SUMMARY OF PRODUCT CHARACTERISTICS

1.NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Product Name : Miopolol ER 25 (Metoprolol Succinate Extended release Tablets USP 25 mg)

Strength : 25 mg

Pharmaceutical Dosage Form : White, oval, biconvex, film-coated tablet, scored and debossed with "2"and "5" on one side and scored on other side.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each extended release tablet contains:
Metoprolol Succinate 23.75 mg equivalent to
Metoprolol Tartrate USP…….25 mg

Quantitative Composition

S. No.	Name of Ingredients
A.	**SEAL COATING**
1	Microcrystalline Cellulose Spheres (Celphere-CP203)
2	Ethylcellulose 10cps
3	Colloidal silicon dioxide
4	Isopropyl Alcohol^
5	Purified Water^
B.	**DRUG COATING**
6	Metoprolol Succinate$
7	Colloidal silicon dioxide
8	Purified Water^
C.	**EXTENDED RELEASE COATING**
9	Ethylcellulose 10cps
10	Hypromellose E05
11	Colloidal silicon dioxide
12	Isopropyl Alcohol^

13	Purified Water^
D.	**PROTECTIVE COATING**
14	Polyethylene Glycol
15	Colloidal silicon dioxide
16	Isopropyl Alcohol^
17	Purified Water^
E.	**LUBRICATION**
18	Microcrystalline Cellulose
19	Polyethylene Glycol 6000
20	Crospovidone XL 10
21	Sodium Stearyl Fumarate
	Film Coating
22	Opadry White
23	Methylene Chloride
24	Methyl Alcohol
	TOTAL

3. PHARMACEUTICAL FORM

White, oval, biconvex, film-coated tablet, scored and debossed with "2"and "5" on one side and scored on other side.

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 hi gh bl ood pr essure should be pa rt of c omprehensive c ardiovascular r isk management, i ncluding, as a ppropriate, lipid c ontrol, di abetes m anagement, 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 a ction, ha ve be en s hown i n r andomized c ontrolled t rials to r educe cardiovascular m orbidity a nd m ortality, a nd it c an be c oncluded that it is bl ood 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 i n t he r isk of s troke, bu t r eductions in m yocardial i nfarction a nd c ardiovascular mortality also have been seen regularly.

Elevated systolic or dias tolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of s evere hype rtension c an pr ovide s ubstantial benefit. R elative r isk r eduction f rom bl ood pressure r eduction i s s imilar a cross popul ations w ith v arying a bsolute risk, s o t he a bsolute benefit i s gr eater i n pa tients w ho a re a t hi gher risk i ndependent of t heir hype rtension (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 a ngina, he art f ailure, or d iabetic ki dney di sease). T hese considerations may guide selection of therapy.

Metoprolol s uccinate e xtended-release t ablets m ay be adm inistered 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 E xtended Release T ablets i s indicated for t he t reatment of st able, symptomatic (N YHA C lass II or I II) h eart f ailure of is chemic, hypertensive, or cardiomyopathic origin. It was studied in patients already receiving ACE inhibitors, diuretics, and, i n t he majority of cases, d igitalis. I n t his popul ation, M etoprolol S uccinate Extended Release T ablets d ecreased the rate of mortality plus ho spitalization, largely through a reduction in cardiovascular mortality and hospitalizations for heart failure.

4.2 Posology and method of administration

Metoprolol Succinate E xtended Release T abletsis an extended-release tablet in tended for once da ily a dministration. F or t reatment of hyp ertension a nd a ngina, when s witching f rom immediate-release metoprolol to extended release metoprolol, use the same total daily dose of

Metoprolol Succinate E xtended R elease T ablets. I ndividualize t he do sage of M etoprolol Succinate Extended Release Tablets. Titration may be needed in some patients.

Metoprolol Succinate Extended Release Tablets are scored and can be divided; however, do not crush or chew the whole or half tablet.

Hypertension

Adults: The usual initial dosage is 25 t o 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); how ever some othe r endpoints de monstrated effectiveness. If s elected for treatment, the r ecommended starting dose of Met oprolol S uccinate Extended Release T abletsis 1.0 mg/kg once daily, but the maximum initial dose should not exceed 50 mg once daily. Dosage should be a djusted a ccording t o bl ood pr essure r esponse. Doses a bove 2.0 mg/kg (or i n excess of 200 mg) once daily have not been studied in pediatric patients.

