SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

SelokenZOC 25 mg prolonged release tablet

SelokenZOC 50 mg prolonged release tablet

SelokenZOC 100 mg prolonged release tablet

SelokenZOC 200 mg prolonged release tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 prolonged release tablet contains: 23.75 mg, 47.5 mg, 95 mg or 190 mg metoprolol succinate corresponding to 25 mg, 50 mg, 100 mg or 200 mg metoprolol tartarte respectively.
For a complete list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet

Prolonged release tablets 25 mg: White, oval with a size of 5.5 mm × 10.5 mm, bisected, marked A/ß.
Prolonged release tablets 50 mg: White, round with a diameter of 9 mm, bisected, marked A/mO. The score mark is not intended to divide the tablet into two equal doses. It is only intended to facilitate swallowing.
Prolonged release tablets 100 mg: White, round with a diameter of 10 mm, bisected, marked A/mS. The score mark is not intended to divide the tablet into two equal doses. It is only intended to facilitate swallowing.
Prolonged release tablets 200 mg: White, oval with a size of 8.5 mm × 17 mm, bisected, marked A/mY. The score mark is not intended to divide the tablet into two equal doses. It is only intended to facilitate swallowing.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
Hypertension. Angina pectoris. Stable symptomatic chronic heart failure with impaired systolic left ventricular function. Prevention of cardiac death and reinfarction after the acute phase of myocardial infarction. Cardiac arrhythmias especially including supraventricular tachycardia, reduction of ventricular rate in atrial fibrillation and in ventricular extrasystoles. Functional heart disorders with palpitations. Migraine prophylaxis.

Children and adolescents aged 6-18 years
Treatment of hypertension.

4.2 Posology and method of administration

SelokenZOC prolonged release tablets are given once daily, preferably in the morning. The prolonged release tablets can be divided. They must not be chewed or crushed. The tablets should be swallowed

together with at least half a glass of liquid. Concomitant intake of food does not influence the bioavailability.
Dosage should be adjusted individually to avoid bradycardia. The following is valid as guidelines:

Hypertension
50-100 mg once daily. In patients not responding to 100 mg, the dose could be combined with other antihypertensive agents, preferably diuretics and calcium antagonists of the dihydropyridine type, or increased.

Angina pectoris
100-200 mg once daily. If needed, the dose can be combined with nitrates or increased.

Therapy supplementary to ACE-inhibitors, diuretics and possibly digitalis in stable symptomatic heart failure.
The patients should have a stable chronic heart failure, without acute failure for the last 6 weeks and an essentially unchanged basal therapy for the last 2 weeks.

Treatment of heart failure with beta-blockers may sometimes cause a temporary exacerbation of the symptoms picture. In some cases, it is possible to continue the therapy or reduce the dose, and in other cases it may be necessary to discontinue the treatment. Initiation of SelokenZOC therapy in patients with severe heart failure (NYHA IV) should only be made by physicians especially trained in treatment of heart failure (see section 4.4).

Dosage in patients with stable heart failure, function class II
A recommended initial dosage for the first two weeks is 25 mg once daily.
After two weeks, the dose can be increased to 50 mg once daily, and thereafter it can be doubled every second week, and the target dose for long-term treatment is 200 mg once daily.

Dosage in patients with stable heart failure, function classes III-IV
Recommended initial dose is 12.5 mg (half a 25 mg tablet) given once daily. The dose should be individually adjusted, and the patient should be closely monitored during the increase of the dosage as heart failure symptoms may be aggravated in some patients. After 1-2 weeks, the dose can be raised to 25 mg given once daily. Then, after further two weeks, the dosage can be increased to 50 mg given once daily. In those patients who tolerate a higher dose, the dosage can be doubled every second week up to a maximal dose of 200 mg daily.

In case of hypotension and/or bradycardia, decrease in concomitant medication or lowering of the SelokenZOC dose may be necessary. Initial hypotension does not necessarily mean that the dose of SelokenZOC cannot be tolerated in chronic treatment, but the dose must not be raised until the condition has been stabilised, and increased control of renal function, among other things, may be required.

Cardiac arrhythmias
100-200 mg once daily. If needed, the dose can be increased.

Prophylactic therapy after myocardial infarction
As maintenance dosage, 200 mg is given once daily.

