For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

TOLOL XR

1. Generic Name

Metoprolol Succinate Prolonged-Release Tablets I.P.

2. Qualitative and quantitative composition

TOLOL XR 12.5

Each film coated prolonged-release tablet contains:

Metoprolol Succinate I.P……. 11.88 mg

equivalent to Metoprolol Tartrate…… 12.5 mg

Excipients…… q.s.

Colours: Red Oxide of Iron & Titanium Dioxide I.P.

The excipients used are Polyvinyl Pyrrolidone K30, Isopropyl Alcohol, Carbopol, Microcrystalline Cellulose, Hydroxy Propyl Methyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Poly Ethylene Glycol, Titanium Dioxide, Red Oxide of Iron.

TOLOL XR 25

Each film coated prolonged-release tablet contains:

Metoprolol Succinate I.P…….. 23.75 mg

equivalent to Metoprolol Tartrate…… 25 mg

Excipients…… q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Polyvinyl Pyrrolidone K30, Isopropyl Alcohol, Carbopol, Microcrystalline Cellulose, Hydroxy Propyl Methyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Poly Ethylene Glycol, Titanium Dioxide.

TOLOL XR 50

Each film coated prolonged-release tablet contains:

Metoprolol Succinate I.P …….47.5 mg

equivalent to Metoprolol Tartrate…… 50 mg

Excipients…… q.s.

Colour: Lake of Sunset Yellow & Titanium Dioxide I.P.

The excipients used are Polyvinyl Pyrrolidone K30, Isopropyl Alcohol, Carbopol, Microcrystalline Cellulose, Hydroxy Propyl Methyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Poly Ethylene Glycol, Titanium Dioxide, Lake Of Sunset Yellow.

TOLOL XR 100

Each film coated prolonged-release tablet contains:

Metoprolol Succinate I.P…… 95 mg

equivalent to Metoprolol Tartrate…… 100 mg

Excipients…… q.s.

Colours: Lake of Brilliant Blue and Titanium Dioxide I.P.

The excipients used are Polyvinyl Pyrrolidone K30, Isopropyl Alcohol, Carbopol, Microcrystalline Cellulose, Hydroxy Propyl Methyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Poly Ethylene Glycol, Titanium Dioxide, Lake Of Brilliant Blue.

3. Dosage form and strength

TOLOL XR 12.5

Film coated prolonged-release tablet 12.5 mg

TOLOL XR 25

Film coated prolonged-release tablet 25 mg

TOLOL XR 50

Film coated prolonged-release tablet 50 mg

TOLOL XR 100

Film coated prolonged-release tablet 100 mg

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of essential hypertension in adults.

4.2 Posology and method of administration

Posology

The dose must always be adjusted to the individual requirements of the patient but should not exceed 400 mg/day. The following are guidelines:

Adults:

Hypertension: Initially 100 mg daily. This may be increased, if necessary, to 200 mg daily in single or divided doses. Combination therapy with another antihypertensive agent may also be considered to further reduce blood pressure.

Angina pectoris: Usually 50-100 mg twice daily. The dose may be further increased or combined with nitrates.

Tachycardiac arrhythmias: A daily dose of 100 -200 mg is usually sufficient. If necessary the dose may be increased.

After acute intravenous treatment of myocardial infarction: Orally, therapy should commence 15 minutes after the last intravenous injection with 50 mg every 6 hours for 48 hours.

Prophylaxis after myocardial infarction: Maintenance dose is 100 mg twice daily.

Prophylaxis of migraine: 50-100 mg twice daily.

Patients with renal impairment

The rate of elimination is insignificantly affected by renal function and therefore no dose adjustment is needed.

Patients with hepatic impairment

Usually metoprolol can be given at the same dose to patients with cirrhosis of the liver as to patients

with normal hepatic function. A dose reduction should only be considered when there are signs of severely impaired hepatic function (i.e. shunt operated patients).

Elderly patients

There are no adequate data from the use in patients above the age of 80. Take special precautions when increasing the dose. However, caution is advised in elderly patients as a fall in blood pressure or excessive bradycardia may have more pronounced effects.

Paediatric population:

There is limited data on the use of metoprolol in children and adolescents, therefore the use of Tolol XR is not recommended.