Metoprolol Succinate Extended Release Tabletsis 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 1 00 m g da ily, gi ven i n a s ingle do se. Gradually i ncrease t he dos age at w eekly 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 25 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 dos age l evel t olerated by t he pa tient or up t o 200 mg o f M etoprolol S uccinate Extended Release Tablets. Initial difficulty with titration should not preclude later attempts to introduce Met oprolol S uccinate E xtended Release T ablets. If pa tients expe rience symptomatic brady cardia, reduce the dos e o f Met oprolol S uccinate E xtended R elease Tablets. If transient worsening of heart failure occurs, consider treating with increased doses of di uretics, l owering t he dos e of M etoprolol S uccinate E xtended Release T abletsor temporarily di scontinuing i t. T he dos e of M etoprolol S uccinate E xtended R elease Tabletsshould not be i ncreased unt il s ymptoms of w orsening he art f ailure ha ve be en stabilized.

4.3 Contraindications

Metoprolol Succinate E xtended R elease T ablets i s contraindicated in severe brad ycardia, second or t hird degree heart bloc k, car diogenic shoc k, decompensated car diac f ailure, sick sinus syndr ome (unless a pe rmanent pa cemaker i s i n place), and in patients w ho are hypersensitive to any component of this product.

4.4 Special warnings and precautions for use

Ischemic Heart Disease

Following a brupt c essation of t herapy w ith c ertain be ta-blocking a gents, e xacerbations o f angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administeredMetoprolol S uccinate Extended Release T ablets, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1 - 2 weeks and monitor t he pa tient. I f a ngina markedly w orsens or a cute c oronary i schemia de velops, promptly r einstate M etoprolol S uccinate E xtended R elease T ablets, a nd t ake measures appropriate for t he management of unstable a ngina. Warn pa tients not t o i nterrupt t herapy without t heir phys ician's a dvice. B ecause c oronary artery disease is c ommon and may be unrecognized, a void a bruptly d iscontinuing Metoprolol S uccinate E xtended R elease Tabletsin patients treated only for hypertension.

Heart Failure

Worsening cardiac failure may occur during up-titration of Metoprolol Succinate Extended Release T ablets. If suc h symptoms oc cur, increase diu retics and restore cl inical st ability before a dvancing the d ose of M etoprolol S uccinate E xtended R elease T ablets. It m ay be necessary to lower the dose of Metoprolol Succinate Extended Release Tabletsor temporarily discontinue it. Such episodes do not preclude subsequent successful t itration of Metoprolol Succinate Extended Release Tablets.

Bronchospastic Disease

PATIENTS W ITH BRONCHOSPASTIC D ISEASES SH OULD, IN GENERAL, NOT RECEIVE BE TA-BLOCKERS. Because of i ts r elative be ta1 cardio-selectivity, h owever, 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 no t abs olute, use t he l owest pos sible dos e of Metoprolol Succinate Extended R elease T ablets. B ronchodilators, i ncluding be ta2-agonists, s hould be r eadily available or administered concomitantly.

Pheochromocytoma

If M etoprolol S uccinate E xtended Release T abletsis us ed i n t he set ting 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 i nitiation of a hi gh-dose r egimen of e xtended-release m etoprolol in pa tients undergoing non-cardiac surgery, since such use i n patients with cardiovascular r isk factors has been associated with bradycardia, hypotension, stroke and death.

Chronically administered beta-blocking t herapy should not be r outinely withdrawn prior t o major s urgery, how ever, the i mpaired a bility o f t he he art t o r espond t o r eflex a drenergic 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 i nitiating M etoprolol S uccinate E xtended R elease Tabletstherapy a t dos es l ower than t hose recommended f or a gi ven i ndication; gr adually i ncrease dos age t o optimize therapy, while monitoring closely for adverse events.

Thyrotoxicosis

Beta-adrenergic blo ckade m ay mask certain clinical signs of hype rthyroidism, such as tachycardia. Abrupt withdrawal of beta-blockade may precipitate a thyroid storm.

