SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TYREZ® 2.5 mg film-coated tablets
TYREZ® 5 mg film-coated tablets
TYREZ® 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TYREZ 2.5 mg film-coated tablets:
Each film-coated tablet contains 2.5 mg of bisoprolol fumarate

TYREZ 5 mg film-coated tablets:
Each film-coated tablet contains 5 mg of bisoprolol fumarate

TYREZ 10 mg film-coated tablets:
Each film-coated tablet contains 10 mg of bisoprolol fumarate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
TYREZ 2.5 mg film-coated tablets are white, round, biconvex, film-coated tablets with bisection line on one side. The tablet can be divided into equal doses.

TYREZ 5 mg film-coated tablets are yellow, round, biconvex, film-coated tablets with bisection line on one side. The tablet can be divided into equal doses.

TYREZ 10 mg film-coated tablets are ochre yellow, round, biconvex, film-coated tablets with bisection line on one side. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

Angina pectoris

Treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally digitalis glycosides (for additional information see section 5.1).

Tyrez is indicated for the treatment of adults.

4.2 Posology and method of administration

Posology:

Hypertension/Angina pectoris
The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day. In some patients 5 mg per day may be adequate..

Patients with renal or liver 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 a daily dose of 10 mg bisoprolol fumarate should not be exceeded. Experience with the use of bisoprolol in renal dialysis patients is limited. However, there is no evidence to suggest that the dosage regime needs to be altered.

Elderly
No dosage adjustment is normally required, but 5mg per day may be adequate. In some patients, as for other adults, dosage may have to be reduced in cases of severe renal or hepatic dysfunction.

Paediatric population
The safety and efficacy of Tyrez in the paediatric population have not yet been established. No data are available.

Discontinuation of treatment:
Treatment should not be stopped abruptly (see section 4.4). The dosage should be diminished slowly by a weekly halving of the dose.

Treatment of stable chronic heart failure
Standard treatment of chronic hearth failure consists of an ACE inhibitor (or an angiotensin receptor blocker in case of intolerance to ACE inhibitors), a beta-blocking agent, 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 up titration in 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 should be considered.
In case of transient worsening of heart failure, hypotension, or bradycardia a dosage adjustment of the concomitant medication should be considered. A temporary decrease in the dose of bisoprolol or discontinuation of the treatment should also be considered.
The reintroduction and/or uptitration of bisoprolol should always be considered when the patient becomes stable again.

Duration of treatment
Treatment of stable chronic heart failure with bisoprolol is generally a long-term treatment.
If discontinuation is considered, gradual dose decrease is recommended, since abrupt withdrawal may lead to acute deterioration of the patients condition.

Renal or liver impairment
There is no information regarding pharmacokinetics of bisoprolol in patients with chronic heart failure and with impaired liver or renal function. Uptitration of the dose in these populations should therefore be made with additional caution.

Elderly
No dosage adjustment is required.

Paediatric population
The safety and efficacy of Tyrez in children have not yet been established.
No data are available.

Method of administration:
Tyrez tablets should be taken in the morning, and can be taken with food. The recommended dose (whole tablet/s and/or half a tablet) should be swallowed whole, with some liquid, and should not be chewed or crushed.

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 treatment;
- 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 and Raynaud's syndrome;
- Untreated phaeochromocytoma (see section 4.4);
- 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).

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 a transient worsening of the heart condition (see section 4.2).

The initiation and cessation of treatment with bisoprolol necessitates regular monitoring. For the posology and method of administration please refer to section 4.2.

There is a risk of myocardial infarction and sudden death if the treatment is suddenly discontinued in patients with ischaemic heart disease (see section 4.2).

Bisoprolol should be used with caution in patients with hypertension or angina pectoris and concomitant heart failure.

There is no therapeutic experience in bisoprolol treatment of heart failure in patients with the following diseases and conditions:
- insulin dependent diabetes mellitus (type I);
- severe impairment of renal function;
- severe impairment of liver function;
- restrictive cardiomyopathy;
- congenital heart disease;
- haemodynamically significant organic valvular disease;
- myocardial infarction within three months.

Bisoprolol must be used with caution in:
- bronchospasm (bronchial asthma, obstructive airway diseases)

Although cardioselective (beta1) 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, Tyrez 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., dyspnea, exercise intolerance, cough). In bronchial asthma or other chronic obstructive lung diseases, which may cause symptoms, bronchodilating therapy may have to be given concomitantly. Occasionally an increase of the airway resistance may occur in patients with asthma; therefore the dose of β2-stimulants may have to be increased.

