SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PULSATYL SDK 100 mg controlled release film coated tablet

2. QUALITATIVE AND QUANTITAVE COMPOSITION

Active ingredient:

Each controlled release film coated tablet contains, 95.00 mg metoprolol succinate equivalent to 100 mg metoprolol tartrate.

Excipients:

Sucrose 29.645 mg
Sodium stearyl fumarate 2.00 mg
See section 6.1 for the full list of excipients.

3. PHARMACEUTICAL FORM

Controlled release film coated tablet
White-colored, round, biconvex, one side scored film-coated tablets.

4. CLINICAL PARTICULARS

4.1.Therapeutic indications

Metoprolol tartrate is indicated in the treatment of hypertension, angina pectoris, stable symptomatic chronic heart failure with impaired systolic left ventricular function, prevention of cardiac death and re-infarction after the acute phase of myocardial infarction, particularly tacardiac arrhythmias including supraventricular tachycardia, reduction of ventricular rate in extrasystoles and atrial fibrillation, prophylaxis of functional heart disorders with palpitations and migraine.

1. Posology and method of administration

Posology:

PULSATYL SDK film coated tablet are given once daily, preferably in the morning. Reception with food does not affect bioavailability. The 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 PULSATYL SDK 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 döşe 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 PULSATYL SDK dose may be necessary. Initial hypotension does not necessarily mean that the dose of PULSATYL SDK 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.

Method of administration:
The controlled release tablets can be divided. Tablets should not be chewed or crushed. The tablets should be swallowed together with at least half a glass of liquid.
The scoreline is not intended for the division of the tablet. The tablet should be swallowed whole.

Additional information on special populations
Renal insufficiency:
The elimination rate is insignificantly affected by renal function, and dose adjustment is therefore not needed in impaired renal function.

Hepatic insufficiency:

Usually PULSATYL SDK 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.

Pediatric population:
Treatment with PULSATYL SDK experience in children is limited.

Geriatric population:
The lowest possible dose should be used initially.

4.3. Contraindications

- Cardiogenic shock.
- Sick-sinus syndrome
- 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 betareceptor 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
- Untreated pheochromocytoma
- Sinus bradycardia associated with clinically

4.4. Special warnings and 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 angına 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. Beta1-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 beta2-stimulants may need to be increased.

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 PULSATYL SDK 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 PULSATYL SDK 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 PULSATYL SDK. It is not recommended to stop beta-blocker treatment in patients undergoing surgery. If desired the cutting of metoprolol, it should be performed at least 48 hours before general anesthesia.

Low dose should be exercised starting at a in the treatment of the elderly.

Anaphylactic shock is more severe in patients treated with beta-blocker.

PULSATYL SDK includes sucrose. Therefore, patients with hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose malabsorption should not take this medicine.

This medicinal product contains less than 1 mmol (23 mg) of sodium in each tablet; no sodium-related side effects are expected at this dose.

5. Interaction with other medicinal products and other forms of interaction

Antihypertensive effect on blood pressure of other drugs are usually additive; dihydropyridine derivatives, tricyclic antidepressants, phenothiazines and barbiturates, and care must be taken to prevent hypotension may occur as a result of simultaneous use.

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 PULSATYL SDK might have to be reduced for patients treated with PULSATYL SDK.

The following combinations with PULSATYL SDK 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 PULSATYL SDK 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 sinüs syndrome” and pathological AV-conduction. The interaction is best documented for disopyramide.

Non-steroidal anti-inflammatory/antirheumatic drugs: NSAIDantiphlogistics 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 nonselective 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.

Additional information on special populations

Paediatric population:
No interaction study performed.

6. Pregnancy and lactation

General recommendations
Pregnancy category: C

Pregnancy potential/Contraception
Studies on animals is not sufficient regarding the influences of pregnancy and embryonal/ fetal development and / or parturition and / or postnatal on development (See section 5.3). The potential risk for humans is unknown.

Pregnancy
Metoprolol should only be given during pregnancy when use is considered essential. 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. PULSATYL SDK 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 should only be given during lactation when use is considered essential. 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 breastfeeding child seems to be low at therapeutic doses of the medicine. The breast-feeding child should however be observed regarding signs of betablockade.

Fertility
Animal studies showed impaired placental blood perfusion associated with fetal death, growth retardation. Abortion have been reported in studies in humans. However, recent analysis has led to the questioning of negative effects with beta-blockers. Metoprolol, as well as all the other beta-blockers, can cause side effects including bradycardia and hyperglycemia especially on breastfeeding and newborn babies.

4.7. Effects on ability to drive and use machines
As dizziness and fatigue may occur in PULSATYL SDK treatment, this should be considered when strict attention is required, e.g. when driving or operating machines.