Anaphylactic Reaction

While ta king beta-blockers, patients w ith a hi story of sev ere ana phylactic r eactions t o 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 si gnificant i notropic and chronotropic ef fects i n patients treated with beta-blockers 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 Tabletsplus 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 beta-blocker 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 Fertility, pregnancy and lactation

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 w eeks. The study did not meet its primary endpoint (dose r esponse f or r eduction i n S BP). S ome pr e-specified s econdary e ndpoints 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 m mHg. Mean r eduction i n h eart r ate r anged f rom 5 t o 7 bpm but c onsiderably gr eater reductions were seen in some individuals.
No clinically relevant d ifferences i n the adv erse eve nt pr ofile w ere o bserved for pediatric patients aged 6 to 16 years as compared with adult patients.
Safety and effectiveness of Met oprolol S uccinate E xtended-Release T ablets ha ve n ot be en established in patients < 6 years of age.

Geriatric Use
Clinical s tudies of M etoprolol Succinate Extended Release Tablets i n hypertension di d 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 t he 1,990 pa tients with he art failure randomized t o Metoprolol Succinate E xtended 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 not able 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 h epatic, r enal, or c ardiac f unction, and of c oncomitant di sease or o ther d rug therapy.

Hepatic Impairment
No studies have be en performed with Metoprolol S uccinate E xtended Release T ablets i n patients with hepatic impairment. Because Metoprolol Succinate Extended Release Tablets is

metabolized by the l iver, metoprolol bl ood levels a re l ikely to increase s ubstantially 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 sys temic ava ilability and half-life of metoprolol in patients w ith renal f ailure 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.

4.8 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 b een m ild a nd r eversible. T he f ollowing e vents ha ve be en r eported a s a dverse events in clinical trials or reported from routine use, mostly with conventional metoprolol.

Cardiovascular: C old extremities, arterial insufficiency (usually of t he R aynaud t ype), palpitations, peripheral edema, syncope, chest pain and hypotension.

Respiratory: Wheezing (bronchospasm), dyspnea. Central Nervous System: Confusion, short-term memory l oss, he adache, s omnolence, ni ghtmares, insomnia, a nxiety/nervousness, hallucinations, paresthesia.

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

Miscellaneous: Mus culoskeletal pa in, arthralgia, blurred vision, decreased libido, male impotence, t innitus, reversible a lopecia, a granulocytosis, d ry e yes, w orsening of ps oriasis, Peyronie's disease, sweating, photosensitivity, taste disturbance.

Potential Adverse Reactions:

In addition, there are adverse reactions not l isted above that have been reported with other beta-adrenergic bl ocking a gents a nd s hould be c onsidered pot ential a dverse r eactions t o Metoprolol Succinate Extended Release Tablets.

Central N ervous S ystem: R eversible m ental d epression progressing t o catatonia; an acute reversible syndrome characterized by disorientation for t ime and place, short-term me mory loss, e motional lability, c louded s ensorium, a nd de creased pe rformance 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: a trioventricular bl ock, he art f ailure, br onchospasm, hypo xia, impairment of consciousness/coma, nausea and vomiting.
Treatment – Consider t reating the pa tient w ith intensive car e. Patients w ith myocardial infarction o r he art f ailure m ay be pr one to s ignificant he modynamic i nstability. S eek consultation with a regional poison control center and a medical toxicologist as needed. Beta-blocker 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: E valuate t he ne ed f or a tropine, a drenergic-stimulating d rugs or p acemaker t o 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 gl ucagon (if ne cessary, f ollowed by a n i ntravenous i nfusion of gl ucagon), 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 pha rmacology s tudies ha ve c onfirmed t he be ta-blocking a ctivity of m etoprolol i n man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of s ystolic b lood pr essure upon e xercise, (3) inhibition of i soproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

Metoprolol is a be ta1-selective (cardioselective) a drenergic re ceptor bl ocking 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 i ntrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable o nly a t pl asma c oncentrations m uch gr eater than r equired f or be ta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.

The r elative be ta1-selectivity of m etoprolol ha s be en c onfirmed by t he f ollowing: (1) In normal s ubjects, metoprolol is unable to reverse the beta2-mediated vasodilating effects of epinephrine. This contrasts with the e ffect 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 re lationship between plasma m etoprolol levels and reduction in e xercise heart rate is independent of the pharmaceutical formulation. Using an Emax model, the maximum effect is a 30% reduction in e xercise h eart ra te, which is a ttributed to beta1-blockade. Beta1-blocking e ffects i n t he r ange of 30-80% of t he m aximal e ffect (approximately 8 -23% reduction in exercise heart rate) correspond to metoprolol plasma concentrations from 30-540 nmol/L. T he r elative b eta1 ¬ s electivity of m etoprolol di minishes a nd bl ockade of be ta2-adrenoceptors increases at plasma concentration above 300 nmol/L.

