In the ivabradine group, 67% of patients were treated with 7.5 mg twice a day. The median follow-up duration was 22.9 months. Treatment with ivabradine was associated with an average reduction in heart rate of 15 bpm from a baseline value of 80 bpm. The difference in heart rate between ivabradine and placebo arms was 10.8 bpm at 28 days, 9.1 bpm at 12 months and 8.3 bpm at 24 months.

The study demonstrated a clinically and statistically significant relative risk reduction of 18% in the rate of the primary composite endpoint of cardiovascular mortality and hospitalisation for worsening heart failure (hazard ratio: 0.82, 95% CI [0.75; 0.90], $p < 0.0001$) apparent within 3 months of initiation of treatment. The absolute risk reduction was 4.2%. The results on the primary endpoint are mainly driven by the heart failure endpoints, hospitalisation for worsening heart failure (absolute risk reduced by 4.7%) and deaths from heart failure (absolute risk reduced by 1.1%).

Treatment effect on the primary composite endpoint, its components and secondary endpoints

| | Ivabradine (N = 3 241) n (%) | Placebo (N = 3 264) n (%) | Hazard ratio [95% CI] | p-value |
|------------------------------------|---|--|----------------------------------|----------------|
| Primary composite endpoint | 793 (24.47) | 937 (28.71) | 0.82 [0.75; 0.90] | < 0.0001 |
| Components of the composite: | | | | |
| – CV death | 449 (13.85) | 491 (15.04) | 0.91 [0.80; 1.03] | 0.128 |
| – Hospitalisation for worsening HF | 514 (15.86) | 672 (20.59) | 0.74 [0.66; 0.83] | < 0.0001 |
| Other secondary endpoints | | | | |
| – All cause death | 503 (15.52) | 552 (16.91) | 0.90 [0.80; 1.02] | 0.092 |
| – Death from HF | 113 (3.49) | 151 (4.63) | 0.74 [0.58; 0.94] | 0.014 |
| – Hospitalisation for any cause | 1 231 (37.98) | 1 356 (41.54) | 0.89 [0.82; 0.96] | 0.003 |
| – Hospitalisation for CV reason | 977 (30.15) | 1 122 (34.38) | 0.85 [0.78; 0.92] | 0.0002 |

The reduction in the primary endpoint was observed consistently irrespective of gender, NYHA class, ischaemic or non-ischaemic heart failure aetiology and of background history of diabetes or hypertension.

In the subgroup of patients with heart rate ≥ 75 bpm ($n = 4\,150$), a greater reduction was observed in the primary composite endpoint of 24% (hazard ratio: 0.76, 95% CI [0.68; 0.85], $p < 0.0001$) and for other secondary endpoints, including all cause death (hazard ratio: 0.83, 95% CI [0.72; 0.96], $p = 0.0109$) and CV death (hazard ratio: 0.83, 95% CI [0.71; 0.97], $p = 0.0166$). In this subgroup of patients, the safety profile of ivabradine is in line with the one of the overall population.

A significant effect was observed on the primary composite endpoint in the overall group of patients receiving beta-blocker therapy (hazard ratio: 0.85, 95% CI [0.76; 0.94]). In the subgroup of patients with heart rate ≥ 75 bpm and on the recommended target dose of beta-blocker, no statistically significant benefit was observed on the primary composite endpoint (hazard ratio: 0.97, 95% CI [0.74; 1.28]) and

other secondary endpoints, including hospitalisation for worsening heart failure (hazard ratio: 0.79, 95% CI [0.56; 1.10]) or death from heart failure (hazard ratio: 0.69, 95% CI [0.31; 1.53]).

There was a significant improvement in NYHA class at last recorded value, 887 (28%) of patients on ivabradine improved versus 776 (24%) of patients on placebo ($p = 0.001$).

In a 97-patient randomised placebo-controlled study, the data collected during specific ophthalmologic investigations, aiming at documenting the function of the cone and rod systems and the ascending visual pathway (i.e. electroretinogram, static and kinetic visual fields, colour vision, visual acuity), in patients treated with ivabradine for chronic stable angina pectoris over 3 years, did not show any retinal toxicity.

