SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bisoprolol Fumarate 2.5 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg of bisoprolol fumarate.

For the full list of excipients, see in section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White to off- white, round, biconvex tablet, with a breakline on one side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of essential hypertension.
- Treatment of chronic, stable angina pectoris
- 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)

4.2 Posology and method of administration

Posology

The dose must be individually adjusted.

Adults:

Essential hypertension.
The dosage should be individually adjusted. It is recommended to start with the lowest possible dose. In some patients, 5 mg per day may be adequate. Depending on the clinical response, the dose can be increased to 10 mg once daily or to the maximum of 20 mg once daily. If satisfactory clinical response can not be achieved using monotherapy, another antihypertensive for example a diuretic can be combined to the medication.

Chronic, stable angina pectoris
The recommended dose is 5 mg once daily. If necessary, this dose can be increased to 10 mg once daily. In exceptional cases this dosage can be increased to maximally 20 mg once daily.

Stable Chronic heart failure
Standard treatment of CHF 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 failure) when bisoprolol treatment is initiated.

It is recommended that 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.

Titration phase

The treatment of stable chronic heart failure with bisoprolol requires a titration phase. The treatment with bisoprolol is to be started with a gradual uptitration according to the following steps:

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

The maximum recommended dose is 10 mg once daily.

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 uptitration of bisoprolol should always be considered when the patient becomes stable again.

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

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

Paediatric population:
There is no experience of the use of bisoprolol in children, therefore its use cannot be recommended in patients under 18 years of age.

Elderly:
No dosage adjustment is required. Aging does not affect the dosing, unless patient has renal or hepatic impairment, see below.

Renal or hepatic Impairment;
In patients with liver or kidney function disorders of mild to moderate severity, no dosage adjustment is normally required. In patients with severe renal impairment (creatinine clearance < 20 ml/min) and in patients with severe liver function disorders, it is recommended that a daily dose of 10 mg bisoprolol fumarate is not exceeded.
Experience with the use of bisoprolol in renal dialysis patients is limited; however, there is no evidence that the dosage regimen needs to be altered.
There is no information about pharmacokinetics of bisoprolol in relation to patients, which have chronic heart failure and impaired renal and hepatic function. In treatment of these patients, the upwards dose titration must be performed with special caution.

Method of Administration:
Bisoprolol Fumarate tablets are taken in the morning with or without food. Tablets are swallowed with some liquid and not to be chewed.

The tablets can be divided into equal doses as follows: Tablets should be placed on a flat, hard surface (e.g. table) and divided by pressing with the index fingers of both hands on the right and left of the score line on the outside of the tablet towards the surface.

Discontinuation of treatment:
Themust not be stopped suddenly, in particular when patient has ischaemic heart disease, instead the dosage should be reduced step by step for example during 1-2 weeks. Otherwise the symptoms of heart disease may get worse.

4.3 Contraindications

- 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,
- sick sinus syndrome,
- sino-atrial block
- atrio-ventricular block of second or third degree,
- symptomatic bradycardia
- symptomatic hypotension,
- untreated phaeochromocytoma, see section 4.4,
- severe bronchial asthma,
- severe forms of peripheral arterial occlusive disease and Raynaud's syndrome,
- metabolic acidosis.

4.4 Special warnings and precautions for use

The treatment of stable chronic heart failure with bisoprolol has to be initiated with a special titration phase (see section 4.2).

Bisoprolol must be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.

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 (serum creatinine over 300 mmol/l),
- impaired liver function,
- restrictive cardiomyopathy,

- congenital heart disease,
- haemodynamically significant organic valvular disease,
- myocardial infarction within 3 months.

Bisoprolol must be used with caution:

- stable chronic heart failure (Bisoprolol indicated for treatment after initial titration phase),
- Bronchospasm (bronchial asthma, obstructive airways diseases),
- diabetes mellitus showing large fluctuations in blood glucose values. Symptoms of hypoglycaemia (e.g tachycardia, palpitations or sweating) 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. Epinephrine 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 $beta_1$-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 of therapy.
- general anaesthesia

In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance of beta-blockade be continued peri-operatively. The anaesthetist must be aware of beta-blockade because of the potential for interactions with other drugs, resulting in bradyarrhythmias, attenuation of reflex tachycardia, and decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

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

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 fornew symptoms (e.g. dyspnea, 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 beta2-stimulants may have to be increased.

