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Updated June 30, 2018 If you are a consumer or patient, visit this version. HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information necessary for the safe and effective use of METOPROLOL PROLONGED-RELEASE SUCCINAT TABLETS. See full prescribing information for METOPROLOL PROLONGED-RELEASE SUCCINATION THE safe and effective use of METOPROLOL PROLONGED-RELEASE SUCCINATION THE safe and effective use of METOPROLOL PROLONGED-RELEASE SUCCINATION THE safe and effective use of METOPROLOL PROLONGED-RELEASE SUCCINATION THE safe and effective use of METOPROLOL PROLONGED-RELEASE SUCCINATION THE safe and effective use of METOPROLOL PROLONGED-RELEASE SUCCINATION THE safe and effective use of METOPROLOL PROLONGED-RELEASE SUCCINATION THE safe and effective use of METOPROLOL PROLONGED-RELEASE SUCCINATION THE safe and effective use of METOPROLOL PROLONGED-RELEASE SUCCINATION THE safe and effective use of METOPROLOL PROLONGED-RELEASE SUCCINATION THE safe and effective use of METOPROLOL PROLONGED-RELEASE SUCCINATION THE safe and effective use of METOPROLOL PROLONGED-RELEASE SUCCINATION THE safe and effective use of METOPROLOL PROLONGED-RELEASE SUCCINATION THE safe and effective use of METOPROLOL PROLONGED-RELEASE SUCCINATION THE safe and effective use of METOPROLOL PROLONGED-RELEASE SUCCINATION THE safe and effective use of METOPROLOL PROLONGED-RELEASE SUCCINATION THE safe and effective use of METOPROLOL PROLONGED-RELEASE SUCCINATION THE safe and effective use of METOPROLONGED-RELEASE SUCCINATION tablets. METOPROLOL SUCCINATE Prolonged-release tablets for oral use Initial approval in the USA: 1992 After abrupt discontinuation or discontinuation of treatment without a doctor's recommendation. (5.1) Prolonged-release metoprolol tablets are beta selective adrenoceptor blockers. Metoprolol prolonged-release tablets are indicated for the treatment of: hypertension, to lower blood pressure. Lowering blood pressure. L heart failure of ischaemic, hypertensive or cardiomyopathic origin. (1.3) Serve once a day. Tapping of prolonged-release metoprolol succinate should be individualised. (2) Heart failure: The recommended starting dose is 12.5 mg or 25 mg is doubled every two weeks to the highest tolerated dose or up to 200 mg. (2.3) Hypertension: The usual starting dose is 25 to 100 mg once a day. The dose may be increased at weekly (or longer) intervals until an optimal reduction in blood pressure is achieved. Doses above 400 mg per day have not been studied. (2.1) Angina Pectoris: The usual starting dose is 100 mg once a day. Gradually increase the dosage at weekly intervals until optimal clinical response is increased or unacceptable bradycardia has been reported. Doses above 400 mg per day have not been studied. (2.2) Switching from immediate-release metoprolol to prolonged-release metoprolol succinate. (2) Prolonged-release tablets: 25 mg, 50 mg, 100 mg and 200 mg. (3) Known hypersensitivity to the components of the medicinal product. (4) Severe bradycardia. (4) Cardiac blockade greater than the first stage. (4) Cardiogenic shock. (4) Decompensated heart failure: Heart failure: Heart failure: (4) Bick sinus syndrome without a pacemaker. (5.2) Bronchospastic disease: Avoid beta blockers. (5.3) Pheochromocytoma: If necessary, first start treatment with an alphablocker. (5.4) Major surgery: Avoid initiation of high-dose, prolonged-release metoprolol in patients undergoing heart-free surgery as it has been associated with bradycardia, hypotension, stroke and hypoglycaemia: May mask mask hypoglycaemia. (5.6) Patients with hepatic impairment: (5.7) Thyroidtoxicosis: Sudden withdrawal in patients with thyrotoxicosis may cause a thyroid storm. (5.8) Anaphylactic reactions: Patients may not respond to the usual doses of adrenaline used to treat an allergic reactions: Patients may not respond to the usual doses of adrenaline used to treat an allergic reactions: Patients may not respond to the usual doses of adrenaline used to treat an allergic reactions: Patients may not respond to the usual doses of adrenaline used to treat an allergic reactions: Patients may not respond to the usual doses of adrenaline used to treat an allergic reactions: Patients may not respond to the usual doses of adrenaline used to treat an allergic reactions: Patients may not respond to the usual doses of adrenaline used to treat an allergic reactions: Patients may not respond to the usual doses of adrenaline used to treat an allergic reactions: Patients may not respond to the usual doses of adrenaline used to treat an allergic reactions: Patients may not respond to the used to treat an allergic reactions: Patients may not respond to the used to treat an allergic reactions: Patients may not respond to the used to treat an allergic reactions: Patients may not respond to the used to treat an allergic reactions: Patients may not respond to the used to treat an allergic reactions: Patients may not respond to the used to treat an allergic reactions: Patients may not respond to the used to treat an allergic reactions: Patients may not respond to the used to treat an allergic reactions: Patients may not respond to the used to treat an allergic reactions: Patients may not respond to the used to treat an allergic reactions: Patients may not respond to the used to treat an allergic reactions: Patients may not respond to the used to treat an allergic reactions: Patients may not respond to the used to treat an allergic reactions: Patients may not