Functional heart disorders with palpitations
100 mg once daily. If needed, the dose can be increased.

Migraine prophylaxis
100-200 mg once daily.

Impaired renal function
The elimination rate is insignificantly affected by renal function, and dose adjustment is therefore not needed in impaired renal function.

Impaired hepatic function
Usually SelokenZOC is given in the same dose to patients suffering from liver cirrhosis as to patients with normal liver function. Only when there are signs of very severe impairment of liver function (e.g. shunt-operated patients), a dose reduction should be considered.

Elderly
Dose adjustment is not needed.

Paediatric population
The safety and efficacy of SelokenZOC in treating children and adolescents for indications other than hypertension has not yet been determined. There is no data available. The recommended starting dose for children over 6 years of age is 0.5 mg/kg not exceeding 50 mg daily, according to the available tablet strength. In patients not responding to 0.5 mg/kg the dose can be increased to a maximum of 2.0 mg/kg. Doses above 200 mg per day have not been studied in children and adolescents.

Efficacy and safety in treating children under 6 years of age have not been studied.

4.3 Contraindications

- Cardiogenic shock.
- Sick-sinus syndrome (provided there is no permanent pacemaker).
- AV-block of second and third degree.
- Patients with unstable, not compensated heart failure (pulmonary oedema, hypoperfusion or hypotension), and patients with continuous or intermittent inotropic therapy acting through beta-receptor agonism.
- Symptomatic bradycardia or hypotension. Metoprolol should not be given to patients with suspected acute myocardial infarction as long as the heart rate is < 45 beats/min, the P-Q interval is > 0.24 sec or the systolic blood pressure is < 100 mm Hg.
- In the indication heart failure, patients with repeated supine blood pressure below 100 mmHg should be re-evaluated before treatment is initiated.
- Serious peripheral vascular disease with gangrene threat.
- Hypersensitivity to the active substance, to other beta-blockers or to any of the excipients specified in section 6.1.

4.4 Special warnings and special precautions for use

Intravenous administration of verapamil should not be given to patients treated with beta-blockers.

Metoprolol may aggravate the symptoms of peripheral arterial circulatory disorders e.g. intermittent claudication. Severely impaired renal function. Serious acute conditions with metabolic acidosis. Concomitant treatment with digitalis.

In patients with Prinzmetal's angina the frequency and the extent of angina attacks may increase due to alpha-receptor mediated contraction of the coronary vessels. For this reason non-selective beta-blockers must not be used in these patients. $Beta_1$-selective receptor blockers should be used with caution.

In bronchial asthma or other chronic obstructive lung diseases, adequate bronchodilating therapy should be given concomitantly. The dose of $beta_2$-stimulants may need to be increased.

During treatment with metoprolol the risk for interfering with carbohydrate metabolism or masking hypoglycaemia is less than with non-selective beta-blockers.

Very rarely, a pre-existing AV conduction disorder of moderate degree may become aggravated (possibly leading to AV block).

Treatment with beta-blockers may aggravate the treatment of an anaphylactic reaction. Adrenaline treatment in normal dose does not always give the expected therapeutic effect. If SelokenZOC is given to a patient with phaeochromocytoma, treatment with an alpha-blocker should be considered.

Efficacy/safety data from controlled clinical studies in severe stable symptomatic heart failure (NYHA class IV) are limited. Treatment of heart failure in these patients should therefore only be initiated by physicians with especial experience and training in this area (see 4.2).

Patients with symptomatic heart failure in association with acute myocardial infarction and unstable angina pectoris were excluded from the study on which the indication of heart failure is founded. Efficacy/safety for treatment of acute myocardial infarction in association with these conditions has therefore not been documented. Use in unstable, not compensated heart failure is contraindicated (see 4.3).

Sudden withdrawal of beta-blockade is hazardous, especially in high-risk patients, may be hazardous and may aggravate chronic heart failure as well as increase the risk of myocardial infarction and sudden death. Any withdrawal of SelokenZOC should therefore, if possible, be made gradually over at least two weeks when the dose is reduced by half in each step, down to the final dose when a 25 mg tablet is reduced to half a tablet. The final dose should be given for at least four days before discontinuation. If symptoms occur, a slower withdrawal rate is recommended.

