1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

1.1 (Invented) Name of the medicinal product

METOPROLOL SUCCINATE EXTENDED RELEASE TABLETS USP 50 MG

1.2 Strength

Each extended release film coated tablet contains:

Metoprolol Succinate USP 47.5 mg
Eq. to Metoprolol Tartrate 50 mg
Excipients Q.S.
Colour: Titanium Dioxide B.P.

1.3 Pharmaceutical Form

Film Coated Tablet

2. Qualitative and Quantitative Formula

Batch Size: 100,000 Tablets

Sr.No.	Ingredients	Label claim (mg)	Actual Qty./Tablet (mg)	Actual Qty./Batch (kg)	Function
Mixing					
1	Metoprolol Succinate USP	--	47.500	4.750	Anti Hypertensive
2	M.C.C.P PH 102 BP	--	87.500	8.750	Diluent
3	Acrypol 971 P		55.000	5.500	Control Release agent
4	Aerosil		4.0000	0.400	Disintegrant
Binding					
5	Iso Propyl Alcohol BP	--	Q.S	Q.S	Vehicles
6	P.V.P K-30 BP	--	23.000	2.300	Binder
Lubrication					
7	Magnesium Stearate BP	--	6.0000	0.600	Lubricant
8	Talcum BP	--	10.000	1.000	Glidant
9	Aerosil BP	--	3.000	0.300	Disintegrant
10	Acrypol 971P BP	--	24.000	2.400	Control Release agent
Total Weight of Uncoated Tablet		--	**260.00mg**	**26.00 kg**	
Coating					
11	Titanium Dioxide BP	--	7.000	0.700	Coating agent
12	Iso Propyl Alcohol BP	--	Q.S	Q.S	Vehicles
13	Methylene Dichloride BP		Q.S	Q.S	Vehicles
Total Weight of Film Coated Tablet		--	**267.00 mg**	**26.70 kg**	

3. Pharmaceutical form

White coloured round shaped biconvex film coated tablet plain on both side.

4. Clinical particulars:

4.1 Therapeutic Indication:

METOPROLOL SUCCINATE EXTENDED RELEASE TABLETS USP 50 MG

Adults

– Hypertension
– Angina pectoris
– Heart arrhythmia, particularly supraventricular tachycardia
– Prophylactic treatment to prevent cardiac death and re-infarction following the acute phase of a myocardial infarction
– Palpitations due to functional cardiac disorders
– Prophylaxis of migraine
– Stable symptomatic heart failure (NYHA II-IV, left ventricular ejection fraction < 40 %), combined with other therapies for heart failure. Children and adolescents 6-18 years of age – Treatment of hypertension.

4.2 Posology and method of administration:

Metoprolol succinate tablets should be taken once daily in the morning. The tablets must be swallowed whole or divided. They must not be chewed or crushed. The tablets should be taken with water (at least half a glass). The dose may be adjusted in accordance with the following guidelines:

Adults

Hypertension: 47.5 mg metoprolol succinate (equivalent to 50 mg metoprolol tartrate) once daily for patients with mild to moderate hypertension. If necessary, the dose may be increased to 95- 190 mg metoprolol succinate (equivalent to 100-200 mg metoprolol tartrate) daily, or another antihypertensive agent may be added to the treatment regimen.

Angina pectoris: 95-190 mg metoprolol succinate (equivalent to 100-200 mg metoprolol tartrate) once daily. If necessary, other medicinal products may be added to the treatment regimen for treatment of arteriosclerosis.

Heart arrhythmia: 95-190 mg metoprolol succinate (equivalent to 100-200 mg metoprolol tartrate) once daily.

Prophylactic treatment following myocardial infarction: 190 mg metoprolol succinate (equivalent to 200 mg metoprolol tartrate) once daily.

Palpitations due to functional cardiac disorders: 95 mg metoprolol succinate (equivalent to 100 mg metoprolol tartrate) once daily. If necessary, the dose may be increased to 190 mg metoprolol succinate (equivalent to 200 mg metoprolol tartrate).

Prophylaxis of migraine: 95-190 mg metoprolol succinate (equivalent to 100-200 mg metoprolol tartrate) once daily.

Stable symptomatic heart failure: The metoprolol succinate dose is determined individually for patients with stable, symptom-producing heart failure regulated by other treatment against heart failure. The recommended initial dose for NYHA III-IV patients is 11.88 mg metoprolol succinate (equivalent to 12.5 mg metoprolol tartrate) once daily for the first week. The dose may possibly be increased to 23.75 mg metoprolol succinate (equivalent to 25 mg metoprolol tartrate) daily for the second week. The recommended initial dose for NYHA II patients is 23.75 mg metoprolol succinate (equivalent to 25 mg metoprolol tartrate) once daily for the first two weeks. It is recommended to double the dose after the first two weeks. The dose should be increased every second week up to

190 mg metoprolol succinate (equivalent to 200 mg metoprolol tartrate) daily or until the maximum tolerated dose is reached. For long-term treatment, the target dose should be fixed at 190 mg metoprolol succinate (equivalent to 200 mg metoprolol tartrate) daily or until the maximum tolerated dose is reached. It is recommended that the treating doctor is familiar with treating stable, symptom-producing heart failure. After each dose increase, the patient's condition should be carefully checked. If the blood pressure drops, it may be necessary to reduce the dose of other concomitant medication. A blood pressure drop is not necessarily an impediment for long-term use of metoprolol, but the dose should be reduced until the patient's condition is stable.

Impaired renal function: Dose adjustment is not required.

Impaired hepatic function: In patients with severe hepatic insufficiency, e.g. when treating patients with portocaval shunt, a dose reduction should be considered.

Elderly: There are no adequate data from the use in patients above the age of 80. Take special precautions when increasing the dose.

Children and adolescents (6-18 years of age): The recommended initial dosage in hypertensive patients ≥6 years is 0.5 mg/kg Metoprolol succinate (0.48 mg/kg metoprolol succinate) once daily. The final dose administered in milligrams should be the closest approximation of the calculated dose in mg/kg. In patients not responding to 0.5 mg/kg, the dose can be increased to 1.0 mg/kg (0.95 mg/kg metoprolol succinate), not exceeding 50mg (47.5 mg metoprolol succinate). In patients not responding to 1.0 mg/kg, the dose can be increased to a maximum daily dose of 2.0 mg/kg (1.9 mg/kg metoprolol succinate). Doses above 200 mg (190 mg metoprolol succinate) once daily have not been studied in children and adolescents.

4.3 Contraindications

Hypersensitivity to metoprolol succinate, other beta blockers or to any of the excipients listed in section 6.1.

– Grade II or III atrioventricular block.
– Untreated heart failure (pulmonary oedema, reduced blood flow or hypotension) and continuous or periodic treatment increasing the heart contractility (beta receptor agonism).
– Manifest and clinically significant sinus bradycardia (heart frequency < 50/min.).
– Sick sinus syndrome.
– Cardiogenic shock.
– Severe peripheral arterial disease.
– Hypotension (systolic < 90 mmHg).
– Metabolic acidosis.
– Severe bronchial asthma or chronic obstructive pulmonary disease. – Untreated phaeochromocytoma
– Concomitant use of MAO inhibitors (except from MAO-B inhibitors).

Metoprolol may not be administered to patients with suspected acute myocardial infarction and a heart rate of < 45 beats/min., PQ interval > 0.24 seconds or systolic blood pressure < 100 mmHg.

In addition, metoprolol is contraindicated in patients with heart failure and with a systolic blood pressure which repeatedly falls below 100 mmHg (examination required before initiating treatment).

Concomitant intravenous administration of calcium blockers of the type verapamil or diltiazem or other antiarrhythmics (such as disopyramide) is contraindicated.

4.4 Special warnings and precautions for use:

Withdrawal

Metoprolol should not be withdrawn abruptly. If withdrawal is required it should be done gradually over a period of 10 – 14 days, in diminishing doses to 25 mg daily for the last 6 days. Abrupt withdrawal may cause an acute aggravation of the patient's condition, particularly in patients with ischaemic heart disease. Hypertension and arrhythmias may occur. Therefore, these patients must be monitored very closely in this period. Risk of ischaemic episodes including sudden death may increase during the gradual reduction of the ß-blockade.

Anaesthesia

Prior to surgery, the anaesthesiologist must be informed that the patient receives metoprolol. It is not generally recommended to stop beta blocker treatment in patients undergoing surgery. If withdrawal of metoprolol is considered desirable, this should, if possible, be completed at least 48 hours before anaesthesia. However, in some patients it may be advisable to administer a beta-blocker as premedication.

Acute initiation with high doses of metoprolol should be avoided in patients undergoing non-cardiac surgery as this has been associated with bradycardia, hypotension and stroke, including a fatal outcome in cardiovascular risk patients.

By shielding the heart against the effects of stress, the beta-blocker may prevent excessive sympathetic stimulation provoking cardiac arrhythmias or acute coronary insufficiency.

If a beta-blocker is given for this purpose, an anaesthetic with little negative inotropic activity should be used.

Heart and circulation

Intravenous administration of calcium antagonists of the verapamil and diltiazem type must not be given to patients being treated with beta-blockers (exception: intensive care unit, see section 4.5).

A severe, sometimes life-threatening, aggravation of cardiac function may occur particularly in patients whose cardiac function depends on sympathetic stimulation. This is not due to the potent beta-blocking effect but because patients with severely reduced cardiac function do not tolerate even very small reductions in the degree of sympathetic stimulation. This will cause a decrease in inotropic effect, decrease in heart rate and delayed AV-conduction. Pulmonary oedema, AV-block and shock may result. In a few isolated cases an aggravation of existing AV-conduction disorders may occur which may result in AV-block.

If the patient develops increasing bradycardia, metoprolol should be administered at lower doses or gradually withdrawn.

Metoprolol may exacerbate the symptoms of peripheral vascular disorders such as Raynaud's syndrome or intermittent claudication due to its antihypertensive effect. If symptoms exacerbate, beta-blockers should be given with extreme caution.

When metoprolol is co-administered with digitalis it should be considered that both medicines prolong AV conduction time. Cardiovascular complications such as dizziness, bradycardia and a tendency to collapse may also develop. In case of increased bradycardia metoprolol should be administered at lower doses or gradually withdrawn.

In patients with Prinzmetal's angina β1 selective agents should be used with care

Asthma
Beta blockers must be administered with caution to asthmatic patients. Although metoprolol at usual doses may have less negative effect on bronchial muscles than nonselective beta-blockers, constant attention is necessary. If an asthmatic needs to be treated with metoprolol, a beta2 agonist (as tablets or by inhalation) should be administered concomitantly. When initiating metoprolol treatment, the dose of the beta2 agonist must be controlled and increased if necessary. Metoprolol prolonged-release tablets affect beta2 receptors to a lesser degree than conventional tablet forms for beta1 selective beta blockers.
Diabetes
Metoprolol may reduce the effect of diabetes treatment and mask the symptoms of hypoglycaemia. The risk of a carbohydrate metabolism disorder or masking of the symptoms of hypoglycaemia is lower when using metoprolol prolonged-release tablets than when using conventional tablet forms for beta1 selective beta blockers and significantly lower than when using non-selective beta blockers.

Special medical surveillance is necessary after a long-term strict diet or vigorous physical exercise (due to the risk of severe hypoglycaemic episodes).

Phaeochromocytoma
When prescribing metoprolol to patients with a phaeochromocytoma an alpha blocker must be used before initiating treatment and during the metoprolol treatment.

Thyrotoxicosis: Metoprolol treatment may possibly mask the symptoms of thyrotoxicosis.

Other
As with other beta blockers, metoprolol may increase both the sensitivity to allergens and the severity of anaphylactic reactions. Therefore beta-blockers must only be used if clearly indicated in patients with a history of severe hypersensitive reactions or undergoing hyposensitisation. A severe form of anaphylactic shock may occur in patients being treated with a beta-blocker.

Adrenalin treatment does not always give the desired therapeutic effect in individuals receiving beta blockers.

Beta blockers may trigger or exacerbate psoriasis. In patients with active, anamnestic or a family history of psoriasis, beta-blockers should only be used after careful consideration of the expected benefits and risks.

In patient with severe hepatic disease reduction of the metoprolol dose may be necessary (see section 4.2.).

As patients with existing severe renal insufficiency in rare cases have experienced aggravation of the renal function during treatment with beta-blockers, treatment with metoprolol should be accompanied by monitoring of the renal function (see section 4.2)

Ostomy patients
As with other prolonged-release medicinal products an individual assessment of the suitability of the medicinal product must be performed prior to the treatment of ostomy patients. Initial treatment must be closely monitored.

Up to the present, there is insufficient data from the use of metoprolol in patients with heart failure and the following accompanying factors:
– Unstable heart failure (NYHA IV).
– Acute myocardial infarction or unstable angina pectoris in the preceding 28 days.
– Impaired renal function.
– Impaired hepatic function.
– Patients above the age of 80.
– Patients under the age of 40.
– Haemodynamically significant valve diseases.
– Hypertrophic obstructive cardiomyopathy.
– During or after cardiac surgery within the last four months before treatment with metoprolol succinate.

4.5 Interaction with other medicinal products and other forms of interaction

Heart and circulation
Calcium antagonists: As with other beta-blockers metoprolol must be used with extreme caution if calcium antagonists are administered concomitantly, as hypotension, bradycardia and other cardiac arrhythmias may occur. This particularly applies to verapamil and to a lesser extent to diltiazem which have an adverse effect on the cardiac contractibility and on AVconduction.
Calcium antagonists of the verapamil type and diltiazem must not be administered intravenously to patients receiving beta blockers. At least 48 hours should elapse between administration of beta-blockers and the intravenous administration of these calcium antagonists (see section 4.4). When given concomitantly with nifedipin a marked drop in blood pressure may occur. The combination can be used when the metoprolol dose is adjusted. In patients with impaired cardiac function these combinations are contraindicated

Antiarrhythmics: Caution must be exercised on concomitant treatment with several antiarrhythmics. The cardio depressive effect of metoprolol and antiarrhythmics may be additive. For example quinidine or propafenone reduce the hepatic metabolism of metoprolol resulting in metoprolol toxicity (i.e. bradycardia). Amiodarone has an enhancing effect on the AV conduction time and a negative inotropic effect resulting in decreased sinus frequency and deterioration of AV block in predisposed patients.

When metoprolol is used concomitantly with lidocaine, the plasma concentration of lidocaine increases by 30% - 40% and lidocaine clearance decreases correspondingly resulting in lidocaine toxicity (hypotension, convulsions, AV block).

Antiarrhythmics should not be administered intravenously in patients being treated with metoprolol (see section 4.3).

Antihypertensives:
Metoprolol may increase the effect of other antihypertensives administered concomitantly with metoprolol. Alpha-stimulation occurs when clonidine is discontinued in concomitant treatment with a non-selective beta-blocker and possibly also with a selective beta-blocker, resulting in severe hypertension (rebound-effect). If concomitant

treatment with clonidine is to be discontinued, metoprolol should be withdrawn several days before clonidine.

There may be a pronounced drop in the heart rate and the heart's conductivity in case of concomitant treatment with metoprolol and reserpine, alpha-methyldopa, clonidine, guanfacine and cardiac glycosides.

Concomitant use of metoprolol and glycerol trinitrate, diuretics, vasodilators or other antihypertensives may result in increased drop in blood pressure.

Enzyme inducers and enzyme inhibitors Enzyme inducing or inhibiting drugs may affect the plasma concentration of metoprolol. Rifampicin may increase the metabolism of metoprolol, thus reducing its plasma concentration, while cimetidine, alcohol and hydralazine may possibly increase the metoprolol plasma concentration.

Metoprolol is metabolised primarily, but not solely, by the hepatic enzyme cytochrome (CYP) 2D6 (see also section 5.2). Substances with an inhibiting effect on CYP 2D6, e.g. selective serotonin reuptake inhibitors (SSRIs) as paroxetine, fluoxetine and sertraline, diphenhydramine, hydroxychloroquine, celecoxib, terbinafine, neuroleptics (e.g. chlorpromazine, triflupromazine, chlorprothixene) and possibly also propafenone may increase the plasma concentration of metoprolol.

Prostaglandin synthetase inhibitors Concomitant use of metoprolol and indometacin or another inhibitor of the prostaglandin synthesis may reduce the antihypertensive effect of beta blockers.

Insulin and oral antidiabetics
The blood sugar lowering effect of insulin and oral antidiabetics may be enhanced by betablockers, particularly by non-selective beta-blockers and may mitigate the symptoms of hypoglycaemia (especially tachycardia and tremor). Therefore blood sugar should be measured regularly and the antidiabetic treatment (insulin and oral antidiabetics) should be adjusted accordingly.

Inhalation anaesthetics
Some inhalation anaesthetics may enhance the cardiodepressant effect of beta blockers.

Concomitant use is not contraindicated (see section 4.4) as beta-blocker may prevent large fluctuations in blood pressure during intubation and rapid antagonism may occur with betasympathomimetic agents.

Sympathetic ganglion blockers, MA-inhibitors and other beta-blockers
If sympathetic ganglion blocking substances are administered concomitantly with other beta blockers (including eye drops) or MAO inhibitors, the patient's condition should be monitored carefully.

When, under certain circumstances, adrenalin is administered to a patient in treatment with beta blockers, cardio-selective beta blockers affect the blood pressure regulation significantly less than non-selective beta blockers.

The effect of adrenalin in the treatment of anaphylactic reactions may be weakened in patients receiving beta blockers.

If metoprolol and noradrenalin, adrenalin or other sympathomimetics are administered concomitantly, the blood pressure can increase significantly.

Patients in concomitant treatment with other beta adrenergic antagonists (e.g. timolol eye drops) must be under close medical supervision.

Other Concomitant use of metoprolol and tricyclic antidepressants, barbiturates and phenothiazines may result in increased drop in blood pressure.

Concomitant use of metoprolol and narcotics may result in increased lowering of blood pressure. The negative inotropic effect of these medicinal products may be additive. A neuromuscular blockade caused by peripheral muscle relaxants (e.g. succinylcholine halid, tubocurrarine) may be increased due to metoprolol's inhibition of beta-receptors. If a treatment with metoprolol cannot be discontinued prior to anaesthesia or prior to the use of muscle relaxants, the anaesthetist must be informed of the metoprolol treatment.

4.6 Adverse Drug Reactions

- Signs of an allergic reaction, like rash; hives; itching; red, swollen, blistered, or peeling skin with or without fever; wheezing; tightness in the chest or throat; trouble breathing, swallowing, or talking; unusual hoarseness; or swelling of the mouth, face, lips, tongue, or throat.
- Low mood (depression).
- Very bad dizziness or passing out.
- Chest pain that is new or worse.
- An abnormal heartbeat that is new or worse.
- Slow heartbeat.
- Shortness of breath, a big weight gain, or swelling in the arms or legs.

4.7 Fertility, Pregnancy and lactation

Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure.

4.7 Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines.

4.9 Overdose:

Symptoms: An overdose of metoprolol may cause severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasms, loss of consciousness (even coma), nausea, vomiting or cyanosis.

The symptoms may be exacerbated by concomitant ingestion of alcohol, antihypertensive agents, chinidine or barbiturates.

The first signs of an overdose present within 20 minutes to 2 hours after taking the medicinal product.

Treatment:
Close supervision. Treatment in an intensive care unit.

In order to prevent absorption of the medicinal product, which still is present in the gastrointestinal tract, gastric lavage, activated charcoal and laxative should be used. Hypotension and shock should be treated with plasma/plasma substitutes.

In case of severe bradycardia atropine 1-2 mg may be given intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute by intravenous infusion may be given.

Dobutamine, because of its positive inotropic effect could also be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

Administration of calcium ions may also be considered. Bronchospasm can usually be reversed by bronchodilators.

5. Pharmacological properties

5.1 Pharmacotherapeutic Group

Pharmacotherapeutic group: Beta blocking agents, selective.
ATC code: C07AB02.

5.2 Pharmacodynamic properties

Metoprolol is a beta1 selective beta blocker, i.e. blocking beta1 receptors in the heart at significantly lower doses than those required for blocking beta2 receptors. Metoprolol only exhibits insignificant membrane stabilising effect and has no agonist effect. Metoprolol reduces or blocks the stimulating effect of catecholamines (particularly released in case of physical or mental stress) on the heart. Metoprolol reduces tachycardia, decreases the cardiac output and the contractility and lowers the blood pressure. The plasma concentrations and effect (beta1 blocking) of prolonged-release tablets with metoprolol succinate are more evenly distributed over a given period in a day than those obtained with traditional tablet forms with beta1 selective beta blockers. As the plasma concentrations are stable, the clinical beta1 selectivity is better than the one obtained with traditional tablet forms with beta1 selective beta blockers. The risk of undesirable effects associated with maximum concentrations is also minimal (e.g. bradycardia or limb weakness). If required, metoprolol may be administered concomitantly with a beta2 agonist to patients with symptoms of obstructive pulmonary disease. Short term studies have shown that metoprolol may cause a slight increase in triglycerides and a decrease in free fatty acids in the blood. In some cases, a small decrease in the high density lipoproteins (HDL) fraction has been observed, although to a lesser extent than that following non selective beta blockers. However, a significant reduction in total serum cholesterol levels has been demonstrated after metoprolol treatment in one study conducted over several years. Effect in hypertension Metoprolol lowers elevated standing and supine blood pressure. A short duration (a few hours) and clinically insignificant increase in peripheral resistance may be observed after the institution of metoprolol treatment. During long-term treatment a reduction in total peripheral resistance, left ventricular hypertrophy may occur and improved left ventricular diastolic function and left ventricular filling.
A reduction in the risk of death from cardiovascular disease in men with mild to moderate hypertension metoprolol has been shown, mainly due to reduced risk for

sudden cardiovascular death, to reduce the risk for fatal and non-fatal infarction and for stroke. Effect on heart failure: The MERIT-HF study (3,991 NYHA II-IV patients, ejection fraction ≤ 40 %), which combined metoprolol with standard heart failure therapy (i.e. diuretics, ACE inhibitors or hydralazine if the patient did not tolerate ACE inhibitors, long-term effective nitrate or angiotensin-II receptor antagonists and, if necessary, cardiac glycosides), showed e.g. a reduction in overall mortality by 34 % (p = 0.0062 (adjusted); p = 0.00009 (nominal)). Mortality (notwithstanding cause) in the metoprolol group was 145 (7.2 % per patient year at follow-up) against 217 (11.0 %) in the placebo group, with a relative risk of 0.66 [95 % CI 0.53-0.81]. Paediatric population In 144 paediatric patients (6 to 16 years of age) with primarily essential hypertension, metoprolol succinate has been shown in a 4-week study to reduce systolic blood pressure by 5.2 mmHg with 0.2 mg/kg (p=0.145), 7.7 mmHg for 1.0 mg/kg (p=0.027) and 6.3mmHg for 2.0 mg/kg doses (p=0.049) with a maximum of 200mg/day compared to 1.9 mmHg on placebo. For diastolic blood pressure, this reduction was 3.1 (p=0.655), 4.9 (p=0.280), 7.5 (p=0.017) and 2.1 mmHg, respectively. No apparent differences in blood pressure reduction were observed based on age, Tanner stage, or race.

5.3 Pharmacokinetic properties

Absorption and distribution:

Metoprolol is completely absorbed after an oral dose. Due to a pronounced first passage metabolism for metoprolol, the bioavailability of a single oral dose is approx. 50 %. The bioavailability of prolonged-release tablets is approx. 20-30 % lower than for regular tablets, but this does not have a significant clinical effect, as the AUC values (pulse) are the same as for regular tablets. Only a small fraction of metoprolol (approx. 5-10 %) binds to plasma proteins.

Each prolonged-release tablet with metoprolol succinate contains a large number of pellets containing metoprolol succinate with controlled release. Each pellet is coated with a polymer coating which controls the metoprolol release speed.

A prolonged-release tablet is quickly triggered, and the controlled release granulate spreads to the gastrointestinal tract where it releases metoprolol continuously over a period of 20 hours. The elimination half-life of metoprolol is 3.5 hours on average (see the section

Biotransformation and elimination). After one daily dose, the maximum plasma concentrations of metoprolol reach approximately twice the trough levels. Biotransformation and elimination:

Metoprolol is metabolised by hepatic oxidation. The three known main metabolites have been shown not to have a clinically significant beta blocking effect. Metoprolol is metabolised primarily, but not solely, by the hepatic enzyme cytochrome (CYP) 2D6. Due to the polymorphy of the CYP 2D6 gene, the turnover rates vary with the individual. Individuals with poor metabolic capacity (approx. 7-8 %) exhibit higher plasma concentrations and slower elimination than individuals with good metabolic capacity. The plasma concentrations are stable and repeatable in the individuals, however.

More than 95 % of an oral dose is excreted in urine. Approximately 5 % of the dose is excreted in unchanged form; in single cases up to an entire 30 %. The elimination half-life of metoprolol in plasma is 3.5 hours on average (interval 1-9 hours). Total clearance is approx. 1 L/min.

Paediatric population The pharmacokinetic profile of metoprolol in paediatric hypertensive patients aged 6-17 years is similar to the pharmacokinetics described previously in adults. Metoprolol apparent oral clearance (CL/F) increased linearly with body weight.

Older people The pharmacokinetics of metoprolol in the elderly is not significantly different from that in younger populations. The systemic bioavailability and elimination of metoprolol is normal in renal failure patients. The elimination of metabolites is slower than normal, however. Significant accumulation of metabolites has been observed in patients with a glomerular filtration rate of less than 5 mL/min. The metabolite accumulation does not potentiate the beta blocking action of metoprolol.

Hepatic impairment Patients with hepatic cirrhosis may experience an increase in the bioavailability of metoprolol and a decline in total clearance. However, the exposure increase only has clinical relevance in patients with severely impaired hepatic function or portocaval shunt. In patients with portocaval shunt, the total clearance is approx. 0.3 L/min, and the AUC values are approx. six times larger than in healthy individuals.

5.4 Preclinical safety data

There are no other relevant preclinical data than those already mentioned in other sections of this summary of product characteristics.

6. Pharmaceutical particulars

6.1 List of Excipients

Name of Material	Specification
M.C.C.P PH 102	BP
Acrypol 971 P	BP
Aerosil	BP
Iso Propyl Alcohol	BP
P.V.P K-30	BP
Magnesium Stearate	BP
Talcum	BP
Titanium Dioxide	BP
Iso Propyl Alcohol	BP
Methylene Dichloride	BP

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months from the date of manufacturing.

6.4 Special precautions for storage

Store in a dry place below 30°C. Protected from light & moisture.

6.5 Nature and contents of container

2 X 14 Tablets Alu – PVC Blisters in printed carton along with package insert.

6.6 Special precautions for disposal

No special requirements.

7. REGISTRANT
SWISS PHARMA PVT. LTD.
Plot No. - 3709, GIDC, Phase-IV, Vatva,
Dist-Ahmedabad-382 445, Gujarat, Country:
India.

8. DATE OF REVISION OF THE TEXT
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9. NAME AND ADDRESS OF MANUFACTURER
SWISS PHARMA PVT. LTD.
Plot No. - 3709, GIDC,
Phase-IV, Vatva, Dist-Ahmedabad-382 445, Gujarat,
Country: India.