respond to the used to treat an allergic reactions: Patients may not respond to the used to treat an allergic reactions: Patients may not respond to the chronotropic effects in patients treated with verapamil and diltiazem calcium channel blockers, caution should be exercised in patients treated with these substances concomitantly. (5.11) The most common adverse reactions; please contact Teva Pharmaceuticals USA, Inc. at 1-888-838-2872 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. Catecholamine-damaging drugs can have an additive effect when administered with beta-blockers. (7.1) CYP2D6 inhibitors are likely to increase metoprolol concentration. (7.2) Concomitant use of glycosides, clonidine and diltiazem and verapamila with betablockers may increase the risk of bradycardia. (7.3) Beta-blockers, including metoprolol, may worsen rebound hypertension, which may follow discontinuation of clonidine. (7.3) Pregnancy only if clearly necessary. (8.1) Nursing mothers: Consider possible exposure of infants (8.3) Paediatrics: Safety and efficacy have not been established in patients less than 6 years of age. (8.4) Geriatrics: No significant difference in efficacy or safety from younger patients. (8.5) Hepatic impairment: Consider starting treatment with metoprolol prolonged-release succinat at low doses and gradually increase the dosage to optimise treatment with metoprolol prolonged-release succinat at low doses and gradually increase the dosage to optimise treatment with metoprolol prolonged-release succinat at low doses and gradually increase the dosage to optimise treatment with metoprolol prolonged-release succinat at low doses and gradually increase the dosage to optimise treatment with metoprolol prolonged-release succinat at low doses and gradually increase the dosage to optimise treatment with metoprolol prolonged-release succinat at low doses and gradually increase the dosage to optimise treatment with metoprolol prolonged-release succinat at low doses and gradually increase the dosage to optimise treatment with metoprolol prolonged-release succinat at low doses and gradually increase the dosage to optimise treatment with metoprolol prolonged-release succinat at low doses and gradually increase the dosage to optimise treatment with metoprolol prolonged-release succinat at low doses and gradually increase the dosage to optimise treatment. adverse reactions. (8.6) See 17 for information on patient counselling. Revised: 6/2018 Contents BOXED WARNING (What is it?) WARNING: ISCHAEMIC HEART DISEASE An exacerbation of angina and in some cases myocardial infarction have occurred after abrupt discontinuation of certain beta-blockers. With discontinuation of chronically administered prolonged-release metoprolol succinate, especially in patients with coronary artery disease, the dose should be gradually reduced over 1 to 2 weeks and the patient closely monitored. If angina deteriorates significantly or acute coronary insufficiency develops, administration of prolonged-release metoprolol succinate should be resumed immediately, at least temporarily, and further measures appropriate to manage unstable angina should be taken. Warn patients before interrupting or stopping treatment without Since coronary artery disease is common and may be unrecogned, it may be prudent to discontinue metoprolol succinate prolonged release treatment abruptly even in patients treated only for hypertension (see Warnings and Precautions (5.1)). Indications and use 1.1 Hypertension Prolonged-release tablets Metoprolol are indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular events, especially strokes and myocardial infarctions. These benefits were observed in controlled antihypertensive studies from a wide range of pharmacological classes including metoprolol. Control of high blood pressure should be part of comprehensive management of cardiovascular risks, including, where appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise and limited sodium intake. Many patients will require more than 1 drug to achieve blood pressure goals. Specific advice on objectives and management can be found in published guidelines, such as those of the Joint National High Blood Pressure Education, Evaluation and Treatment of High Blood Pressure (JNC) of the National High Blood Pressure Education, have been demonstrated in randomized controlled trials to reduce cardiovascular morbidity and mortality, and can be concluded that there is a decrease in blood pressure and not some other pharmacological properties of the drug that is largely responsible for these benefits. The greatest and most consistent benefit of cardiovascular outcomes was a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality were also regularly observed. Increased systolic or diastolic pressures, so even a slight reduction in severe hypertension can provide a substantial benefit. The relative reduction in blood pressure lowering risk is similar in populations with different absolute risks, so the absolute benefit is greater in patients at higher risk regardless of their hypertension (e.g. patients with diabetes or hyperlipidaemia) and such patients are expected to benefit from more aggressive treatment to a lower blood pressure target. Some antihypertensive drugs have fewer effects on blood pressure (such as monotherapy) in black patients, and many antihypertensive drugs have other approved indications and effects (eg, on angina, heart failure, or diabetic kidney disease). These considerations may lead to the choice of treatment. Metoprolol Succinate tablets are indicated in the long-term treatment of angina pectoris, to reduce attacks of angina pectoris and to improve exercise tolerance. 