Although b eta-adrenergic r eceptor bloc kade i s useful i n t he t reatment of a ngina, hypertension, and heart failure there are situations in which sympathetic stimulation is vital. In pa tients with s everely da maged he arts, a dequate ve ntricular f unction m ay de pend on sympathetic dri ve. In the presen ce of A V bl ock, be ta-blockade m ay prevent the n ecessary facilitating effect of sympathetic activity on conduction. Beta2-adrenergic blockade results in passive b ronchial c onstriction by i nterfering w ith e ndogenous a drenergic b ronchodilator activity in patients s ubject t o br onchospasm a nd may also i nterfere w ith e xogenous bronchodilators in such patients.

In other studies, treatment with Metoprolol Succinate Extended Release Tablets produced an improvement in left ve ntricular e jection fraction. Metoprolol S uccinate 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 c onventional m etoprolol t ablets, h owever, a pproximate 50% of l evels following i ntravenous a dministration, i ndicating a bout 50% f irst-pass m etabolism. Metoprolol cr osses t he blood -brain ba rrier and ha s be en r eported i n t he C SF i n 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 m ainly by bi otransformation i n t he l iver, a nd t he plasma ha lf-life r anges fr om approximately 3 to 7 h ours. L ess t han 5% of a n or al do se of m etoprolol i s r ecovered 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 f ailure do not di ffer to a c linically significant de gree f rom thos e in normal s ubjects. 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 b y a num ber of dr ugs. P oor m etabolizers a nd e xtensive m etabolizers w ho concomitantly us e C YP2D6 i nhibiting dr ugs w ill ha ve i ncreased (several-fold) m etoprolol blood levels, decreasing metoprolol's cardioselectivity.

In c omparison t o c onventional metoprolol, t he pl asma metoprolol levels f ollowing 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 on e-fourth t o o ne-half t he peak pl asma l evels obt ained f ollowing a c orresponding dose of conventional metoprolol, administered once daily or in divided doses. At steady state the a verage bi oavailability of metoprolol f ollowing a dministration of M etoprolol Succinate Extended R elease T ablets, a cross t he dos age r ange of 50 t o 400 m g onc e da ily, was 77% relative to t he c orresponding s ingle or di vided dos es of c onventional m etoprolol.

Nevertheless, ove r t he 24 -hour dosing interval, β1-blockade i s c omparable a nd dos e. T he bioavailability of metoprolol s hows a dos e-related, a lthough not di rectly pr oportional, increase with dose and is not significantly affected by f ood following Metoprolol Succinate Extended Release Tablets administration.

Pediatrics: The pha rmacokinetic p rofile of Met oprolol S uccinate E xtended Release T ablets was studied in 120 pediatric hypertensive patients (6-17 years of age) receiving doses ranging from 12.5 t o 200 mg once daily. The pharmacokinetics of metoprolol were similar to those described previously in adults. Age, gender, race, and ideal body w eight had no s ignificant effects on metoprolol pharmacokinetics. Metoprolol apparent oral clearance (CL/F) increased linearly w ith body w eight. M etoprolol pha rmacokinetics h ave not b een i nvestigated i n patients < 6 years of age.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose Spheres USP-NF, Ethylcellulose USP-NF, Colloidal Silicon Dioxide USP-NF, Isopropyl Alcohol USP, Hypromellose USP, Polyehtylene Glycol 6000 USP-NF, Microcrystalline Cellulose USP-NF, Crospovidone XL USP-NF, Sodium Stearyl Fumarate USP-NF, Opadry White In House , Methylene Chloride USP-NF , Methyl Alcohol USP-NF
.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Store below 30 °C . Protect from light and moisture. Keep out of reach of children.

6.5 Nature and contents of container

Blister of 10 Tablets.
Box containing 30 tablets

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER-

MEGA LIFESCIENCE (AUSTRAUA) PTY LTD
Victoria 3810, Australia.

8. MARKETING AUTHORISATION NUMBER(S)—

08726/NMR/2020

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

Jul 21, 2023

10. DATE OF REVISION OF THE TEXT—NA