Prior to surgery the anaesthetist should be informed that the patient is receiving SelokenZOC. It is not recommended to stop beta-blocker treatment in patients undergoing surgery. Acute initiation of high-dose metoprolol to patients undergoing non-cardiac surgery should be avoided, since it has been associated with bradycardia, hypotension and stroke including fatal outcome in patients with cardiovascular risk factors.

This medicine contains less than 1 mmol sodium (23 mg) per prolonged release tablet, that is to say essentially 'sodium-free'.

4.5 Interactions with other medicinal products and other forms of interaction

Metoprolol is a CYP2D6-substrate. Drugs that inhibit CYP2D6 can have an effect on the plasma concentration of metoprolol. Examples of drugs that inhibit CYP2D6 are quinidine, terbinafine, paroxetine, fluoxetine, sertraline, celecoxib, propafenon and difenhydramine. When treatment with these drugs is initiated the dose of SelokenZOC might have to be reduced for patients treated with SelokenZOC.

The following combinations with SelokenZOC should be avoided:

Barbituric acid derivatives: Barbiturates (investigated for pentobarbital) induce the metabolism of metoprolol by enzyme induction.

Propafenone: Upon administration of propafenone to four patients on metoprolol therapy, the plasma concentrations of metoprolol increased 2-5 fold and two patients experienced side-effects typical of metoprolol. The interaction was confirmed in eight healthy volunteers. The interaction is probably explained by the fact that propafenone, similarly to quinidine, inhibits the metabolism of metaprolol via cytochrome P450 2D6. The combination is probably difficult to handle since propafenone also has beta-receptor blocking properties.

Verapamil: In combination with beta-receptor blocking drugs (described for atenolol, propranolol and pindolol) verapamil may cause bradycardia and fall in blood pressure. Verapamil and beta-blockers have additive inhibitory effects on AV-conduction and sinusnode function.

The following combinations with SelokenZOC may require modified drug dosage:
Amiodarone: A case report suggests that patients treated with amiodarone may develop pronounced sinus bradycardia when treated simultaneously with metoprolol. Amiodarone has extremely long half-life (around 50 days), which implies that interactions can occur for a long time after withdrawal of the drug.

Antiarrythmics, class I: Class I-antiarrythmics and beta-receptor blocking drugs have additive negative inotropic effects which may result in serious haemodynamic side effects in patients with impaired left ventricular function. The combination should also be avoided in "sick sinus syndrome" and pathological AV-conduction. The interaction is best documented for disopyramide.

Non-steroidal anti-inflammatory/antirheumatic drugs: NSAID-antiphlogistics have been shown to counteract the antihypertensive effect of beta-receptor blocking drugs. Primarily, indomethacin has been studied. This interaction probably does not occur with sulindac. A negative interaction study on diclofenac has been performed.

Digitalis glycosides: digitalis glycosides in association with β-blockers, may increase atrioventricular conduction time and may induce bradycardia.

Diphenhydramin: Diphenhydramin decreases (2.5 times) clearance of metoprolol to alpha-hydroximetoprolol via CYP 2D6 in fast hydroxylating persons. The effects of metoprolol are enhanced.

Diltiazem: Diltiazem and beta-receptor blockers have additive inhibitory effects on the AV-conduction and sinusnode function. Pronounced bradycardia has been observed (case reports) during combination treatment with diltiazem.

Epinephrine: There are about ten reports on patients treated with non-selective beta-receptor blockers (including pindolol and propranolol) that developed pronounced hypertension and bradycardia after administration of epinephrine (adrenaline). These clinical observations have been confirmed in studies in healthy volunteers. It has also been suggested that epinephrine in local anestethics may provoke these reactions upon intravasal administration. The risk is probably less with cardioselective beta-receptor blockers.

Phenylpropanolamine: Phenylpropanolamine (norephedrine) in single doses of 50 mg may increase the diastolic blood pressure to pathological values in healthy volunteers. Propranolol generally counteracts the rise in blood pressure induced by phenylpropanolamine. However, beta-receptor blockers may provoke

paradoxical hypertensive reactions in patients who take high doses of phenylpropranolamine. Hypertensive crises during treatment with only phenylpropanolamine have been described in a couple of cases.

Quinidine: Quinidine inhibits the metabolism of metoprolol in so-called rapid hydroxylators (more than 90% in Sweden) with markedly elevated plasma levels and enhanced beta-blockade as a result. A corresponding interaction might occur with other beta-blockers metabolised by the same enzyme (cytochrome P450 2D6).