1. Heart failure of ischaemic, hypertensive or cardiomyopathic origin. It has been studied in patients who had already received ACE inhibitors, diuretics and, in most cases, digitalis. In this population, metoprolol succinate prolonged-release tablets reduced mortality rates plus hospitalizations, largely through reduced mortality and hospitalizations for heart failure. 2 POSOLOGY AND ADMINISTRATION Prolonged-release metoprolol tablets are intended for once daily administration. For the treatment of hypertension and angina, use the same total daily dose of methotoprolol prolonged-release metoprolol succinate as the same total daily dose of prolonged-release metoprolol succinate. Titration may be required in some patients. Metoprolol prolonged-release tablets are scored and can be divided; do not crush or swallow all or half of the tablet. 2.1 Hypertension Adults: The usual starting dose is 25 to 100 mg per day per dose. The dose may be increased at weekly (or longer) intervals until an optimal reduction in blood pressure is achieved. In general, the maximum effect of any given dose level will be apparent after 1 week of treatment. Doses above 400 mg per day have not been studied. Paediatric hypertensive patients greater than or equal to 6 years: Paediatric clinical hypertension study in patients 6 to 16 years of age did not meet its primary endpoint (dose response to SBP reduction); however, some other endpoints have shown efficacy (see Use in specific populations) (8.4)). If published for treatment, the recommended starting dose of prolonged-release metoprolol succinate is 1.0 mg/kg once daily, but the maximum starting dose should not exceed 50 mg once daily have not been studied in paediatric patients (see clinical pharmacology (12.3) Prolonged-release metoprolol succinate is not recommended in paediatric patients less than 6 years of age (see Use in a specific population (8.4)). 2.2 Angina Pectoris Individualize dosage of metoprolol succinate prolonged release. The usual starting dose is 100 mg per day, given in a single dose. Gradually increase the dosage at weekly intervals until an optimal clinical response is achieved or a significant slowing of heart rate is achieved. Doses above 400 mg per day have not been studied. If treatment is to be discontinued, reduce the dose for 1 to 2 weeks (see [see and precautions (5)). 2.3 Heart failure The dosage should be individualised and closely monitored during titration. Before starting metoprolol succinate prolonged release, stabilize the dose of other heart failure drug therapy. The recommended starting dose of prolonged metoprolol release is 25 mg once daily in patients with more severe heart failure. Double the dose every two weeks to the highest dose level tolerated by the patient or up to 200 mg of prolonged-release metoprolol succinate. If patients experience symptomatic bradycardia, reduce the dose of prolonged-release metoprolol succinate. If there is a transient worsening of heart failure, consider treatment with increased doses of diuretes, dose reduction of prolonged-release succinate metoprolol or temporary discontinuation. The dose of prolonged release of metoprolol, USPs are available as follows: 25 mg – Each white to stokiela, capsuleshaped film-coated tablet, raised on one side and A9 on the other side and with a score on both sides, contains 23.75 mg metoprolol succinate, USP equivalent to 25 mg metoprolol succinate, USP equivalent to 50 mg metoprolol tartate, USP. 100 mg – Each white to stokiela, capsule shaped, film-coated tablet, with carved and 677 on one side and scored on the other side contains 95 mg metoprolol succinate, USP. 200 mg – Each white to stokiela, capsule shaped, film-coated tablet, with raised and 678 on one side and scored on the other side contains 190 mg metoprolol succinate, USP equivalent to 200 mg metoprolol tartate, USP. Contraindications To metoprolol prolonged-release succinate is contraindicated in severe bradycardia, second or third degree cardiac blockade, cardiogenic shock, decompensated heart failures, sick sinus syndrome (unless a permanent pacemaker is in place) and in patients who are hypersensitive to any component of this medicinal product. 5 WARNINGS AND PRECAUTIONS 5. With discontinuation of chronically administered prolonged release of metoprolol succinate, especially in patients with coronary artery disease, 1 to 2 weeks and monitor the patient. If angina deteriorates significantly or acute coronary ischaemia develops, immediately restore metoprolol prolonged-release succinate and take appropriate measures to manage unstable angina. Warn patients not to stop treatment without your doctor's advice. Since coronary artery disease is common and may be unrecogned, avoid abrupt termination of metoprolol succinate prolonged release in patients treated only for hypertension. 5.2 Heart failure Worsening of heart failure may occur during prolonged-release metoprolol succinate titration. If such symptoms occur, increase diuretics and restore clinical stability prior to administration (2)). It may be necessary to reduce the dose of metoprolol prolonged-release succinate or temporarily discontinue it. Such episodes do not exclude subsequent successful titration of prolonged-release metoprolol succinate. 