Method of administration

The tablets should be taken on an empty stomach. The tablet should not be swallowed as a whole. It should not be crushed or chewed.

4.3 Contraindications

- Hypersensitivity to metoprolol, other beta blockers or to any of the excipients
- Grade II or III atrioventricular block.
- Patients with unstable or acute decompensated heart failure (pulmonary oedema, hypoperfusion or hypotension), in which case continuous or periodical intrave nous inotropic β receptor agonist therapy is indicated.
- 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.
- Higher grade sinoatrial block

Metoprolol may not be administered to patients with suspected acute myocardial infarct ion and a heart rate of < 50 beats/min., PQ interval > 0.24 seconds or systolic blood pressure < 100 mmHg.

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

Untreated phaeochromocytoma.

4.4 Special warnings and precautions for use

Beta blockers must be administered with caution to asthmatics. If an asthmatic uses a beta-2 agonist (as tablets or by inhalation) when initiating metoprolol treatment, the dose

of the beta-2 agonist must be controlled and increased if necessary.

Metoprolol may reduce the effect of diabetes treatment and mask the symptoms of hypoglycaemia.

AV conduction disorders may be aggravated in rare cases in connection with metoprolol treatment (possible atrioventricular block). Beta-blockers should be given only with caution to patients with first degree atrioventricular block.

Metoprolol may exacerbate the symptoms of peripheral vascular disorders due to its antihypertensive effect.

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

In patients with Prinzmetal's angina β1 selctive agents should be used with care because may increase the number and duration of angina attacks.

Metoprolol treatment may possibly mask the symptoms of thyreotoxicosis. Therefore, metoprolol should be administered with caution to patients having or suspected of developing thyreotoxicosis and both thyroid and cardiac functions should be monitored closely.

Before surgery, the anaesthesiologist must be informed that the patient takes beta blockers. It is not recommended to discontinue beta blocker treatment during a surgical procedure.

Beta blocker treatment must not be suddenly discontinued. If the treatment is to be discontinued, it must, where possible, be gradually reduced over a period of at least two weeks during which the dose is withdrawn gradually, the doses diminishing to 25 mg for the last 6 days before the treatment is discontinued. If the patient presents with any symptoms, the dose should be reduced at a lower rate. Sudden discontinuation of beta blockers may possibly exacerbate heart failure and increase the risk of myocardial infarction and sudden death.

Like other beta blockers, metoprolol may also increase both the sensitivity to allergens and the severity of anaphylactic reactions. Adrenalin treatment does not always give the desired therapeutic effect in individuals receiving beta blockers.

Beta blockers may trigger or exacerbate psoriasis.

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.

In the case of increasing bradycardia the dosage should be reduced, or treatment gradually discontinued.

Metoprolol may not be administered to patients with untreated congestive heart failure. The congestive heart failure needs to be brought under control first of all. If concomita nt digoxin treatment is taking place, it must be borne in mind that both medicina l products slow AV conduction and that there is therefore a risk of AV dissociation. In addition, mild cardiovascular complications may occur, manifesting as dizziness, bradycardia, and a tendency to collapse.

Dry eyes either alone or, occasionally, with skin rashes has occurred. In most cases the symptoms cleared

when metoprolol treatment was withdrawn. Patients should be observed carefully for potential ocular effects. If such effects occur, discontinuation of metoprolol should be considered.

4.5 Drugs interactions

The following combinations with metoprolol should be avoided:

Barbituric acid derivatives Barbiturates (studied for pentobarbital) induce the metabolism of metoprolol through enzyme induction.

Propafenon When propafenon was commenced in four patients, who were then treated with metoprolol, the plasma concentrations of metoprolol increased 2-5-fold and two patients suffered typical metoprolol side effects. The interaction was confirmed in a study involving eight healthy research subjects. The interaction is probably due to the fact that propafenon, like quinidine, inhibits the metabolism of metoprolol via cytochrome P450 2D6. The combination is probably difficult to manage due to the fact that propafenon also has beta-receptor blocking properties.