Paediatric population

A 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 twice daily in age-subset [6 – 12] months, 0.05 mg/kg twice daily in [1 – 3] years and [3 – 18] years < 40 kg, and 2.5 mg twice daily in [3 – 18] years and ≥ 40 kg. The dose was adapted depending on the therapeutic response with maximum doses of 0.2 mg/kg twice daily, 0.3 mg/kg twice daily and 15 mg twice daily, 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 twice daily, 0.10 ± 0.04 mg/kg twice daily and 4.1 ± 2.2 mg twice daily 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 medicinal product containing ivabradine in all subsets of the paediatric population for the treatment of angina pectoris (see section 4.2 for information on paediatric use).

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

5.2 Pharmacokinetic properties

Under physiological conditions, ivabradine is rapidly released from tablets and is highly water-soluble ($> 10 \text{ mg/mL}$). 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 (see section 4.2).

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 P4503A4 (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 (see section 4.5).

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_{max}) have been observed between elderly (≥ 65 years) or very elderly patients (≥ 75 years) and the overall population (see section 4.2).

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 (see section 4.2).

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 (see sections 4.2 and 4.3).

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 (see sections 4.3, 4.4 and 4.5).

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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on 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 I_f 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol
Crospovidone (type A)
Magnesium stearate

Film-coating

Hypromellose (6 mPa·s, type 2910)
Titanium dioxide (E172)
Macrogol 400
Glycerol (E422)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25 °C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

OPA/Alu/PVC-Alu blisters

Ivabradine Zentiva 5 mg film-coated tablets

Pack sizes: 14, 28, 56, 84, 98, 100, 112 film-coated tablets

Ivabradine Zentiva 7.5 mg film-coated tablets

Pack sizes: 14, 28, 56, 84, 98, 100, 112 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Zentiva, k.s.
U Kabelovny 130
102 37 Prague 10
Czech Republic

8. MARKETING AUTHORISATION NUMBER(S)

Ivabradine Zentiva 5 mg film-coated tablets

EU/1/16/1144/001
EU/1/16/1144/002
EU/1/16/1144/003
EU/1/16/1144/004
EU/1/16/1144/005
EU/1/16/1144/006
EU/1/16/1144/007

Ivabradine Zentiva 7.5 mg film-coated tablets

EU/1/16/1144/008
EU/1/16/1144/009
EU/1/16/1144/010
EU/1/16/1144/011
EU/1/16/1144/012
EU/1/16/1144/013
EU/1/16/1144/014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 November 2016
Date of latest renewal: 29 September 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Zentiva, k.s.
U Kabelovny 130
Dolni Měcholupy
102 37 Prague 10
Czech Republic

S.C. Zentiva S.A
50 Theodor Pallady Blvd,
District 3,
032266 Bucharest
Romania

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Ivabradine Zentiva 5 mg film-coated tablets
ivabradine

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 5 mg ivabradine (as hydrochloride).

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

14 film-coated tablets
28 film-coated tablets
56 film-coated tablets
84 film-coated tablets
98 film-coated tablets
100 film-coated tablets
112 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25 °C. Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Zentiva, k.s.
U Kabelovny 130
102 37 Prague 10
Czech Republic

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1144/001
EU/1/16/1144/002
EU/1/16/1144/003
EU/1/16/1144/004
EU/1/16/1144/005
EU/1/16/1144/006
EU/1/16/1144/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE**

| |
|-----------------------------------|
| 16. INFORMATION IN BRAILLE |
|-----------------------------------|

Ivabradine Zentiva 5 mg

| |
|---|
| 17. UNIQUE IDENTIFIER – 2D BARCODE |
|---|

2D barcode carrying the unique identifier included.

| |
|--|
| 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA |
|--|

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**Blister****1. NAME OF THE MEDICINAL PRODUCT**