Clonidine: The hypertensive reaction when clonidine is suddenly withdrawn may be potentiated by beta-blockers. If concomitant treatment with clonidine is to be discontinued, the beta-blocker medication should be withdrawn several days before clonidine.

Rifampicin: Rifampicin may induce the metabolism of metoprolol resulting in decreased plasma levels.

Patients receiving concomitant treatment with other beta-blockers (i.e. eye drops) or MAO-inhibitors should be kept under close surveillance. In patients receiving beta-receptor blocker therapy, inhalation anaesthetics enhance the cardio-depressant effect. The dosages of oral antidiabetics may have to be readjusted in patients receiving beta-blockers. The plasma concentration of metoprolol can increase when cimetidine or hydralazine are administered simultaneously.

4.6 Fertility, pregnancy and lactation

Pregnancy
SelokenZOC should only be given during pregnancy and lactation when use is considered essential. In general, β-blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion and early labour. It is therefore suggested that appropriate maternofetal monitoring be performed in pregnant women treated with metoprolol. Beta-receptor blockers may cause bradycardia in the foetus and in the new-born infant. This should be considered if these drugs are prescribed in the last trimester and in association with delivery. SelokenZOC should gradually be withdrawn 48-72 hours before planned childbirth. If this is not possible the newborn infant should be supervised during 48-72 hours postpartum for signs and symptoms of beta-blockade (e.g. heart- and lung complications).

Lactation
Metoprolol is concentrated in human breast milk in a quantity that corresponds to approximately three times the quantity found in the plasma of the mother. The risk for harmful reactions with respect to the breast-feeding child seems to be low at therapeutic doses of the medicine. The breast-feeding child should however be observed regarding signs of beta-blockade.

4.7 Effect on ability to drive and use machines

As dizziness and fatigue may occur in SelokenZOC treatment, this should be considered when strict attention is required, e.g. when driving or operating machines.

4.8 Undesirable effects

Adverse reactions occur in approximately 10% of the patients and they are usually dose-related. Adverse reactions, related to metoprolol are presented below according to organ class and frequency. The frequencies are defined as following: very common (≥1/10), common (≥1/100, <1/10), less common (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000) and frequency unknown (cannot be calculated from available data)
Blood and lymphatic system
Rare Thrombocytopenia

Psychiatric disorders

Less common	Depression, nightmares, sleeping disturbance
Rare	Memory impairment, confusion, hallucinations, nervousness, anxiety
Frequency unknown	Impaired concentration ability

Central and peripheral nervous system

Very common	Fatigue
Common	Dizziness, headache
Less common	Paraesthesiae
Rare	Taste disturbances
Frequency unknown	Muscular cramps

Eyes

Rare	Visual disturbances, dry and/or irritated eyes
Unknown frequency	Conjunctivitis-like symptoms

Ears and balance organ

Rare	Tinnitus

Heart

Common	Peripheral coldness in extremities, bradycardia, palpitations
Less common	Transient aggravation of heart failure, cardiogenic shock in patients with acute myocardial infarction
Rare	Prolonged AV-conduction time, cardiac arrhythmias
Frequency unknown	Gangrene in patients with severe peripheral vascular disorders

Respiratory

Common	Shortness of breath when physically active
Less common	Bronchospasm in patients with bronchial asthma or asthmatic problems

Frequency unknown	Rhinitis

Gastrointestinal

Common	Abdominal pain, nausea, vomiting, diarrhoea, constipation
Frequency unknown	Dry mouth

Liver and biliary tracts

Rare	Elevated transaminases
Frequency unknown	Hepatitis

Skin and subcutaneous tissue

Less common	Hypersensitivity reactions in the skin
Rare	Aggravated psoriasis, photosensitivity reactions, hyperhidrosis, hair loss

Musculoskeletal system and connective tissue

Frequency unknown	Arthralgia

Reproductive organs and mammary glands

Rare	Reversible libido dysfunction

General

Less common	Chest pain, oedema, weight gain

Reporting of suspected adverse reactions

It is important to report adverse reactions after the medicinal product has been approved. This makes it possible to continue monitoring the product's benefit-risk balance. Healthcare professionals are encouraged to report every suspected adverse reaction to (see details below=.