5.3 Patients with bronchospastic disease who do not respond to or tolerate other antihypertensive therapy. Since beta1 selectivity is not absolute, use the lowest possible dose of prolonged-release metoprolol succinate. Bronchodilatancies, including beta2-agonists, should be readily available or administration (2)). 5.4 Pheochromocytoma If prolonged-release metoprolol succinate is used in the pheochromocytoma setting, it should be administered in combination with an alpha blocker and only after initiation of the alpha-blocker. The administration of beta-blockers alone in the pheochromocytoma environment has been associated with a paradoxical increase in blood pressure due to the suppression of beta-mediated vasodilation in the skeletal muscle. 5.5 Major Surgery Avoid initiation of a high dose prolonged-release metoprolol regimen in patients undergoing heart-free surgery, as such use in patients with cardiovascular risk factors has been associated with bradycardia, hypotension, stroke and death. Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery, however impaired heart responsiveness to reflex adrenergic stimuli may increase the risk of general anesthesia and surgery. 5.6 Diabetes and Hypoglycaemia Beta blockers may mask tachycardia occurring with hypoglycaemia, but other manifestations such as dizziness and sweating may not be significantly affected. 5.7 Hepatic impairment Consider initiating treatment with prolonged-release metoprolol succinate at doses lower than those recommended for the indication; gradually increase optimise treatment while closely monitoring adverse events. 5. 8 Thyrotoxicosis Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism, such as tachycardia. Sudden withdrawal of beta-blockade can precipitating a storm of the thyroid gland. 5.9 Anaphylactic reaction While taking beta-blockers, patients with a history of severe anaphylactic reactions to various allergens may be more reactive to repeated calls and may not respond to the usual doses of adrenaline used to treat an allergic reaction. 5.10 Peripheral vascular disease. 5.11 Calcium channel blockers Caution should be exercised in patients treated with verapamil and diltiazem calcium channel blockers and verapamil and diltiazem. Adverse reactions The following adverse reactions are described elsewhere on the label: 6.1 Clinical trial experience Because clinical studies are conducted under very different conditions, adverse reaction rates observed in clinical trials of another medicinal product and may not reflect the rates observed in practice. However, information on adverse reactions from clinical studies provides a basis for identifying adverse events that appear to be related to drug use and for approximation rates. Hypertension and angina: Most adverse reactions were mild and transient. Most common (more than 2%) adverse reactions are fatigue, dizziness, depression, diarrhoea, shortness of breath, bradycardia and rash. Heart failure: In a MERIT-HF study comparing prolonged release of metoprolol succinate at daily doses up to 200 mg (mean dose 159 mg once daily; n=1990) with placebo (n=2001), 10.3% of patients with extended-release metoprolol discontinued treatment of adverse reactions in the MERIT-HF study that occurred with an incidence greater than or equal to 1% in the prolonged-release metoprolol group and greater than placebo by more than 0.5%, regardless of causality assessment. Postoperative adverse events: In a randomised, a double-blind, placebo-controlled study in 8351 patients with atherosclerotic disease or at risk of disease who had undergone non-kalative surgery and who did not take beta-blockers, metoprolol prolonged-release succinate 100 mg began 2 to 4 hours prior to surgery and then continued for 30 days at 200 mg daily. The use of prolonged-release metoprolol succinate was associated with a higher incidence of bradycardia (6.6% vs. 2.4%; HR 1.23; ci 1.03, 1.74), compared to placebo. 6.2 Postmarketing Experience The following adverse reactions have been identified during the post-approval use of methotoprolol. Since these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship with drug exposure. Cardiovascular: Cold extremities, arterial insufficiency (usually of raynaud's type), palttention, peripheral edem, syncope, chest pain and hypotension. Respiratory: Wheezing (bronchospasm), dyspnea. Central nervous system: Confusion, short-term memory loss, headache, somnolence, nightmares, insomnia, anxiety / nervousness, hallucinations, paraesthesia. Gastrointestinal: Nausea, dry mouth, constipation, bloating, heartburn, hepatitis, vomiting. Hypersensitivity reactions: Pruritus. Miscellaneous: Musculoskeletal pain, arthralgia, blurred vision, decreased libido, male impotence, tinnitus, reversible alopecia, agranulocytosis, dry eyes, worsening of psoriasis, Peyronie's disease, sweating, photosensitivity, taste disturbance. Potential adverse reactions: In addition, there are adverse reactions not mentioned above that have been reported with other beta-adrenergic blockers and potential adverse reactions to the widespread release of metoprolol should be considered. Central nervous system: Reversible mental depression progresses to catatonia; acute reversible syndrome characterised by time and location disorientation, short-term memory loss, emotional lability, cloudy sensoriom and reduced neuropsychometric performance. Hematological: Agranulocytosis, nethrombocytopenic purpura, thrombocytopenic purpura. Hypersensitivity reactions: Laboratory test results Clinical laboratory test results Clinical laboratory findings may include elevated levels of serum transamises, alkaline phosphatase and lactate dehydrogenase. 7 Drug interactions 7.1 Catecholamine-damaging medicines Catecholamine (e.g. reserpine, monoamine oxidase inhibitors (MAO) may have an additive effect when administered with beta-blockers. Monitor patients treated with metoprolol prolonged-release succinate plus catecholamine depletor for evidence of hypotension or marked bradycardia that may induce vertigo, syncope or postural hypotension. 7.2 CYP2D6 inhibitors The medicinal products inhibit CYP2D6, such as quinidine, fluoxetine, paroxetine and propafenone, are likely to increase metoprolol concentration. In healthy subjects with extensive CYP2D6 metaboliser phenotype, quinidine 100 mg coordinate and immediate-release metoprolol 200 mg, the concentration of S-metoprolol tripled and doubled the elimination half-life of metoprolol. Four patients with cardiovascular disease 150 mg three times daily resulted in a two to five-fold increase in steady-state metoprolol concentration. This increase in plasma concentration would reduce the cardiorecectivity of metoprolol. 7.3 Digitalis, Clonidine and calcium channel blockers Digitalis glycosides, clonidine, diltiazem and verapamil slow atrioventricular conduction and beta blockers may increase the risk of bradycardia. If clonidine and beta blockers may increase the risk of bradycardia. the gradual discontinuation of clonidine, since beta-blockers, postpone the introduction of beta-blockers a few days after clonidine administration has stopped (see Warnings and precautions (5.11)). Use in specific populations 8.1 Pregnancy teratogenic effects: Pregnancy category C Metoprolol tartrate has been shown to increase post-implantation loss and reduce neonatal survival in rats at doses up to 22 times, based on mg/m2, daily dose of 200 mg in a 60 kg patient. Distribution studies in mice confirm foetal exposure when metoprolol tartate is administered to pregnant animals. These studies did not reveal any evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Since animal reproduction studies are not always predictive of human response, use this drug during pregnancy only when clearly necessary. 8.3 Lactating mothers Metoprolol is excreted in breast milk in very small amounts. An infant consuming 1 litre of breast milk per day will receive a dose of less than 1 mg of the medicine. Consider possible exposure of the infant when metoprolol prolonged-release succinate is administered to a breast-feeding woman. Paediatric use One hundred and forty-four hypertensive paediatric use One hundred and fort metoprolol succinate dose (0.2, 1.0 or 2.0 mg/kg once daily) followed by 4 weeks. The study did not meet its primary endpoint (dose responses to DBP reduction, 1.0 mg/kg versus placebo for SBP and DBP change. The mean placebo corrected reductions in SBP ranged from 3 to 6 mmHg and DBP from 1 to 5 mmHg. The mean reduction in heart rate ranged from 5 to 7 beats per minute, but some subjects experienced significantly greater reductions in heart rate ranged from 5 to 7 beats per minute. reactions compared to adult patients. Patients. Patients. Patients. Prolonged release of metoprolol in patients less than 6 years of age has not been established. 8.5 Geriatric use Extended release of metoprolol succinate in hypertension did not include a sufficient number of subjects 65 years of age has not been established. reported clinical experience in hypertensive patients did not identify differences in responses between elderly and younger patients. Of the 1,990 heart failure patients. Of the 1,990 heart failure patients in responses between elderly and younger patients. Of the 1,990 heart failure patients did not identify differences in efficacy or adverse reaction rates between elderly and younger patients. In general, use a low starting dose in elderly patients due to their higher frequency of decreased liver, kidney or heart function and concomitant disease or other drug treatment. Since metoprolol succinate extended-release is metabolized in the liver, metoprolol levels in the blood are likely to increase significantly with poor liver function. Therefore, start treatment at doses lower than those recommended for the indication; gradually increase doses in patients with renal failure do not differ to a clinically relevant extent from that in normal subjects. No dose reduction is necessary in patients with chronic renal failure (see clinical pharmacology (12.3.). 10 OVERDOSAGE Signs and symptoms - Overdose of metoprolol succinate prolonged release can lead to severe bradycardia, hypotension, and cardiogenic shock. Clinical presentation may also include: atrioventricular block, heart failure, bronchospasm, hypoxia, deterioration of consciousness/coma, nausea and vomiting. Treatment - Consider treating the patient with intensive care. Patients with myocardial infarction or heart failure may be prone to significant haemodynamic instability. If necessary, consult a regional poison control centre and a medical toxicologist. Overdose with beta-blockers may result in significant resistance to resuscitation with adrenergic agents, including beta-agonists. On the basis of pharmacological measures are used. There is very limited experience with using hemodialysis to remove metoprolol, but metoprolol, but metoprolol, but metoprolol, but metoprolol, the following measures are used. atropine, adrenergic stimulators or pacemakers to treat bradycardia and conduction disorders. Hypotension: Treat basic bradycardia. Consider intravenous infusion of glucagon (if necessary followed by intravenous infusion of glucagon), injection of glucagon), intravenous administration of adrenergic drugs such as dobutamine, with α1 receptor agonist drugs added in the presence of vasodilation. Bronchospasm: Can usually be reversed bronchodilatancies. DESCRIPTION Metoprolol succinate, USP is a beta1-selective (cardioselective) adrenoceptor blocking agent for oral administration, available as prolonged-release tablets. Metoprolol succinate prolonged-release tablets, USP have been formulated to control and predictably release metoprolol for once-daily administration. The tablets contain a multi-unit system containing metoprolol succinate, USP in a number of controlled-release pellets. dosing interval. The tablets contain 23, 75, 47, 5, 95 and 190 mg metoprolol succinate, USP equivalent to 25, 50, 100 and 200 mg metoprolol tartate USP. Its structural formula is: Metoprolol succinate, USP is a white crystalline powder with a molecular weight of 652,8. It is freely soluble in water; soluble in methanol; moderately soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically soluble in ethyl acetate, acetone, diethyl ether and heptane. Inactive ingredients: acetyltributyl citrate, colloidal silica, crospovidone, denatured alcohol, ethylcellulose, hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, polysorbate 80, polyethylene glycol 400, polyethylene glycol 8000, talc and titanium dioxide. The USP dissolution test awaits. CLINICAL PHARMACOLOGY 12. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines on peripheral (especially cardiac) adrenergic neurons, which leads to a decrease in cardiac output; (2) a central effect leading to a reduction in sympathetic outflow to the periphery; and (3) suppression of retinal activity. Heart failure: The exact mechanism for beneficial effects of beta-blockers in heart failure: The exact mechanism for beneficial effects of beta-blockers in heart failure: The exact mechanism for beneficial effects of beta-blockers in heart failure has not been used. 12.2 Pharmacodynamics Clinical pharmacological studies have confirmed the beta-blockers in heart failure: The exact mechanism for beneficial effects of beta-blockers in heart failure has not been used. demonstrated (1) by a decrease in heart rate and cardiac output at rest and during exercise, (2) by lowering systolic blood pressure during exercise, (3) by inhibiting isoproterenol-induced tachycardia and (4) by reducing reflex orthostatic Metoprolol is a beta1-selective (cardioselective) adrenergic receptor blocking agent. However, this preferential effect is not absolute and at higher plasma concentrations metoprolol also inhibits beta2-adrenoreceptors, which are mainly found in bronchial and vascular muscles. Metoprolol has no internal sympathomimetic activity and membrane stabilisation activity is only detectable at plasma concentrations much greater than necessary for beta-blockade. Experiments in animals and humans indicate that metoprolol slows down the rate of cavities and reduces AV node conduction. The relative beta1-selectivity of metoprolol has been confirmed by the following: (1) In normal individuals, metoprolol is unable to reverse the beta2-mediated vasodilating effects of adrenaline. (2) at equivalent doses blocking beta-blocker, progranolol, at equivalent doses blocking beta-blocker, progranolol, at equivalent doses blocking beta trace of exercise is independent of the dosage form. Using the Emax model, the maximum effect is a 30% reduction in the heart rate of exercise is independent of the dosage form. Using the Emax model, the maximum effect is a 30% reduction in the heart rate of exercise is independent of the dosage form. rate of exercise, which is attributed to beta1-blockade. Beta1 blocking effects in the range of 30 to 80% of the maximum effect (approximately an 8 to 23% reduction in exercise heart rate) correspond to plasma concentrations of metoprolol from 30 to 540 nmol/l. The relative beta1-selectivity of metoprolol decreases and the blockade of beta2-adrenoceptors increases at plasma concentrations above 300 nmol/l. Although beta-adrenergic receptor blockade is useful in the treatment of angina, hypertension and heart failure there are situations in which sympathetic drive. In the presence of an AV block, beta-localisation may prevent the necessary facilitation of the effect of sympathetic activity on the conduction. Beta2-adrenergic blockade results in passive bronchoilating activity in patients with eroneous bronchoilated patients. In other studies, treatment with metoprolol succinate enhanced release produced an improvement in left ventricular ejecation fraction. It has also been shown that the widespread release of metoprolol delayed the increase in terminal systolic and end diastolic left ventricular volumes after 6 months of treatment. 12.3 Pharmacokinetics Adults: In humans, absorption of metoprolol is rapid and complete. However, plasma levels following oral administration of conventional metoprolol tablets are approximately 50% of the levels after intravenous administration, indicating about 50% of first-pass metabolism. crosses the blood brain barrier and has been reported in CSF at a concentration of 78% of current plasma concentration. Achieved plasma levels are very variable after oral administration. Only a small fraction of the drug (about 12%) bound to human serum albumin. Metoprolol is a racemic mixture of R- and S-enantiomers and is primarily metabolised by CYP2D6. When administered orally, it exhibits a stereoselective metabolism that is dependent on the oxidative phenotype. Elimination is mainly a biotransformation in the liver and the plasma half-life ranges from approximately 3 to 7 hours. Less than 5% of the oral dose of metoprolol is obtained unchanged in the urine; the residue is excreted by the kidneys as metabolites that appear to be meta with renal failure do not differ to a clinically significant extent from that in normal subjects. As a result, no dose reduction of metoprolol is metabolised predominantly by CYP2D6, an enzyme that is absent in about 8% of caucasal gates (bad metabolisers) and about 2% of most other populations. CYP2D6 may be inhibited by a number of medicines. Poor metabolisers and extensive metabolisers taking CONCOMITANT CYP2D6 inhibiting medicinal products will have elevated (multiple) levels of metoprolol, plasma levels of metoprolol are characterised by lower peaks, longer peak times and significantly lower variations in peak to trough after prolonged release of metoprolol. Maximum plasma levels obtained after the corresponding dose of conventional methotoprolol. administered once daily or in divided doses. At steady state, the mean bioavailability of metoprolol following prolonged release of metoprolol. However, during the 24-hour dose interval, β 1-blockade is comparable and dose-related (see clinical pharmacology (12)). The bioavailability of metoprolol shows an increase in dose, although not directly dose proportional, and is not significantly affected by food after administration of prolonged-release metoprolol succinate. Paediatrics: The pharmacokinetic profile of prolonged release of metoprolol succinate has been studied in 120 paediatric hypertensive patients (aged 6 to 17 years) who received doses of 12.5 to 200 mg once daily. The pharmacokinetics of metoprolol were similar to those previously described in adults. Age, gender, race and ideal body weight. The pharmacokinetics of metoprolol. The apparent oral clearance of metoprolol (CL/F) increased linearly with body weight. The pharmacokinetics of metoprolol are not studied in patients less than 6 years of age. Non-clinical toxicology 13. In a 2-year rat study at three oral dose levels up to 800 mg/kg/day (41 times, based on mg/m2, daily dose of 200 mg for a 60-kg patient), there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histological changes that appeared to be drug-related were an increased incidence of generally mild focal accumulation of foam macrophages in pulmonary alveols and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral doses up to 750 mg/kg/day (18 times, based on mg/m2, daily dose of 200 mg for a 60 kg patient), benign lung tumours (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumours, nor in the overall incidence of tumours. This 21-month study was repeated in CD-1 mice and no statistically or biologically significant differences were observed between treated and control mice of both sexes for any type of tumour. All genotoxicity tests performed on metoprolol tartrate (dominant summer study in mice, somatic interphase nuclei) and metoprolol-succinate (salmonella/mammalian-microsome mutagenicity test) were negative. In a rat study at doses of up to 22 times, per mg/m2, no evidence of impaired fertility due to metoprolol tartate, daily doses of prolonged-release metoprolol succinate and immediate-release metoprolol were compared in terms of the extent and duration of beta 1 blockade produced. Both formulations were administered in a dose range equal to 100 to 400 mg immediate-release metoprolol per day. In these studies, methotoprolol per day. daily dose of these two forms. In each study, beta1-blockade was expressed percentage change in exercise heart rate from baseline after standardised maximum exercise tolerance tests at steady state. Methotoprolol prolonged-release succinate administered once daily and immediate-release metoprolol administered once to four times daily provided a comparable total beta1 blockade over 24 hours (area under the beta1 blockade curve versus time) in the dose range of 100 to 400 mg. At a dose of 50 mg once a day, metoprolol succinate prolonged release of metoprolol succinate produced significantly higher total beta1-blockade over 24 hours than immediate release of metoprolol. For metoprolol succinate produced significantly higher total beta1-blockade over 24 hours than immediate release of metoprolol. was relatively stable throughout the dosing interval and the beta1-blockade level increased with increasing doses from 50 to 300 mg per day. Effects on tip/troy (i.e. 24 hours after doses), there were: 14/9, 16/10, 24/14, 27/22 and 27/20% reductions in heart rate at doses of 50, 100, 200, 300 and 400 mg of succirolol prolonged release once daily. Unlike methotoprolol prolonged release once daily. Unlike methotoprolol prolongedrelease succinate, immediate-release metoprolol administered at a dose of 50 to 100 mg once daily had a significantly greater peak effect on exercise tachycardia, but the prolonged dosing regimen of metoprolol in the dosing range of 200 to 400 mg, an immediate-release metoprolol was required three to four times daily. A controlled cross-study in patients with heart failure compared plasma concentrations and beta1-blocking effects of immediate-release succinate once daily. A dose of 50 mg immediate-release metoprolol three times daily. produced peak plasma levels of metoprolol similar to the maximum level observed with 200 mg metoprolol prolonged-release succinate. A dose of metoprolol prolonged-release succinate 200 mg produced a greater effect on the suppression of exercise-induced heart rate and holter-monitored heart rate for 24 hours compared to 50 mg three times a day of immediate-release metoprolol. In a double-blind study, 1092 patients with mild to moderate hypertension were randomised to prolonged-release felodipine tablets, combination or placebo. After 9 weeks, metoprolol prolonged-release succinate alone lowered sitting blood pressure by 6 to 8/4 to 7 mmHg (placebo-corrected change from baseline) 24 hours after dose. The combination of metoprolol succinate with prolonged-release tablets of felodipine has a greater effect on blood pressure. In the audited studies, the immediate-release dosage form of metoprolol was an effective antihypertensive thiazide diuretics at doses of 100 to 450 mg per day. Metoprolol prolonged-release succinate at doses of 100 to 400 mg once daily produces a similar β1 blockade to conventional metoprolol tablets given two to four times a day. In addition, methotoprolol prolonged-release succinate administered at a dose of 50 mg once daily lowered blood pressure 24 hours after dosing in placebo-controlled studies. In controlled, comparative clinical trials, immediate-release metoprolol appeared comparable to an antihypertensive agent with propranolol, myloop and thiazide-type diuretics and affected blood pressure on the back and standing. Due to the variable plasma concentration of the drug, the choice of the correct dosage requires individual titration. 14. Angina Pectoris By blocking the increase in heart rate induced by catecholamine, the speed and extent of myocardial contraction and blood pressure, metoprolol has been shown to be an effective antianginal agent, reducing the number of angina attacks and increasing exercise tolerance. The dosage used in these studies ranged from 100 to 400 mg once daily has been shown to have a beta-blockade similar to conventional metoprolol tablets administered two to four times daily. 14.2 Merit-HF heart failure was a double-blind, placebo-controlled, extended-release study of metoprolol succinate conducted in 14 countries, including the United States. It randomized 3,991 patients (1990 to metoprolol succinate extended-release) with ejection fractions less than or equal to 0.40 and NYHA Class II-IV heart failure attributed to ischaemia, hypertension, or cardiomyopathy. The protocol excluded patients with contraindications to the use of beta-blocker, patients expected to undergo heart surgery, and patients within 28 days after myocardial infarction or unstable angina. The primary endpoints of the study were (1) all-cause mortality plus all-cause mortality plus all-cause mortality plus all-cause mortality plus all-cause hospitalisation (time to first event) and (2) all-cause mortality. Patients were stabilised for optimal concomitant treatment of heart failure, including diuretics, ACE inhibitors, cardiac glycosides and nitrates. At randomization, 41% of NYHA Class II patients; 55% of NYHA Class III; 65% of patients; 48% had a history of myocardial infarction. Among patients in the study, 90% were on diuretics, 89% were on ACE inhibitors, 64% on digitalise, 27% were on lipid, lipid-lowering agents, anticoagulant and the mean daily dose of prolonged release of metoprolol succinate was 159 mg. The study was terminated prematurely due to a statistically significant reduction in all-cause mortality (34%, nominal p = 0.00009). The risk of all-cause mortality and heart failure-related mortalit results of the overall study population. The figure below illustrates the main results for a wide range of subgroup comparisons, including those in the USA compared to non-US population and heart failure hospitalizations showed consistent effects in the overall study population and subgroups, including women and the U.S. population. However, in the SUBGROUP USA (n=1071) and in women (n=898), overall mortality and cardiovascular mortality difficult to interpret and it is not known whether they represent real differences or effects of chance. 15 REFERENCES Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC et al. Effects of metoprolol prolonged-release succinate in patients undergoing heart surgery (POISE study): randomised controlled trial. Lancet. 2008; 371:1839-47. AS SUPPLIED/STORAGE AND HANDLING Prolonged-release metoprolol tablets, USP is supplied as follows: 25 mg - Each white to insole, capsule-shaped film-coated tablet, marked on one side and A9 on the other side and with a score on both sides, contains 23.75 mg metoprolol succinate, USP is supplied in 100 bottles (NDC 45963-709-11) and 1000 bottles (NDC 45963-709-96). 50 mg – Each white to stokiela, capsule shaped, film-coated tablet, with a shot and 676 on one side and scored on the other side contains 47.5 mg metoprolol tartate, USP. The tablets are supplied in bottles of 100 s (NDC 45963-676-11) and bottles of 1000 (NDC 45963-676-96). 100 mg – Each

white to stokiela, capsule shaped, film-coated tablet, with carved and 677 on one side and scored on the other side contains 95 mg metoprolol succinate, USP equivalent to 100 mg metoprolol succinate, USP. The tablets are supplied in 100 bottles (NDC 45963-677-11) and 1000 bottles (NDC 45963-677-96). 200 mg – Each white to off-white, capsule-shaped, film-shaped tablets, tablets,

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