Ivabradine Zentiva 5 mg film-coated tablets
ivabradine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Zentiva logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

| | |
|------------|-------------|
| Mon. [sun] | Mon. [moon] |
| Tue. [sun] | Tue. [moon] |
| Wed. [sun] | Wed. [moon] |
| Thu. [sun] | Thu. [moon] |
| Fri. [sun] | Fri. [moon] |
| Sat. [sun] | Sat. [moon] |
| Sun. [sun] | Sun. [moon] |

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Ivabradine Zentiva 7.5 mg film-coated tablets
ivabradine

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 7.5 mg ivabradine (as hydrochloride).

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

14 film-coated tablets
28 film-coated tablets
56 film-coated tablets
84 film-coated tablets
98 film-coated tablets
100 film-coated tablets
112 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25 °C. Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Zentiva, k.s.
U Kabelovny 130
102 37 Prague 10
Czech Republic

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1144/008
EU/1/16/1144/009
EU/1/16/1144/010
EU/1/16/1144/011
EU/1/16/1144/012
EU/1/16/1144/013
EU/1/16/1144/014

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Ivabradine Zentiva 7.5 mg

| |
|--|
| 17. UNIQUE IDENTIFIER – 2D BARCODE |
|--|

2D barcode carrying the unique identifier included.

| |
|---|
| 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA |
|---|

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**Blister****1. NAME OF THE MEDICINAL PRODUCT**

Ivabradine Zentiva 7.5 mg film-coated tablets
ivabradine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Zentiva logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

| | |
|------------|-------------|
| Mon. [sun] | Mon. [moon] |
| Tue. [sun] | Tue. [moon] |
| Wed. [sun] | Wed. [moon] |
| Thu. [sun] | Thu. [moon] |
| Fri. [sun] | Fri. [moon] |
| Sat. [sun] | Sat. [moon] |
| Sun. [sun] | Sun. [moon] |

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ivabradine Zentiva 5 mg film-coated tablets **Ivabradine Zentiva 7.5 mg film-coated tablets** ivabradine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- 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. See section 4.

What is in this leaflet

1. What Ivabradine Zentiva is and what it is used for
2. What you need to know before you take Ivabradine Zentiva
3. How to take Ivabradine Zentiva
4. Possible side effects
5. How to store Ivabradine Zentiva
6. Contents of the pack and other information

1. What Ivabradine Zentiva is and what it is used for

Ivabradine Zentiva (ivabradine) 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. The most common symptom of angina is chest pain or discomfort.

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 Ivabradine Zentiva work?

The specific heart rate lowering action of ivabradine helps:

- to control and reduce the number of angina attacks by lowering heart's need for oxygen,
- to improve the heart functioning and vital prognosis in patients with chronic heart failure.

2. What you need to know before you take Ivabradine Zentiva

Do not take Ivabradine Zentiva

- if you are allergic to ivabradine or any of the other ingredients of this medicine (listed in section 6).
- 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 (sick sinus syndrome, sino-atrial block, AV-block of 3rd degree).
- 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 Ivabradine Zentiva

- 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 Ivabradine Zentiva.

Children and adolescents

Do not give this medicine to children and adolescents younger than 18 years. Available data are insufficient in this age group.

Other medicines and Ivabradine Zentiva

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 Ivabradine Zentiva 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).

Ivabradine Zentiva with food and drink

Avoid grapefruit juice during treatment with Ivabradine Zentiva.

Pregnancy and breast-feeding

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.

Do not take Ivabradine Zentiva if you are pregnant or are planning to have a baby (see “Do not take Ivabradine Zentiva”).

If you are pregnant and have taken Ivabradine Zentiva, talk to your doctor.

Do not take Ivabradine Zentiva if you are able to become pregnant unless you use reliable contraceptive measures (see “Do not take Ivabradine Zentiva”).

Do not take Ivabradine Zentiva if you are breast-feeding (see “Do not take Ivabradine Zentiva”). Talk to your doctor if you are breast-feeding or intending to breast-feed as breast-feeding should be discontinued if you take Ivabradine Zentiva.

