Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bisoprolol Zentiva 7.5mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 7.5 mg bisoprolol fumarate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Yellow to dark yellow rounded tablets with embossing 7.5 and with randomly distributed spots of colourant and diameter 6 mm ± 0.3 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bisoprolol Zentiva is indicated for treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides (for additional information see section 5.1).

In addition, Bisoprolol Zentiva 5 mg and 10 mg are indicated for treatment of hypertension and ischemic heart disease (angina pectoris).

4.2 Posology and method of administration

Treatment of stable chronic heart failure
Standard treatment of chronic heart failure consists of an ACE inhibitor (or an angiotensin receptor blocker in case of intolerance to ACE inhibitors), a beta-blocker, diuretics, and when appropriate cardiac glycosides. Patients should be stable (without acute heart failure) when bisoprolol treatment is initiated.

Recommendation: the treating physician should be experienced in the management of chronic heart failure.

Transient worsening of heart failure, hypotension, or bradycardia may occur during the titration period and thereafter.

Posology
Titration phase
The treatment of stable chronic heart failure with bisoprolol requires gradual dose titration.

The treatment with bisoprolol is to be started with a gradual up-titration according to the following steps:

- 1.25 mg once daily for 1 week. If this dose is well tolerated, increase to
- 2.5 mg once daily for 1 further week. If this dose is well tolerated, increase to
- 3.75 mg once daily for 1 further week. If this dose is well tolerated, increase to
- 5 mg once daily for the following 4 weeks. If this dose is well tolerated, increase to
- 7.5 mg once daily for the following 4 weeks. If this dose is well tolerated, increase to
- 10 mg once daily for the maintenance therapy.

The maximum recommended dose is 10 mg.

In case Bisoprolol Zentiva 1.25 mg, 3.75 mg or 7.5 mg is not registered in your country, the dosages can be achieved by other bisoprolol products that are available.

Close monitoring of vital signs (heart rate, blood pressure) and symptoms of worsening heart failure is recommended during the titration phase. Symptoms may already occur within the first day after initiating the therapy.

Treatment modification

If the maximum recommended dose is not well tolerated, gradual dose reduction may be considered.

In case of transient worsening of heart failure, hypotension, or bradycardia reconsideration of the dosage of the concomitant medication is recommended. It may also be necessary to temporarily lower the dose of bisoprolol or to consider discontinuation.

The reintroduction and/or up-titration of bisoprolol should always be considered when the patient becomes stable again.

If discontinuation of treatment is considered, gradual dose decrease is recommended, since abrupt withdrawal may lead to acute deterioration of the patient's condition.

Treatment of stable chronic heart failure with bisoprolol is generally a long-term treatment.

Renal or hepatic impairment

There is no information available regarding pharmacokinetics of bisoprolol in patients with chronic heart failure and with impaired hepatic or renal function. Up-titration of the dose in these patients should therefore be made with additional caution.

Treatment of hypertension and treatment of ischemic heart disease (angina pectoris)

In general, treatment should start with small doses and increased gradually. Dosage should be determined on an individual-case basis, primarily taking into account the heart rate and the success of treatment.

Posology

Treatment of hypertension

The recommended dose is 5 mg bisoprolol fumarate once daily.

In less severe cases of hypertension (diastolic blood pressure of up to 105 mmHg), treatment with 2.5 mg once daily may be sufficient, using other medicinal products with appropriate strength.

If necessary, the dose may be increased to 10 mg once daily. Additional dose increases are justified only in exceptional cases. The maximum recommended dose is 20 mg once daily.

Treatment of ischemic heart disease (angina pectoris)
The recommended dose is 5 mg bisoprolol fumarate once daily.

If necessary, the dose may be increased to 10 mg once daily. Additional dose increases are justified only in exceptional cases. The maximum recommended dose is 20 mg once daily.

Duration of administration
There is no limit to the duration of administration. It depends on the type and the severity of the symptoms.