8. Undesirable effects
The frequency of adverse reactions listed below is defined using the following convention:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000), not known (cannot be estimated from the available data)

Diseases of blood and lymph system
Rare: Thrombocytopenia

Psychiatric disorders
Uncommon: Depression, concentration disorders, drowsiness or insomnia, nightmares
Rare: Irritability, anxiety, impotence / sexual dysfunction
Very rare: Memory impairment, confusion, hallucinations, nervousness, anxiety

Nervous system diseases
Common: Headache, dizziness, vertigo
Uncommon: Sleep disorders, paraesthesiae
Rare: Nightmares, depression, memory difficulties, confusion, irritability, anxiety, hallucinations
Not known: Concentration disorder

Eyes diseases
Rare: Visual disturbances, dry and/or irritated eyes
Not known: Conjunctivitis-like symptoms

Ears diseases
Rare: Tinnitus

Cardiac diseases
Common: Bradycardia, palpitations

Uncommon: Transient aggravation of heart failure, cardiogenic shock in patients with acute myocardial infarction, chest pain, first-degree heart block
Rare: Prolonged AV-conduction time, cardiac arrhythmias
Vascular diseases
Common: Cooling of the extremities
Rare: Edema, syncope
Not known: Gangrene in patients with severe peripheral vascular disorders

Respiratory, thoracic and mediastinal diseases
Uncommon: Shortness of breath, bronchospasm in patients with bronchial asthma or asthmatic problems
Not known: Rhinitis

Gastrointestinal diseases
Common: Abdominal pain, nausea, vomiting, diarrhoea, constipation
Rare: Taste disorders
Not known: Dry mouth

Hepatobiliary diseases
Rare: Elevated transaminases
Not known: Hepatitis

Skin and subcutaneous tissue diseases
Rare: Hypersensitivity reactions in the skin,aggravated psoriasis, photosensitivity reactions, hyperhidrosis, hair loss

Reproductive system and breast diseases
Rare: Reversible libido dysfunction

Musculoskeletal system and connective tissue diseases
Not known: Arthralgia, muscle cramps

General disorders and administration site disorders
Common: Fatigue
Uncommon: Weight gain

In a trial of 46000 patients with acute myocardial infarction, the incidence was increased %0,4 compared to plasebo; the incidence of cardiogenic shock occured in %2,3 of patients taking metoprolol versus, %1,9 of subgroup patients with low shock risk index treated with placebo.
Shock risk index is based on absoluteshock risk of all patients arising from age, gender, delay, killlip class, blood pressure, heart rate, abnormality of ECG and hypertension history. Patient group with low shock risk index is corresponded to the patients which are suggested the use of metoprolol in acute myocardial infaction.

4.9. Overdose and treatment

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, central nervous system symptoms and respiratory depression may dominate

Bradycardia, AV-block I-III, QTprolongation (exceptional cases), asystole, fall in blood pressure, poor peripheral perfusion, cardiac insufficiency, cardiogenic shock. Respiratory depression, apnoea.

Other symptom: 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: If justified, gastric lavage and/or activated charcoal can be used. Atropine should be given against the risk of gastric lavage before vagal stimulation (intravenous, 0,25-0,50 mg for adults, 10-20 mcg / kg for children). Intubation and mechanical ventilation should be done with very broad indication. Adequate fluid support, glucose infusion should be done with ECG monitoring. Intravenously 1.0 - 2.0 mg atropine (to prevent vagal stimulation) is given, repeated if required.

Dobutamine and dopamine infusion and 10-20 ml, 9 mg / ml calcium glubiyonat are given in myocardial depression. Since it takes longer than one minute intravenously 50-150 mcg / kg glucagon is given, then it can be applied infusion. Amrinone can be given. In some cases, epinephrine (adrenaline) was found to be useful adding. In QRS complex sodium (as chloride and bicarbonate) infusion is applied for arrhythmias and dilatation. The pacemaker may be necessary. Prolonged resuscitation may be needed in case of cardiac arrest. When seen bronchospasm, terbutaline (by injection or inhalation) may be given. Symptomatic treatment is applied.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

Metoprolol is a beta1-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 PULSATYL SDK 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 beta1-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 nonselective beta-blockers. This property enables treatment of patients with bronchial asthma or other pronounced obstructive lung diseases with metoprolol in combination with beta2-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, PULSATYL SDK 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. 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), PULSATYL SDK 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 PULSATYL SDK 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

General

Absorption:

The bioavailability of PULSATYL SDK is 30-40%. Half-life in plasma is 3-5 hours. The absorption is complete after oral administration and the substance is absorbed along the whole gastrointestinal tract, also in colon.

Distribution:

The PULSATYL SDK controlled 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.

Biotransformation:

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.

Elimination:
Metoprolol is excreted to approximately 5% in unchanged form via the kidneys, the remaining dose as metabolites.

5.3. Pre-clinical 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
Corn starch
Sucrose
Colloidal silicon dioxide
Hypromellose
Ethylcellulose N50
Polyethylene glycol 6000
Talc
Magnesium stearate
Microcrystalline cellulose
Hydrogenated vegetable oil
Sodium Stearyl Fumarate
Opadry OY-S-28924 (hypromellose, polyethylene glycol/macrogol and titanium dioxide)

6.2. Incompatibilities
Not applicable.

3. Shelf life
24 months

6.4. Special precautions for storage
Store at room temperature below 30^{o}C.

6.5. Nature and content of packaging
20 tablets in Al/PVC/PVDC blisters in box.

6. Disposal of waste materials of human medicinal product and other special precautions
Unused products or wastes should be disposed in line with “Medical Wastes Control Guidelines” and “Package and Package wastes control Guidelines”.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

TAN 21 HM 0326

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

2021-08-20

10. DATE OF RENEWAL OF SPC