Driving and using machines

Ivabradine Zentiva 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.

3. How to take Ivabradine Zentiva

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

If you are being treated for stable angina pectoris

The starting dose should not exceed one tablet of Ivabradine Zentiva 5 mg twice daily. If you still have angina symptoms and if you have tolerated the 5 mg twice daily dose well, the dose may be increased. The maintenance dose should not exceed 7.5 mg twice daily. Your doctor will prescribe the right dose for you. The usual dose is one tablet in the morning and one tablet in the evening. In some cases (e.g. if you are aged 75 years or more), your doctor may prescribe half the dose i.e., one half 5 mg tablet of Ivabradine Zentiva 5 mg (corresponding to 2.5 mg ivabradine) in the morning and one half 5 mg tablet in the evening.

If you are being treated for chronic heart failure

The usual recommended starting dose is one tablet of Ivabradine Zentiva 5 mg twice daily increasing if necessary to one tablet of Ivabradine Zentiva 7.5 mg twice daily. Your doctor will decide the right dose for you. The usual dose is one tablet in the morning and one tablet in the evening. In some cases (e.g. if you are aged 75 years or more), your doctor may prescribe half the dose i.e., one half 5 mg tablet of Ivabradine Zentiva 5 mg (corresponding to 2.5 mg ivabradine) in the morning and one half 5 mg tablet in the evening.

Method of administration

Tablets must be taken orally twice daily, i.e. once in the morning and once in the evening during meals. Ivabradine Zentiva 5 mg film-coated tablet can be divided into equal doses. Use a tablet cutter to divide the tablet.

If you take more Ivabradine Zentiva than you should

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

If you forget to take Ivabradine Zentiva

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

If you stop taking Ivabradine Zentiva

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 Ivabradine Zentiva 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.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

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

Very common (may affect more than 1 in 10 people)

- 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 (may affect up to 1 in 10 people)

- 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:

Common (may affect up to 1 in 10 people)

- Irregular rapid contraction of the heart (atrial fibrillation), abnormal perception of heartbeat (bradycardia, ventricular extrasystoles, AV 1st degree block (ECG prolonged PQ interval)), uncontrolled blood pressure, headache, dizziness and blurred vision (cloudy vision).

Uncommon (may affect up to 1 in 100 people)

- Palpitations and cardiac extra beats, feeling sick (nausea), constipation, diarrhoea, abdominal pain, spinning sensation (vertigo), difficulty breathing (dyspnoea), muscle spasms, 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 (may affect up to 1 in 1 000 people)

- Urticaria, itching, skin reddening, feeling unwell.

Very rare (may affect up to 1 in 10 000 people)

- Irregular heartbeats (AV 2nd and 3rd degree block, sick sinus syndrome).

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ivabradine Zentiva

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after “EXP”. The expiry date refers to the last day of that month.

Store below 25 °C. Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ivabradine Zentiva contains

- The active substance is ivabradine (as hydrochloride). Each film-coated tablet contains 5 mg ivabradine (as hydrochloride) or 7.5 mg ivabradine (as hydrochloride).
- The other ingredients are:
tablet core: mannitol, crospovidone (type A), magnesium stearate,
film-coating: hypromellose (6 mPa·s, type 2910), titanium dioxide (E172), macrogol 400, glycerol (E422).

What Ivabradine Zentiva looks like and contents of the pack

Ivabradine Zentiva 5 mg film-coated tablets are round, biconvex white tablets with deep breakline on one side and ‘5’ debossing on other side with diameter 6.5 mm. The tablet can be divided into equal doses.

Ivabradine Zentiva 7.5 mg film-coated tablets are white to off white, round tablets with diameter 7.1 mm.

Ivabradine Zentiva is packed in OPA/Alu/PVC-Alu blisters and in paper carton.

Tablets are available in packs of 14, 28, 56, 84, 98, 100, 112 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Czech Republic

Manufacturer(s)

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or

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.