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

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

Patient 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.

The initiation and cessation of treatment of stable chronic heart failure with bisoprolol necessitates regular monitoring. For the dosage and method of administration see section 4.2

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 (see section 4.2)
Excipient(s)

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations not recommended:

Applies only to CHF:

- Class-I antiarrhythmics (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide, propafenone): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Applies to all indications:

- Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type: Negative effect 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 (e.g. clonidine, methyldopa, moxonidine, rilmenidine): Concomitant use of centrally acting antihypertensive medicinal products 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:

Applies only to hypertention or agina pectoris:

- Class-I antiarrhythmic drugs: Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Applies to all indications:

- Calcium antagonists such as dihydropyridine derivatives with negative inotropic effect (eg, amlodipine, felodipine and nifedipine). Nifedipine decrease myocardial contractility by affecting the amount of calcium. Its concomitant use in patients on beta-blocker treatment may increase the risk of hypotension and reduction of the ventricular pump function with possible development of heart failure in patients with latent cardiac insufficiency. The negative inotropism of nifedipine may precipitate or exacerbate heart failure.
- Class-III antiarrhythmics (e.g. amiodarone): Effect on atrio-ventricular
- conduction time may be potentiated..
- 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,
- Topical beta-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.
- Digitalis glycosides: Increase of atrio-ventricular conduction time, reduction in
- heart rate

- Parasympathomimetic drugs: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.
- Insulin and oral antidiabetics drugs: Increase of blood sugar lowering effect. Blockade of beta-adrenoceptors 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)
- Non-steroidal antiflammatory drugs (NSAIDS): NSAIDS may reduce the hypotensive effect of bisoprolol.
- Beta-sympathomimetics (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both agents.
- Concomitant use with antihypertensive agents as well as with other drugs with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.
- Moxisylate: Possibly causes severe postural hypertension.

Combinations to be considered:

- Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the beta-blockers but also a risk of hypertensive crisis.
- Mefloquine: increased risk of bradycardia,
- Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.
- Rifampicin: Slight reduction of the half-life of bisoprolol possible due to the induction of hepatic drug metabolising enzymes. Normally no dosage adjustment is necessary

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-adrenoceptor blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g.hypoglycemia and bradycardia) may occur in the foetus and newborn infant. If treatment with beta-adrenoceptor blockers is necessary, beta1-selective adrenoceptor blockers are preferable.

Bisoprolol should not be used during pregnancy, unless clearly necessary. If treatment with bisoprolol is considered necessary, uteroplacental blood flow and the 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:

There are no data on the excretion of bisoprolol in human breast milk or the safety of bisoprolol exposure in infants. 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

The frequency classification of adverse effects is following:

- very common (≥ 1/10)
- common (≥ 1/100, < 1/10)
- uncommon (≥ 1/1 000, < 1/100)
- rare (≥ 1/10 000, < /1 000)
- very rare (≥ 1/10 000), not known (can not be estimated from the available data).

Psychiatric disorders	
Uncommon:	Depression, sleep disorders
Rare:	Nightmares, hallucinations
Nervous system disorders	
Common:	Dizziness*, headache*
Rare:	Syncope
Eye disorders	
Rare:	Reduced tear flow (to be considered if the patient uses contact 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 pre-existing heart failure (in patients with chronic heart failure)
Uncommon:	AV-conduction disturbances, 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 (especially in patients with heart failure)
Uncommon:	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Bronchospasm in patients with bronchial asthma or a history of obstructive airway 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 such as itching, 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 and administration site conditions

Common	Asthenia (in patients with chronic heart failure), fatique*
Uncommon	Asthenia (in patients with hypertension or angina pectoris)

Investigations

Rare	Increased triglycerides, increased liver enzymes (ALAT, ASAT)

Applies to hypertension and angina pectoris:
*These symptoms especially occur at the beginning of therapy. They are generally mild and usually disappear within 1 to 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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 overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. To date a few cases of overdose (maximum: 2000mg) 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 inter-individual 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 stoppedand supportive and symptomatic treatment should be provided.

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 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 infusion or temporary cardiac pacing (transcutaneous or transvenous method). Acute worsening of heart failure: Administer i.v. diuretics, inotropic agents, vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, beta2-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

Limited data suggest that bisoprolol is hardly dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-blocking agents ,Selective

ATC code: C07AB07.