Calcium antagonists In the case of the concomitant use of calcium antagonists of the verapamil or diltiazem types, an increase in negative inotropic and chronotropic effects can occur. Calcium antagonists of the verapamil type should not be administered intravenously to patients who are being treated with beta blockers, due to the risk of hypotension, AV conduction disturbances, and left ventricular insufficiency. In patients with impaired cardiac function, the combination is contraindicated. As with other beta- blockers, concomitant therapy with dihydropyridines (such as nifedipine and amlodipine), may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

The following combinations with metoprolol may require dose adjustment:

Amiodarone One case history indicates that patients treated with amiodarone can develop severe sinus bradycardia during concomitant treatment with metoprolol. Amiodarone has an extremely long half-life (approximately 50 days), which means that interactions can occur a long time after discontinuation of the preparation.

Class I-antiarrhythmics Class I-antiarrhythmics and beta-receptor blockers have additive negative inotropic effects, which can result in serious haemodynamic adverse reactions in patients with impaired left-ventricular function. The combination should be avoided in "sick sinus syndrome" and pathological AV-conduction. The interaction is best documented for disopyramide.

Non-steroidal anti-inflammatory drugs/antirheumatic agents (NSAID) NSAID-type antiphlogistics counteract the antihypertensive effect of beta-receptor blocking agents. Studies have primarily been performed on indomethacin. This interaction is not believed to occur with sulindac. It has not been possible to demonstrate such an interaction in a study relating to diclofenac.

CYP2D6 inhibitors Metoprolol is a CYP2D6-substrate. Drugs which inhibit this enzyme may increase the plasma concentration of metoprolol. Examples of clinically significant inhibitors of CYP2D6 are antidepressants such as fluoxetine, paroxetine or bupropion, antipsychotics such as thioridazine, antiarrhythmics such as propafenone, antiretrovirals such as ritonavir, antihistamines such as diphenhydramine, antimalarials such as hydroxychloroquine or quinidine, antifungals such as terbinafine and medications for stomach ulcers such as cimetidine. On commencement of treatment with these medicinal products in patients being treated with metoprolol the dose of metoprolol may need to be reduced.

Diphenhydramine Diphenhydramine reduces (2.5 times) clearance of metoprolol to alpha-hydroxymetoprolol in fast hydroxylaters via CYP 2 D6, at the same time as the effects of metoprolol are increased.

Digitalis glycosides Digitalis glycosides in connection with beta-receptor blockers, can increase the atrioventricular conduction time and induce bradycardia.

Epinephrine A dozen reports exist in respect of severe hypertension and bradycardia in patients treated with non-selective beta-receptor blockers (including pindolol and propanalol), who were administered epinephrine (adrenaline). These clinic a l observations have been confirmed in studies on healthy research subjects. It has also been suggested that epinephrine, administered as local anaesthesia, may give rise to these reactions on intravasal administration. The risk should be considerably less with cardioselective beta-receptor blockers.

Phenylpropanolamine Phenylpropanolamine (norephedrine) in single doses of 50 mg may increase the diastolic blood pressure to pathological levels in healthy research subjects. In general, propanolol counteracts the rise in blood pressure triggered by phenylpropanolamine. Beta-receptor blockers may, however, trigger paradoxical hypertensive reactions in patients taking high doses of phenylpropanolami ne.

Hypertensive crises during treatment solely with phenylpropanolamine have been described in a couple of cases.

Quinidine Quinidine inhibits the metabolism of metoprolol in so-ca led "fast hydroxylaters" (just over 90% in Sweden), with significantly increased plasma values and resultant increase in beta blockade. Similar reaction might be expected to occur with other beta-blockers which are metabolized by the same enzyme (cytochrome P450 2 D6).

Sympathetic ganglion blockers, or other beta blockers Patients who are concomita ntly receiving sympathetic ganglion blockers, or other beta blockers (including in the form of eye drops) must continue being monitored.

MAO inhibitors MAO inhibitors should be used with caution as concomita nt administration with beta-blockers may result in bradycardia and an enhanced hypotensive effect. Monitoring of blood pressure and heart rate are recommended during initial use.

Centrally-acting antihypertensives (clonidine, guanfacin, moxonidine, methyldopa, rilmenidine) Abrupt withdrawal, particularly if prior to beta-blocker discontinuat io n, may increase risk of "rebound hypertension".

The concomitant use of clonidine with a non-selective beta blocker, and possibly also with a selective beta blocker, increases the risk of rebound hypertension. If clonidine is administered concomitantly, the administration of the clonidine medication needs to be continued for some time after beta-blocker therapy is discontinued.