Medical Products Agency
Box 26
751 03 Uppsala Sweden
Website: www.lakemedelsverket.se

4.9 Overdose

Toxicity

7.5 g to an adult caused lethal intoxication. 100 mg to a 5-year old gave no symptoms after gastric lavage. 450 mg to a 12-year old and 1.4 g to an adult gave moderate intoxication, 2.5 g to an adult caused serious intoxication, and 7.5 g to an adult gave very serious intoxication.

Symptom

Cardiovascular symptoms are most important, but in some cases, especially in children and young individuals, CNS symptoms and respiratory depression may dominate. Bradycardia, AV-block I-III, QT-prolongation (exceptional cases), asystole, fall in blood pressure, poor peripheral perfusion, cardiac insufficiency, cardiogenic shock. Respiratory depression, apnoea. Others: Fatigue, confusion, unconsciousness, fine tremor, cramps, perspiration, paraesthesiae, bronchospasm, nausea, vomiting, possibly oesophageal spasm, hypoglycaemia (especially in children) or hyperglycaemia, hyperkalaemia. Effect on the kidneys. Transient myasthenic syndrome. Concomitant ingestion of alcohol antihypertensives, quinidine or barbiturates may aggravate the patient's condition. The first signs of overdosing may be seen 20 minutes to 2 hours after ingestion.

Management
Care should be provided at a unit that can offer suitable support measures, monitoring and supervision.

If justified, gastric lavage and/or activated charcoal can be used.

Atropine, adrenoceptor stimulant or pacemaker for treatment of bradycardia and conduction disorders.

Intubation and mechanical ventilation should be done with very broad indication. Pacemaker is option. With circulatory arrest in connection with overdose, resuscitation measures for several hours may be warranted.

Hypotension, acute myocardial infarction and shock should be treated with appropriate volume expansion, administration of glucagon (followed by intravenous infusion of glucagon if necessary), intravenous administration of an adrenoceptor stimulant, such as dobutamine, with the addition of α_1 receptor agonists upon vasodilation. Intravenous use of Ca^{2+} may also be considered.

Bronchospasm can usually be reversed through bronchodilators.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-receptor blocker, selective
ATC code: C07A B02

Metoprolol is a $beta_1$-selective receptor blocker, i.e. metoprolol affects the $beta_1$-receptors of the heart in lower doses than needed to affect $beta_2$-receptors in peripheral vessels and bronchi. The selectivity for SelokenZOC is dose dependent, but, as the peak plasma concentration for this dosage form is significantly lower compared to the same dose given as ordinary tablets, a higher degree of $beta_1$-selectivity is obtained with the ZOC-dosage form.
Metoprolol has no beta-stimulating effect and has little membrane- stimulating effect. Beta-receptor blockers have negative inotropic and chronotropic effect.
Metoprolol therapy reduces the effect of catecholamines in association with physical and psychic strain and gives lower heart rate, cardiac output and blood pressure. In stress situations with an increased release of adrenaline from the adrenal glands, metoprolol does not prevent the normal physiological vascular dilation. In therapeutic doses,
metoprolol has less contractile effect on the bronchial muscles than non-
selective beta-blockers. This property enables treatment of patients with bronchial asthma or other pronounced obstructive lung diseases with metoprolol in combination with $beta_2$-receptor stimulants.
Metoprolol influences insulin release and carbohydrate metabolism to less extent than non-selective beta-

blockers and therefore it can also be given to patients with diabetes mellitus. The cardiovascular reaction in hypoglycaemia, e.g. tachycardia, is less influenced by metoprolol and the return of blood sugar level to normal is faster than for non-selective beta-receptor blockers.

In hypertension, SelokenZOC lowers the blood pressure significantly for more than 24 hours both in lying and standing position as well as during exercise. In treatment with metoprolol an increase in the peripheral vascular resistance is observed initially. In long-term treatment, however, the obtained lowering in blood pressure may be due to reduced peripheral vascular resistance and unchanged cardiac output.

Paediatric population
In a four-week study with 144 patients between 6 and 16 years old with essential hypertension, doses of 1.0 and 2.0 mg/kg of SelokenZOC decreased placebo-corrected systolic blood pressure by 4-6 mmHg. Diastolic blood pressure showed a placebo-corrected decrease for the higher dose with 5 mmHg and a dose-dependent decrease for 0.2, 1.0 and 2.0 mg/kg. No noticeable differences between ages, Tanner scale (adolescent physical development) or race.