- diabetes mellitus with 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 give the expected therapeutic effect.
- first degree AV block
- Prinzmetal's angina
- peripheral arterial occlusive disease (worsening of symptoms might happen especially during the start 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 beta-blockade be continued peri-operatively. The anaesthesist must be aware of beta-blockade because of the potential for interactions with other medicinal products, resulting in bradyarrhythmias, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocking agent therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.
Combination of bisoprolol with calcium antagonists of the verapamil or diltiazem type, with Class I antiarrhytmic drugs and with centrally acting antyhypertensive drugs is generally not recommended (for details please refer to section 4.5).

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

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

Under treatment with bisoprolol the symptoms of a thyrotoxicosis may be masked.

The use of bisoprolol can lead to positive results in doping controls. The use of bisoprolol as a doping agent can endanger health.

4.5 Interaction with other medicinal products and other forms of interaction

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.

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

Centrally acting antihypertensive agents, such as clonidine and others (e.g. methyldopa, moxonidine, rilmenidine): Concomitant use of centrally acting antihypertensive agents may further decrease the central sympathetic tonus (decreased heart rate and cardiac output, vasodilation) and result in the worsening of heart failure. Abrupt withdrawal of treatment, particularly if prior to the discontinuation of beta-blocker treatment, may increase the 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 further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Class III antiarrhythmic drugs (e.g. amiodarone): Effects on atrio-ventricular conduction time may be potentiated.

Topical beta-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.

Parasympathomimetic drugs: Concomitant use may prolong the atrio-ventricular conduction time and increase the risk of bradycardia.

Insulin and oral anti-diabetic drugs: Blood glucose lowering effect is enhanced. Blockade of beta-adrenoreceptors may mask the symptoms of hypoglycaemia.

Anaesthetic agents: Attenuation of the reflex tachycardia and increased risk of hypotension (for further details on general anaesthesia see section 4.4).

Digitalis glycosides: Reduction of the heart rate and an increase in the atrio-ventricular conduction time.

Non-Steroidal Anti-Inflammatory medicinal products (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol.

Beta-sympathicomimetic agents (e.g. isoprenaline, dobutamine) concominant use with bisoprolol may attenuate the effect of both agents.

Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. noradrenaline, adrenaline): Concomitant use with bisoprolol may unmask the alpha-adrenoceptor-mediated vasoconstrictor effects of these agents, leading to increased blood pressure and exacerbated

intermittent claudication. Such interactions are considered to be more likely with non-selective beta-blockers.

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.

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 a risk of hypertensive crisis.

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. In general, beta-adrenoceptor blocking agents reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the fetus and newborn infant. If treatment with beta-adrenoceptor blocking agents is necessary, $beta_1$-selective adrenoceptor blocking agents are preferable.

Bisoprolol should not be used during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, monitoring of the uteroplacental blood flow and the fetal growth is recommended. In case of harmful effects on pregnancy or the fetus 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, breastfeeding 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 of the side effects specified in this section is categorised as follows:
Very common (≥1/10),

Common (≥1/100 to <1/10),
Uncommon (≥1/1,000 to <1/100),
Rare (≥1/10,000 to <1/1,000),
Very rare (1/10,000),
Not known (cannot be estimated from the available data).

Psychiatric disorders:
Uncommon: sleep disturbances, depression.
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: impaired hearing.

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 disorders. aggravation of existing heart failure (in patients with hypertension or angina pectoris), bradycardia (in patients with hypertension or angina pectoris).

Vascular disorders:
Common: feeling of coldness and 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 airway disease.
Rare: allergic rhinitis.

Gastrointestinal disorders:
Common: gastrointestinal problems such as nausea, vomiting, diarrhoea and constipation.

Hepatobiliary disorders:
Rare: hepatitis.

Skin and subcutaneous tissue disorders:
Rare: hypersensitivity reactions (itching, erythema, rash and angioedema).
Very rare: beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia.

Musculoskeletal and connective tissue disorders:

Uncommon: muscular weakness and cramps.

Reproductive system and breast disorders:
Rare: potency disorders.

General disorders:
Common: asthenia (in patiens suffering from chronic heart failure), fatigue*
Uncommon: asthenia (in patiens suffering from angina pectoris or hypertension).