Treatment with Bisoprolol Zentiva should not be abruptly discontinued, particularly in patients with coronary heart disease, since this can lead to an acute exacerbation of the patient's condition. In case discontinuation of the treatment is necessary, the dose should be reduced gradually (e.g. by halving the dose every week).

Hepatic or renal impairment
In patients with mild to moderate hepatic or renal impairment, dosage adjustment is not normally necessary. In patients with severe renal impairment (creatinine clearance < 20 ml/min) and in patients with severe hepatic impairment, the daily dose should not exceed 10 mg bisoprolol fumarate. Experience with the use of bisoprolol in patients on dialysis is limited and there is no indication for the need to change the dosing regimen.

Elderly
No dosage adjustment is required for elderly patients.

Paediatric population
There is no paediatric experience with bisoprolol. Therefore its use cannot be recommended in paediatric patients.

Method of administration
The tablets should be taken in the morning with or without food. They should be swallowed with liquid and should not be chewed. The score line is not intended for breaking the tablet.

4.3 Contraindications

Bisoprolol is contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy;
- cardiogenic shock;
- second or third-degree AV block;
- sick sinus syndrome;
- sinoatrial block;
- symptomatic bradycardia;
- symptomatic hypotension;
- severe bronchial asthma;
- severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome;
- untreated phaeochromocytoma (see section 4.4);
- metabolic acidosis.

4.4 Special warnings and precautions for use

Applies to all indications
Bisoprolol should be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.

The initiation and cessation of treatment with bisoprolol necessitates regular monitoring.

Especially in patients with ischaemic heart disease the cessation of therapy with bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition.

Bisoprolol must be used with caution in:

- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia can be masked;
- strict fasting;
- ongoing desensitisation therapy. As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Adrenalin treatment does not always yield the expected therapeutic effect.
- first degree AV block;
- Prinzmetal's angina: cases of coronary vasospasm have been observed. Despite its high beta1-selectivity, angina attacks cannot be completely excluded when bisoprolol is administered to patients with Prinzmetal's angina;

- peripheral arterial occlusive disease. Aggravation of symptoms may occur especially when starting therapy.

General anaesthesia
In patients undergoing general anaesthesia, beta-blockers reduce the incidence of arrhythmias and myocardial ischaemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance beta-blocker therapy be continued peri-operatively. The anaesthetist must be aware of the beta-blocker therapy because of the potential for interactions with other pharmaceuticals, resulting in bradyarrhythmias, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. If discontinuation of the beta-blocker therapy prior to surgery is necessary, the dose should be reduced gradually and the reduction should be complete approx. 48 hours before anaesthesia.

Although cardioselective ($beta_1$) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, bisoprolol may be used with caution.

In patients with obstructive airways diseases, the treatment with bisoprolol should be started at the lowest possible dose and patients should be carefully monitored for new symptoms (e.g. dyspnoea, exercise intolerance, cough). In bronchial asthma or other chronic obstructive pulmonary diseases, which may cause symptoms, concomitant bronchodilating therapy is recommended. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of $beta_2$-stimulants may have to be increased.

Patients with psoriasis or with a history of psoriasis should only be given beta-blockers (e.g. bisoprolol) after a careful balancing of benefits against risks.

In patients with phaeochromocytoma bisoprolol must not be administered until after alpha-receptor blockade.

The symptoms of thyrotoxicosis may be masked under treatment with bisoprolol.

Combination of bisoprolol with calcium antagonists of the verapamil or diltiazem type, with Class I antiarrhythmic drugs and with centrally acting antihypertensive drugs is generally not recommended, for details please refer to section 4.5.

Additional warnings applicable to stable chronic heart failure
The treatment of stable chronic heart failure with bisoprolol has to be initiated with a special titration phase.

There is no therapeutic experience of bisoprolol treatment of heart failure in patients with the following diseases and conditions:

- insulin dependent diabetes mellitus (type I);
- severely impaired renal function;
- severely impaired hepatic function;
- restrictive cardiomyopathy;
- congenital heart disease;
- haemodynamically significant organic valvular disease;
- myocardial infarction within 3 months.