Metoprolol reduces the risk of cardiovascular-related deaths in men with moderate/serious hypertension. There is no disturbance in the electrolyte balance.

Effect in chronic heart failure: In MERIT-HF, a survival study comprising 3,991 patients with heart failure (NYHA II-IV) and decreased ejection fraction (≤ 0.40), SelokenZOC has been shown to increase survival and to reduce the number of hospitalisations. In long-term treatment the patients experience a general improvement of symptoms (New York Heart Association class and Overall Treatment Evaluation score).

In addition, it has been shown that SelokenZOC therapy increases the ejection fraction and reduces the left ventricular end systolic and end diastolic volumes.

In tachyarrhythmias the effect of increased sympatholytic activity is blocked and this gives a lower heart rate primarily by reduced automatisation in the pacemaker cells, but also through a prolonged supraventricular conduction time. Metoprolol reduces the risk of reinfarction and cardiac death, especially sudden death after myocardial infarction.

5.2 Pharmacokinetic properties

The SelokenZOC prolonged release tablet consists of micro-encapsulated beads of metoprolol succinate, and each bead is a separate depot unit. Each bead is coated with a polymeric membrane, which controls the rate of drug release. The tablet disintegrates rapidly in contact with fluid whereby the beads are dispersed over a large surface in the gastrointestinal tract. The release is independent of the pH of the surrounding fluid and goes on with an almost constant rate for about 20 hours. The dosage form gives an even plasma concentration and effect duration over 24 hours.
The absorption is complete after oral administration and the substance is absorbed along the whole gastrointestinal tract, also in colon. The bioavailability of SelokenZOC is 30-40%. Metoprolol is metabolised in the liver mainly by CYP2D6. Three main metabolites have been identified, though none has a beta-blocking effect of clinical importance. Metoprolol is excreted to approximately 5% in unchanged form via the kidneys, the remaining dose as metabolites.

The pharmacokinetics of metoprolol in children and young adults, 6 – 17 years, resembles that of adults. Clearance of orally given metoprolol (CL/F) increased with linear relation to the bodyweight.

5.3 Preclinical safety data

Metoprolol has been tested clinically to a very large extent. Relevant information for the prescriber can be found in other parts of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethylcellulose, hydroxypropyl cellulose, hypromellose, microcrystalline
cellulose, paraffin, macrogol, anhydrous non-colloidal silicon dioxide,sodium stearyl fumarate, titanium dioxide (E 171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special storage instructions.

6.5 Nature and contents of container

Blister (aluminium/PVC/PVDC or PVC):
Prolonged release tablets 25 mg (28’s)
Prolonged release tablets 50 mg (28’s, 98’s)
Prolonged release tablets 100 mg (28’s, 98’s)
Prolonged release tablets 200 mg (98’s)

Unit-dose container (aluminium/PVC/PVDC or PVC):
Prolonged release tablets 25 mg (50’s)
Prolonged release tablets 50 mg (50´s)
Prolonged release tablets 100 mg (50´s)

Tablet container (HDPE):
Prolonged release tablets 25 mg (30’s, 100`s)
Prolonged release tablets 50 mg (100’s)
Prolonged release tablets 100 mg (100’s)

Tablet container (HDPE) for dose dispensation:
Prolonged release tablets 25 mg (1000`s)
Prolonged release tablets 50 mg (1000’s)
Prolonged release tablets 100 mg (500’s)

6.6 Special precautions for disposal

Not applicable.

7. MARKETING AUTHORIZATION HOLDER

AstraZeneca AB
151 85 Södertälje

8. MARKETING AUTHORIZATION NUMBERS

Prolonged release tablets 25 mg: 16016
Prolonged release tablets 50 mg: 10786
Prolonged release tablets 100 mg: 10490
Prolonged release tablets 200 mg: 10491

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Prolonged release tablets 25 mg: 2000-07-21/2010-09-08
Prolonged release tablets 50 mg: 1988-04-29/2010-09-08
Prolonged release tablets 100 mg: 1986-12-12/2010-09-08
Prolonged release tablets 200 mg: 1986-12-12/2010-09-08

10. DATE OF REVISION OF THE TEXT

2020-11-16