Mechanism of action

Bisoprolol is a competitive, strongly beta1-selective adrenergic antagonist without the partial agonist (intrinsic sympathomimetic activity, ISA) or membrane-stabilising properties. It has very low affinity to the beta2-receptors of bronchial tree or smooth musculature of blood vessels and only a small affinity to the beta2-receptors participating in the regulation of metabolism. Therefore bisoprolol, is usually not expected to affect respiratory tracts resistance to flow and beta2-mediated metabolic effects at therapeutic doses. The beta1-selectivity is reduced if the dose increases above 20 mg and blockade of beta2-receptors may also occur. By blocking the cardiac beta1-receptors, bisoprolol reduces the sympatoadrenergic activity. This causes heart rate slowdown and reduces the stroke volume and thus reduces the cardiac output. Thus myocardial oxygen consumption is reduced, which is a desirable effect in therapy of ischemic chest pain related to activity

Clinical efficacy and safety

In the heart the function cycle of sinus node and its refractory time are prolonged similarly to the AV-nodal functional refractory time and the AV-conduction time. Negative inotropic effect is small. Systolic function is preserved and diastolic function is improved in patients with hypertension and left ventricular hypertrophy, because in long term treatment, the mass and thickness of the ventricular walls are reduced. Bisoprolol lowers the plasma renin level also if diuretics or ACE-inhibitors are used concomitantly. The peripheral resistance is gradually reduced.

It has been established in the clinical trials that a daily dose 10 mg of bisoprolol is comparable to a daily 100 mg dose of atenolol or metoprolol or 160 mg dose of propranolol. Maximal antihypertensive effect when using beta-blockers is usually achieved within two weeks.

The CIBIS-II study involved 2647 patients, of which 83% of patients belonged to NYHA III class and 17% in NYHA IV class. The patients had stable, symptomatic, systolic heart failure (with ejection fraction ≤ 35% determined by echocardiography). The overall mortality decreased from 17.3% to 11.8%, relative reduction was 34%. The decrease of the number of sudden deaths was also observed (3.6 % versus 6.3%, relative reduction 44%) and reduction of heart failure seizures which require hospitalization (12% versus 17.6%, relative reduction

of 36%). In addition, the significant improvement in patients' functional performance was proved according to NYHA classification. In the beginning of bisoprolol treatment and in titration stage of treatment, there were observed a few cases of bradycardia (0.53%), hypotension (0.23%) and acute cardiac decompensation (4.97%) but the number of these cases was not higher than in the placebo group (0%, 0.3 % and 6.74%). During trials, the amounts of seizures, which lead to death or functional performance failure, were 20 in the bisoprolol group and 15 in the placebo group.
The CIBIS III trial investigated 1010 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 disease.

Bisoprolol is already used for the treatment of hypertension and angina. As with other β1-blocking agents, the mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma rennin levels.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases. Hence bisoprolol is effective in elimatinating or reducing the symptoms

5.2 Pharmacokinetic properties

Absorption
Bisoprolol is absorbed and has a biological availability of about 90% after oral administration.
Distribution
The plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg.

Biotransformation and Elimination
Total clearance is approximately 15 l/h. The half-life in plasma of 10-12 hours gives a 24 hour effect after dosing once daily. Bisoprolol is excreted from the body by two 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 unmetabolised form. Since the elimination takes place in the kidneys and the liver to the same extent a dosage adjustment is not required for patients with impaired liver function or renal insufficiency. The pharmacokinetics in patients with stable chronic heart failure and with impaired liver or renal function has not been studied.

Linearity/non-linearity
The kinetics of bisoprolol are linear and independent of age.

In patients with chronic heart failure (NYHA stage III) the plasma levels of bisoprolol are higher and the half-life is prolonged compared to healthy volunteers. Maximum plasma concentration at steady state 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. Like other beta-blocking agents, bisoprolol caused maternal (decreased food intake and decreased body weight) and embryo/fetal 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
Silica, colloidal anhydrous
Croscarmellose sodium
Sodium starch glycolate (type A)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

OPA foil blisters, sealed with 20 µm aluminium foil.
Packs of 20, 21, 28, 30, 50, 56, 60, 90 and 100 tablets (not all pack sizes may be marketed).

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited,
Ridings Point,
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WF10 5HX,
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8. MARKETING AUTHORISATION NUMBERS

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12/05/2024