4.5 Interaction with other medicinal products and other forms of interaction

Applies to all indications

Combinations not recommended

- Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type: Negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrio-ventricular block.
- Centrally-acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonidine, rilmenidine): Concomitant use of centrally-acting antihypertensive drugs may worsen heart failure by a decrease in the central

sympathetic tonus (reduction of heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of "rebound hypertension".

Combinations to be used with caution

- Calcium antagonists of the dihydropyridine type (such as felodipine and amlodipine): Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.
- Class-III antiarrhythmic drugs (such as amiodarone): Effect on atrioventricular conduction time may be potentiated.
- Topical beta-blockers (such as timolol eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.
- Parasympathomimetic drugs such as tacrine or carbachol: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.
- Insulin and oral antidiabetic drugs: Increase of blood sugar lowering effect. Blockade of beta-adrenoreceptors may mask symptoms of hypoglycaemia.
- Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension (for further information on general anaesthesia see also section 4.4).
- Digitalis glycosides: Reduction of heart rate, increase of atrio-ventricular conduction time.
- Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol.
- Beta-sympathomimetic agents (such as isoprenaline, dobutamine, orciprenaline): Combination with bisoprolol may reduce the effect of both agents. The treatment of allergic reactions may require increased adrenaline doses.
- Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. noradrenaline, adrenaline): Combination with bisoprolol may unmask the alpha-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective beta-blockers.
- Concomitant use with antihypertensive agents as well as with other drugs with blood pressure lowering potential (such as tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.

Combinations to be considered

- Mefloquine: increased risk of bradycardia.
- Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the beta-blockers, but also risk for hypertensive crisis.

Applies to stable
chronic heart failure

Combinations not recommended

- Class I antiarrhythmic medicines (such as quinidine, disopyramide, lidocaine, phenytoin, flecainide, propafenone): Effect on atrioventricular conduction time may be potentiated and negative inotropic effect increased.

Applies to hypertension and ischemic heart disease (angina pectoris)

Combinations to be used with caution

- Class I antiarrhythmic medicines (such as quinidine, disopyramide, lidocaine, phenytoin, flecainide, propafenone): Effect on atrioventricular conduction time may be potentiated and negative inotropic effect increased.

4.6 Fertility, pregnancy and lactation

Pregnancy

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, beta-blockers reduce placental perfusion.

This has been associated with intrauterine growth retardation, foetus death, abortion or early labour. Adverse effects (such as hypoglycaemia and bradycardia) may occur in the foetus and newborn infant. If treatment with a beta-blocker is necessary, $beta_1$-selective adrenoceptor blockers are preferable.

Bisoprolol should not be used during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, the uteroplacental blood flow and foetal growth should be monitored. In case of harmful effects on pregnancy or the foetus, alternative treatment should be considered. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

Breast-feeding

It is not known whether this drug is excreted in human milk. Therefore, breast-feeding is not recommended during administration of bisoprolol.

4.7 Effects on ability to drive and use machines

In a study with coronary heart disease patients, bisoprolol did not impair driving performance. However, due to individual variations in reactions to the drug, the ability to drive a vehicle or to operate machinery may be impaired. This should be considered particularly at start of treatment and upon change of medication as well as in conjunction with alcohol.

4.8 Undesirable effects

Tabulated list of adverse reactions

The following terminologies have been used in order to classify the occurrence of adverse reactions: very common (≥ 1/10 to < 1/10); common (≥ 1/100 to < 1/10)); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000< 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Frequency	Adverse reaction
Psychiatric disorders	Uncommon	Sleep disorders, depression
	Rare	Nightmare, hallucinations
Nervous system disorders	Common	Dizziness*, headache*
	Rare	Syncope
Eye disorders	Rare	Reduced tear flow (to be considered if the patient uses lenses)
	Very rare	Conjunctivitis
Ear and labyrinth disorders	Rare	Hearing disorders
Cardiac disorders	Very common	Bradycardia (in patients with chronic heart failure)
	Common	Worsening of heart failure (in patients with chronic heart failure)
	Uncommon	AV-conduction disorder, worsening of pre-existing heart failure (in patients with hypertension or angina pectoris), bradycardia (in patients with hypertension or angina pectoris)
Vascular disorders	Common	Feeling of coldness or numbness in the extremities, hypotension
	Uncommon	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	Bronchospasm in patients with bronchial asthma or a history of obstructive airways disease
	Rare	Allergic rhinitis
Gastrointestinal disorders	Common	Gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation
Hepatobiliary disorders	Rare	Hepatitis
Skin and subcutaneous tissue disorders	Rare	Hypersensitivity reactions (pruritus, flush, rash and angioedema)
	Very rare	Alopecia, beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash

Musculoskeletal and connective tissue disorders	Uncommon	Muscle weakness, muscle cramps
Reproductive system and breast disorders	Rare	Erectile dysfunction
General disorders	Common	Asthenia(in patients with chronic heart failure), fatigue*
	Uncommon	Asthenia (in patients with hypertension or angina pectoris)
Investigations	Rare	Increased triglycerides, increased liver enzymes (ALAT, ASAT)

Applies only to hypertension or angina pectoris:
*These symptoms especially occur at the beginning of the therapy. They are generally mild and usually disappear within 1 - 2 weeks.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517. Website: www.hpra.ie, E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms
With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness have been reported. In general the most common signs expected with overdosage of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. To date a few cases of overdose (maximum: 2,000 mg) with bisoprolol have been reported in patients suffering from hypertension and/or coronary heart disease showing bradycardia and/or hypotension; all patients recovered.

There is a wide interindividual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive. Therefore it is mandatory to initiate the treatment of these patients with a gradual up-titration according to the scheme given in section 4.2.

Management
If overdose occurs, bisoprolol treatment should be stopped and supportive and symptomatic treatment should be provided. Limited data suggest that bisoprolol is hardly dialysable.
Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures should be considered when clinically warranted.

Bradycardia: Administer intravenous atropine. If the response is inadequate, isoprenaline, orciprenaline or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.

Hypotension: Intravenous fluids and vasopressors should be administered.
Intravenous glucagon may be useful.

AV block (second or third degree): Patients should be carefully monitored and treated with isoprenaline/orciprenaline infusion or transvenous cardiac pacemaker insertion.

Acute worsening of heart failure: Administer *i.v.* diuretics, inotropic agents, vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as isoprenaline or orciprenaline, $beta_2$-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer *i.v.* glucose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective;

ATC code: C07AB07

Mechanism of action

Bisoprolol is a highly beta$_1$-selective adrenoceptor-blocking agent lacking intrinsic stimulating and relevant membrane-stabilising activity. Bisoprolol shows only low affinity to the beta$_2$-receptors of the smooth muscles of bronchi and vessels as well as to the beta$_2$-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not expected to influence the airway resistance and beta$_2$-mediated metabolic processes. The beta$_1$-selectivity of bisoprolol extends beyond the therapeutic dose range.

Bisoprolol has no significant negative inotropic effect.

Bisoprolol achieves maximum effect 3-4 hours after oral intake. The maximum anti-hypertensive effect of bisoprolol is generally achieved after 2 weeks.

In patients with coronary heart disease and without chronic heart failure, acute administration of bisoprolol reduces the heart rate and stroke volume and therefore the cardiac output and oxygen consumption. The initially elevated peripheral resistance decreases in chronic administration. Among other things, the suppression of plasma renin activity as a mechanism of action is discussed for the anti-hypertensive effect of the beta-blockers.

Bisoprolol suppresses the response to sympatho-adrenergic activity by blocking cardiac beta$_1$-receptors. This causes a decrease in heart rate and contractility, thereby reducing myocardial oxygen consumption, which is the desired effect in angina pectoris with coronary heart disease.

Clinical efficacy and safety

Treatment of stable chronic heart failure

In total 2,647 patients were included in the CIBIS II trial. 83% (n = 2,202) were in NYHA class III and 17% (n = 445) were in NYHA class IV. They had stable symptomatic systolic heart failure (ejection fraction < 35%, based on echocardiography). Total mortality was reduced from 17.3% to 11.8% (relative reduction 34%). A decrease in sudden death (3.6% vs. 6.3%, relative reduction 44%) and a reduced number of heart failure episodes requiring hospital admission (12% vs. 17.6%, relative reduction 36%) was observed. Finally, a significant improvement of the functional status according to NYHA classification has been shown. During the initiation and titration of bisoprolol hospital admission due to bradycardia (0.53%), hypotension (0.23%), and acute decompensation (4.97%) were observed, but they were not more frequent than in the placebo-group (0%, 0.3% and 6.74%). the numbers of fatal and disabling strokes during the total study period were 20 in the bisoprolol group and 15 in the placebo group.

The CIBIS III trial investigated 1,010 patients aged ≥ 65 years with mild to moderate chronic heart failure (CHF; NYHA class II or III) and left ventricular ejection fraction 35%, who had not been treated previously with ACE inhibitors, beta-blockers, or angiotensin receptor blockers. Patients were treated with a combination of bisoprolol and enalapril for 6 to 24 months after an initial 6 months treatment with either bisoprolol or enalapril.

There was a trend toward higher frequency of chronic heart failure worsening when bisoprolol was used as the initial 6 months treatment. Non inferiority of bisoprolol-first versus enalapril-first treatment was not proven in the per-protocol analysis, although the two strategies for initiation of CHF treatment showed a similar rate of the primary combined endpoint death and hospitalization at study end (32.4% in the bisoprolol-first group vs. 33.1% in the enalapril-first group, per-protocol population). The study shows that bisoprolol can also be used in elderly chronic heart failure patients with mild to moderate symptoms.

5.2 Pharmacokinetic properties

Absorption

Bisoprolol is absorbed after intake from the gastrointestinal tract by more than 90%. The absorption rate is independent of food intake.

The first pass effect is ≤10%. This results in an absolute bioavailability of approx. 90% after oral intake.

Distribution

The distribution volume is 3.5 l/kg. The plasma protein binding of bisoprolol is about 30%.

Biotransformation and elimination
Bisoprolol is excreted from the body by two equivalent routes. 50% is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in an unchanged form.

Total clearance is approximately 15 l/h. The plasma elimination half-life of 10 – 12 hours results in a 24 hour effect after administration once daily.

Linearity
The kinetics of bisoprolol is linear and independent of age.

Special population
Since elimination takes place in the kidneys and the liver to the same extent, a dosage adjustment is usually not required for patients with impaired liver or kidney function (see section 4.2). There is no information available regarding pharmacokinetics of bisoprolol in patients with chronic heart failure and with impaired hepatic or renal function.

In patients with chronic heart failure (NYHA stage III), the bisoprolol levels in plasma are higher and the half-life is prolonged compared to healthy volunteers. The maximum concentration in plasma under steady-state conditions is 64 ± 21 ng/ml at a daily dose of 10 mg and the half-life is 17 ± 5 hours.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity.

Reproduction
In studies on reproduction toxicity, bisoprolol was not found to impact fertility or reproductive behaviour.

Like other beta-blockers, bisoprolol caused maternal (decreased food intake and decreased body weight) and embryo/foetal toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development) at high doses but was not teratogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline (PH 102)
Starch, pregelatinised (maize)
Crospovidone (type A)
Silica, colloidal anhydrous
Magnesium stearate
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

For products packed in OPA/Alu/PVC100//Alu or OPA/Alu /PVC60//Alu blisters:
Store below 30 °C. Store in the original package in order to protect from moisture.

For products packed in white PVC/PVdC foil //Alu blisters:
Store below 25 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

OPA/Alu/PVC100//Alu or PVC/PVdC //Alu blisters, in paper box.

Pack sizes:
28, 30, 50, 56, 60 or 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Waste material should be disposed of safely. Patients/carers should be encouraged to return any unused product to the pharmacy, where it should be disposed of in accordance with national and local requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA1701/010/005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd June 2023
Date of last renewal: 17th February 2026

10 DATE OF REVISION OF THE TEXT

August 2025