Investigations:
Rare: increased level of triglycerides, increased level of liver enzymes (ALT, AST).

* These symptoms occur particularly at the beginning of treatment in patients with hypertension or angina pectoris. They are generally mild and disappear within 1–2 weeks.

Reporting of side effects

If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly to the information database on adverse reactions (actions) to medicinal products, including reports of drug inefficiency, identified in the territory of the EAEU member states.

«SCIENTIFIC CENTRE OF DRUG AND MEDICAL TECHNOLOGY EXPERTISE AFTER ACADEMICIAN E. GABRIELYAN» CJSC
49/5 Komitas av.,Yerevan 0051, Republic of Armenia,
Phone: (+374 60)83-00-73, (+374 10)23-08-96, (+374 10)23-16-82
Hot Line: (+374 10) 20-05-05, (+374 96) 22-05-05
E-mail: naira@pharm.am,vigilance@pharm.am

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

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 overdose of a beta-blocking agent are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. To date a few cases of overdose (maximum: 2000 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 most likely to be very sensitive. Therefore it is mandatory to initiate the treatment of these patients with a gradual uptitration 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 pharmacological actions and recommendations for other beta-blocking agents, 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 transvenous cardiac pacemaker insertion.

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

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, beta$_2$-sympathomimetic medicinal products 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 and pharmacodynamic effects
Bisoprolol is a highly beta-1 selective adrenoreceptor blocking agent, lacking intrinsic sympathomimetic activity and clinically relevant membrane stabilising activity. It only shows low affinity to the beta-2 receptors of the bronchial and vascular smooth muscles as well as to the beta-2 receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not expected to influence airway resistance nor the metabolic effects that are mediated by beta-2 receptors. The beta-1 selectivity of bisoprolol extends beyond the therapeutic range.
As with other beta-1 blocking agents, the mechanism of the anti-hypertensive effect of bisoprolol is unclear. However, bisoprolol is known to markedly reduce plasma renin activity.
Antianginal mechanism: By inhibiting cardiac beta receptors bisoprolol inhibits the response to sympathetic activation. This causes a decrease in the heart rate and contractility resulting in a reduced oxygen demand of the cardiac muscle.

Clinical efficacy and safety
Bisoprolol is used in the treatment of hypertension, angina pectoris and heart failure.
The indication heart failure was investigated in the CIBIS II trial. In total 2647 patients were included, 83% (N = 2202) 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 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-blocking agents, or angiotensin receptorblockers. 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.

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.

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 approximately 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.

The kinetics of bisoprolol is linear and independent of the patient's 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±21ng/ml at a daily dose of 10 mg and the half-life is 17±5 hours.

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 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

TYREZ 2.5 mg film-coated tablets:
Tablet core:
silicified microcrystalline cellulose (cellulose, microcrystalline and silica, colloidal anhydrous), crospovidone, glycerol dibehenate.
Film-coating:
Opadry Y-1-7000 white:
hypromellose (E 464),
titanium dioxide (E 171),
macrogol 400.

TYREZ 5 mg film-coated tablets:
Tablet core:
silicified microcrystalline cellulose (cellulose, microcrystalline and silica, colloidal anhydrous), crospovidone,
glycerol dibehenate.
Film-coating:
Opadry 02B32859 yellow:
hypromellose (E 464),
titanium dioxide (E 171),
macrogol 400,
iron oxide yellow (E 172).

TYREZ 10mg film-coated tablets:
Tablet core:
silicified microcrystalline cellulose (cellulose, microcrystalline and silica, colloidal anhydrous), crospovidone,
glycerol dibehenate.

Film-coating:
Opadry 02F32202 yellow:
hypromellose (E 464),
titanium dioxide (E 171),
macrogol 400,
iron oxide yellow (E 172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 (three) years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The tablets are available in perforated PVC/PVDC/aluminium unit dose blister packs. Each blister pack contains 10 tablets. The printed cardboard box contains 30 tablets (3 blister packs) and a package leaflet.

6.6 Special precautions for disposal and other handling

The film-coated tablet may be divided into two halves when placed on a hard surface, scored side up. By pressing the centre of the tablet lightly with the thumb, the tablet will break in half.
No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

ALKALOID AD Skopje
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tel. + 389 2 31 04 000
fax: +389 2 31 04 021

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT