SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Product Name **:** JUVETA ER 50 (Metoprolol Succinate Extended release Tablets USP 50 mg)

Strength **:** 50 mg

Distribution category: Prescription Only Medicine (POM)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each extended release tablet contains:

Metoprolol Succinate 47.5 mg

equivalent to Metoprolol Tartrate USP..... 50 mg

Excipients q.s

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Extended release Tablets.

White, round, biconvex, film-coated tablets, scored on one side and debossed with "24" on other side.

The tablet can be divided into two equal halves; however, the whole or half tablet should be swallowed whole and not chewed or crushed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

Metoprolol Succinate Extended Release Tablets is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure lowers the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including metoprolol.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as 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.

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (eg, on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

Metoprolol succinate extended-release tablets may be administered with other antihypertensive agents.

Angina Pectoris

Metoprolol succinate extended-release tablet is indicated in the long-term treatment of angina pectoris, to reduce angina attacks and to improve exercise tolerance.

Heart Failure

Metoprolol Succinate Extended Release Tablets is indicated for the treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin. It was studied in patients already receiving ACE inhibitors, diuretics, and, in the majority of cases, digitalis. In this population, Metoprolol Succinate Extended Release Tablets decreased the rate of mortality plus hospitalization, largely through a reduction in cardiovascular mortality and hospitalizations for heart failure.

4.2 Posology and method of administration

Metoprolol Succinate Extended Release Tablets is an extended-release tablet intended for once daily administration. For treatment of hypertension and angina, when switching from immediate-release metoprolol to extended release metoprolol, use the same total daily dose of Metoprolol Succinate Extended Release Tablets. Individualize the dosage of Metoprolol Succinate Extended Release Tablets. Titration may be needed in some patients.

Metoprolol Succinate Extended Release Tablets are scored and can be divided into two equal halves; however, the whole or half tablet should be swallowed whole and not chewed or crushed.

Hypertension

Adults: The usual initial dosage is 50 to 100 mg daily in a single dose. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. Dosages above 400 mg per day have not been studied.

Pediatric Hypertensive Patients ≥ 6 Years of age: A pediatric clinical hypertension study in patients 6 to 16 years of age did not meet its primary endpoint (dose response for reduction in SBP); however some other endpoints demonstrated effectiveness. If selected for treatment, the recommended starting dose of Metoprolol Succinate Extended Release Tablets is 1.0 mg/kg once daily, but the maximum initial dose should not exceed 50 mg once daily. Dosage should be adjusted according to blood pressure response. Doses above 2.0 mg/kg (or in excess of 200 mg) once daily have not been studied in pediatric patients.

Metoprolol Succinate Extended Release Tablets is not recommended in pediatric patients < 6 years of age.

Angina Pectoris

Individualize the dosage of Metoprolol Succinate Extended Release Tablets. The usual initial dosage is 100 mg daily, given in a single dose. Gradually increase the dosage at weekly intervals until optimum clinical response has been obtained or there is a pronounced slowing of the heart rate. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, reduce the dosage gradually over a period of 1 - 2 weeks.

Heart Failure

Dosage must be individualized and closely monitored during up-titration. Prior to initiation of Metoprolol Succinate Extended Release Tablets, stabilize the dose of other heart failure drug therapy. The recommended starting dose of Metoprolol Succinate Extended Release Tabletsis 50 mg once daily for two weeks in patients with NYHA Class II heart failure and 12.5 mg once daily in patients with more severe heart failure. Double the dose every two weeks to the highest dosage level tolerated by the patient or up to 200 mg of Metoprolol Succinate Extended Release Tablets. Initial difficulty with titration should not preclude later attempts to introduce Metoprolol Succinate Extended Release Tablets. If patients experience symptomatic bradycardia, reduce the dose of Metoprolol Succinate Extended Release Tablets. If transient worsening of heart failure occurs, consider treating with increased doses of diuretics, lowering the dose of Metoprolol Succinate Extended Release Tabletsor temporarily discontinuing it. The dose of Metoprolol Succinate Extended Release Tablets should not be increased until symptoms of worsening heart failure have been stabilized.

4.3 Contraindications

Metoprolol Succinate Extended Release Tablets is contraindicated in severe bradycardia, second or third degree heart block, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), and in patients who are hypersensitive to any component of this product.

Effect of food on medicine administration

Compared to fasted state administration, high-fat, high-calorie meal (54.3% fat, 15.6% proteins and 30.1% carbohydrates) did not have a significant effect on the absorption of metoprolol succinate extended-release capsule.

200 mg metoprolol succinate extended release capsule administered under fasting conditions to healthy adults by sprinkling the entire contents on one-tablespoon (15 mL) of applesauce did not significantly affect T_{max}, C_{max}, and AUC of metoprolol

4.4 Special warnings and precautions for use

Ischemic Heart Disease

Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing

chronically administered Metoprolol Succinate Extended Release Tablets, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1 - 2 weeks and monitor the patient. If angina markedly worsens or acute coronary ischemia develops, promptly reinstate Metoprolol Succinate Extended Release Tablets, and take measures appropriate for the management of unstable angina. Warn patients not to interrupt therapy without their physician's advice. Because coronary artery disease is common and may be unrecognized, avoid abruptly discontinuing Metoprolol Succinate Extended Release Tabletsin patients treated only for hypertension.

Heart Failure

Worsening cardiac failure may occur during up-titration of Metoprolol Succinate Extended Release Tablets. If such symptoms occur, increase diuretics and restore clinical stability before advancing the dose of Metoprolol Succinate Extended Release Tablets. It may be necessary to lower the dose of Metoprolol Succinate Extended Release Tablets or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of Metoprolol Succinate Extended Release Tablets.

Bronchospastic Disease

PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative beta1 cardio-selectivity, however, Metoprolol Succinate Extended Release Tablets may be used in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Because beta1-selectivity is not absolute, use the lowest possible dose of Metoprolol Succinate Extended Release Tablets. Bronchodilators, including beta2-agonists, should be readily available or administered concomitantly.

Pheochromocytoma

If Metoprolol Succinate Extended Release Tablets is used in the setting of pheochromocytoma, it should be given in combination with an alpha blocker, and only after the alpha blocker has been initiated. Administration of beta-blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure due to the attenuation of beta-mediated vasodilatation in skeletal muscle.

Major Surgery

Avoid initiation of a high-dose regimen of extended-release metoprolol in patients undergoing non-cardiac surgery, since 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, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Diabetes and Hypoglycemia

Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Hepatic Impairment

Consider initiating Metoprolol Succinate Extended Release Tablets therapy at doses lower than those recommended for a given indication; gradually increase dosage to optimize therapy, while monitoring closely for adverse events.

Thyrotoxicosis

Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of beta-blockade may precipitate a thyroid storm.

Anaphylactic Reaction

While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge and may be unresponsive to the usual doses of epinephrine used to treat an allergic reaction.

Peripheral Vascular Disease

Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.

Calcium Channel Blockers

Because of significant inotropic and chronotropic effects in patients treated with betablockers and calcium channel blockers of the verapamil and diltiazem type, caution should be exercised in patients treated with these agents concomitantly.

4.5 Interaction with other medicinal products and other forms of interaction

Catecholamine Depleting Drugs

Catecholamine depleting drugs (eg, reserpine, monoamine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents. Observe patients treated with Metoprolol Succinate Extended Release Tablets plus a catecholamine depletor for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

CYP2D6 Inhibitors

Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone are likely to increase metoprolol concentration. In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg and immediate-release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, coadministration of propafenone 150 mg t.i.d. with immediate-release metoprolol 50 mg t.i.d. resulted in two- to five-fold increases in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardioselectivity of metoprolol.

Digitalis, Clonidine, and Calcium Channel Blockers

Digitalis glycosides, clonidine, diltiazem and verapamil slow atrioventricular conduction and decrease heart rate. Concomitant use with beta blockers can increase the risk of bradycardia. If clonidine and a beta blocker, such as metoprolol are coadministered, withdraw the betablocker several days before the gradual withdrawal of clonidine because beta-blockers may exacerbate the rebound hypertension that can follow the withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, delay the introduction of beta-blockers for several days after clonidine administration has stopped

4.6 Pregnancy and lactation

Pregnancy

Pregnancy Category C

Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 22 times, on a mg/m2 basis, the daily dose of 200 mg in a 60-kg

patient. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.

Nursing Mothers

Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Consider possible infant exposure when Metoprolol Succinate Extended Release Tablets is administered to a nursing woman.

Pediatric Use

One hundred forty-four hypertensive pediatric patients aged 6 to 16 years were randomized to placebo or to one of three dose levels of Metoprolol Succinate Extended Release Tablets (0.2, 1.0 or 2.0 mg/kg once daily) and followed for 4 weeks. The study did not meet its primary endpoint (dose response for reduction in SBP). Some pre-specified secondary endpoints demonstrated effectiveness including:

• Dose-response for reduction in DBP,

• 1.0 mg/kg vs. placebo for change in SBP, and

• 2.0 mg/kg vs. placebo for change in SBP and DBP.

The mean placebo corrected reductions in SBP ranged from 3 to 6 mmHg, and DBP from 1 to 5 mmHg. Mean reduction in heart rate ranged from 5 to 7 bpm but considerably greater reductions were seen in some individuals.

No clinically relevant differences in the adverse event profile were observed for pediatric patients aged 6 to 16 years as compared with adult patients.

Safety and effectiveness of Metoprolol Succinate Extended-Release Tablets have not been established in patients < 6 years of age.

Geriatric Use

Clinical studies of Metoprolol Succinate Extended Release Tablets in hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience in hypertensive patients has not identified differences in responses between elderly and younger patients.

Of the 1,990 patients with heart failure randomized to Metoprolol Succinate Extended Release Tablets in the MERIT-HF trial, 50% (990) were 65 years of age and older and 12% (238) were 75 years of age and older. There were no notable differences in efficacy or the rate of adverse reactions between older and younger patients.

In general, use a low initial starting dose in elderly patients given their greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic Impairment

No studies have been performed with Metoprolol Succinate Extended Release Tablets in patients with hepatic impairment. Because Metoprolol Succinate Extended Release Tablets is metabolized by the liver, metoprolol blood levels are likely to increase substantially with poor hepatic function. Therefore, initiate therapy at doses lower than those recommended for a given indication; and increase doses gradually in patients with impaired hepatic function.

Renal Impairment

The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. No reduction in dosage is needed in patients with chronic renal failure.

4.7 Effects on ability to drive and use machines

Dizziness or tiredness may occur during treatment with Metoprolol Succinate Extended Release Tablets. These effects can influence reactions to such an extend that the ability to drive, use machine and work in potentially hazardous situations may be impaired. This is particularly the case after concomitant ingestion of alcohol and also after a changeover of the preparation.

4.8 Undesirable effects

The following are the adverse reactions:

• Worsening angina or myocardial infarction.

• Worsening heart failure.

• Worsening AV block.

Hypertension and Angina Most adverse effects have been mild and transient. The following adverse reactions have been reported for Metoprolol Succinate Extended Release Tablets.

Metoprolol Succinate Extended Release Tablets is well tolerated and adverse reactions have generally been mild and reversible. The following events have been reported as adverse events in clinical trials or reported from routine use, mostly with conventional metoprolol. Cardiovascular: Cold extremities, arterial insufficiency (usually of the Raynaud type), palpitations, peripheral edema, syncope, chest pain and hypotension.

Respiratory: Wheezing (bronchospasm), dyspnea. Central Nervous System: Confusion, short term memory loss, headache, somnolence, nightmares, insomnia, anxiety/nervousness, hallucinations, paresthesia.

Gastrointestinal: Nausea, dry mouth, constipation, flatulence, heartburn, hepatitis, vomiting.

Hypersensitive 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 listed above that have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Metoprolol Succinate Extended Release Tablets.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, clouded sensorium, and decreased performance on neuropsychometrics.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Laryngospasm, respiratory distress.

Laboratory Test Findings Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

4.9 Overdose

Signs and Symptoms - Overdosage of Metoprolol Succinate Extended Release Tablets may lead to severe bradycardia, hypotension, and cardiogenic shock. Clinical presentation can also include: atrioventricular block, heart failure, bronchospasm, hypoxia, impairment 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 hemodynamic instability. Seek

consultation with a regional poison control center and a medical toxicologist as needed. Betablocker overdose may result in significant resistance to resuscitation with adrenergic agents, including beta-agonists. On the basis of the pharmacologic actions of metoprolol, employ the following measures.

There is very limited experience with the use of hemodialysis to remove metoprolol, however metoprolol is not highly protein bound.

Bradycardia: Evaluate the need for atropine, adrenergic-stimulating drugs or pacemaker to treat bradycardia and conduction disorders.

Hypotension: Treat underlying bradycardia. Consider intravenous vasopressor infusion, such as dopamine or norepinephrine.

Heart failure and shock: May be treated when appropriate with suitable volume expansion, injection of glucagon (if necessary, followed by an intravenous infusion of glucagon), intravenous administration of adrenergic drugs such as dobutamine, with α1 receptor agonistic drugs added in presence of vasodilation.

Bronchospasm: Can usually be reversed by bronchodilators.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties:

Pharmacotherapeutic group: beta blockers

ATC code: C07AB02

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

Metoprolol is a beta1-selective (cardioselective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits beta2-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade.

Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.

The relative beta1-selectivity of metoprolol has been confirmed by the following: (1) In normal subjects, metoprolol is unable to reverse the beta2-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective beta-blockers, which completely

reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, metoprolol reduces FEV1 and FVC significantly less than a nonselective beta-blocker, propranolol, at equivalent beta1-receptor blocking doses.

The relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation. Using an Emax model, the maximum effect is a 30% reduction in exercise heart rate, which is attributed to beta1-blockade. Beta1-blocking effects in the range of 30-80% of the maximal effect (approximately 8-23% reduction in exercise heart rate) correspond to metoprolol plasma concentrations from 30-540 nmol/L. The relative beta1 ¬ selectivity of metoprolol diminishes and blockade of beta2-adrenoceptors increases at plasma concentration 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 stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta-blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta2-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

In other studies, treatment with Metoprolol Succinate Extended Release Tablets produced an improvement in left ventricular ejection fraction. Metoprolol Succinate Extended Release Tablets was also shown to delay the increase in left ventricular end-systolic and end-diastolic volumes after 6 months of treatment.

5.2 Pharmacokinetic properties

Adults: In man, absorption of metoprolol is rapid and complete. Plasma levels following oral administration of conventional metoprolol tablets, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism.

Metoprolol crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration.

Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Metoprolol is a racemic mixture of R- and S- enantiomers, and is primarily metabolized by CYP2D6. When administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype. Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from

approximately 3 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no beta-blocking activity.

Following intravenous administration of metoprolol, the urinary recovery of unchanged drug is approximately 10%. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in metoprolol succinate dosage is usually needed in patients with chronic renal failure.

Metoprolol is metabolized predominantly by CYP2D6, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by a number of drugs. Poor metabolizers and extensive metabolizers who concomitantly use CYP2D6 inhibiting drugs will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity.

In comparison to conventional metoprolol, the plasma metoprolol levels following administration of Metoprolol Succinate Extended Release Tablets are characterized by lower peaks, longer time to peak and significantly lower peak to trough variation. The peak plasma levels following once-daily administration of Metoprolol Succinate Extended Release Tablets average one-fourth to one-half the peak plasma levels obtained following a corresponding dose of conventional metoprolol, administered once daily or in divided doses. At steady state the average bioavailability of metoprolol following administration of Metoprolol Succinate Extended Release Tablets, across the dosage range of 50 to 400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol.

Nevertheless, over the 24-hour dosing interval, β1-blockade is comparable and dose. The bioavailability of metoprolol shows a dose-related, although not directly proportional, increase with dose and is not significantly affected by food following Metoprolol Succinate Extended Release Tablets administration.

Pediatrics: The pharmacokinetic profile of Metoprolol Succinate Extended Release Tablets was studied in 120 pediatric hypertensive patients (6-17 years of age) receiving doses ranging from 12.5 to 200 mg once daily. The pharmacokinetics of metoprolol were similar to those described previously in adults. Age, gender, race, and ideal body weight had no significant effects on metoprolol pharmacokinetics. Metoprolol apparent oral clearance (CL/F) increased linearly with body weight. Metoprolol pharmacokinetics have not been investigated in patients < 6 years of age.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose Spheres (Celphere-CP203) USP-NF, Ethylcellulose 10cps USP-NF, Colloidal silicon dioxide USP-NF, Isopropyl Alcohol USP, Purified Water USP Metoprolol Succinate USP, Colloidal silicon dioxide USP-NF, Hypromellose E05 USP, Polyethylene Glycol 6000 USP-NF, Crospovidone XL 10 USP-NF, Sodium Stearyl Fumarate USP-NF, Opadry White IH, Methylene Chloride USP-NF, Methyl Alcohol USP-NF.

Qualitative composition of Opadry white 03B28796

Ingredients/Compendial Reference	% w/w	CFR Reference
HPMC 2910/ Hypromellose (USP/NF, PhEur, JP)	62.5 %	172.874
Titanium Dioxide (USP, FCC, PhEur, JP)	31.50 %	73.575, 73.15,75
Macrogol/PEG (NF, FCC, PhEur, JECFA, JP)	6.50 %	172.820

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Keep out of the reach and sight of children.

Protect from light and moisture.

Do not store above 30oC

6.5 Nature and contents of container

Tablets are packed in Alu/Alu blisters of 3 x 10's.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER-

Applicant:

MEGA LIFESCIENCE (AUSTRAUA) PTY LTD

Victoria 3810, Australia.

Manufactured by:

Inventia Healthcare Limited,

F1-F1/1-F75/1, Additional Ambernath M.I.D.C,

Ambernath (East), Thane 421506

Maharashtra State, India.

8. MARKETING AUTHORISATION NUMBER(S)—NA

08790/08727/NMR/2020
09526/08791/VAR/2023

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION--

Mar 12, 2024

10. DATE OF REVISION OF THE TEXT—NA