Paroxetine may increase plasma levels of metoprolol resulting in increased beta- blocking effects

Ergotamine As beta-blockers may affect the peripheral circulation, care should be exercised when drugs with similar activity, e.g. ergotamine are given concurrently

Nitrates Nitrates may enhance the hypotensive effect of metoprolol

Parasympathomimetics Concurrent use of parasympathomimetics may result prolonged bradycardia.

Sympathomimetics Metoprolol wi l antagonize the β1 effect of sympathomimetic agent but should have little influence on the bronchodilator effects of β2 agonists at normal therapeutic dose.

General anaesthetics An increase in the cardio-depressive effect due to the concomita nt administration of inhalational anaesthetics is possible; however, since beta blockade can prevent excessive fluctuations in blood pressure whilst the patient is intubated and is rapidly antagonised with beta sympathomimetics, concomitant use is not contraindicated.

Insulin and oral antidiabetic agents The blood glucose-reducing effect of insulin and oral blood glucose-reducing drugs can be intensified by beta blockers, in particular non-

selective beta blockers. In this case, the dosage of the oral blood glucose-reducing drug must be adjusted.

Alpha blockers such as prazosine, tamsulosin, terazosine, doxazosine Increased risk of hypotension, especially severe orthostatic hypotension.

Floctafenine: Beta blockers may impede the compensatory cardiovascular reactions associated with hypotension or shock that may be induced by floctafenine

Skeletal muscle relaxant Curare muscle relaxant with metoprolol enhanced neuromuscular blockade. Blood pressure should be monitored and dosage adjustment of the antihypertensive be made if necessary.

Lidocaine Metoprolol can reduce the clearance of lidocaine.

Hepatic enzyme inducers Enzyme inducing agents (e.g. rifampicin) may reduce plas ma concentrations of metoprolol.

Mefloquine Increased risk of bradycardia

Antacid An increase in the plasma concentrations of metoprolol has been observed when the drug was coadministered with an antacid.

Alcohol During concomitant ingestion of alcohol and metoprolol the concentration of blood alcohol may reach higher levels and may decrease more slowly.

The effects of metoprolol and other antihypertensive drugs on blood pressure are usually additive. Care should be taken when combining with other antihypertens ive drugs or drugs that might reduce blood pressure, such as tricyclic antidepressants, barbiturates and phenothiazines. However, combinations of antihypertensive drugs may often be used with benefits to improve control of hypertension.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy:

Since there are no well-controlled studies of the use of metoprolol in pregnant women, metoprolol may only be used during pregnancy if the benefits to the mother outweigh the risk to the embryo/foetus.

Beta blockers reduce placental perfusion and may cause foetal death and premature birth. Intrauterine growth retardation has been observed after long term treatment of pregnant women with mild to moderate hypertension. Beta blockers have been reported to cause prolonged delivery and bradycardia in the foetus and the newborn child. There are also reports of hypoglycaemia, hypotension, increased bilirubinaemia and inhib ited response to anoxia in newborn children. Therefore the lowest possible dose should be used, and treatment should be discontinued 48-72 hours before the calculated birth date. If this is not possible, the newborn child should be monitored for 48-72 hours post partum for signs and symptoms of beta blocking (e.g. cardiac and pulmonar y complications).

Beta blockers have not shown potential teratogenic activity in animals, but reduced blood flow in the umbilical cord, growth retardation, reduced ossification and increased numbers of foetal and post-natal deaths.

Breast-feeding:

The concentration of metoprolol in breast milk is approximately three times higher than the one in the mother's plasma. Even though the risk of adverse effects in the breastfeeding baby would appear to be low after administration of therapeutic doses of the medicinal product (except in individuals with poor metabolic capacity), breastfeeding babies should be monitored for signs of beta blocking.

4.7 Effects on ability to drive and use machines

As with all beta-blockers, metoprolol may affect patients' ability to drive and operate machinery. It

should be taken into account that occasionally dizziness or fatigue may occur. Patients should be warned accordingly. These effects may possibly be enhanced in case of concomitant ingestion of alcohol or after changing to another medicina l product.

4.8 Undesirable effects

Metoprolol is well tolerated, and the undesirable effects are generally mild and reversible. The most commonly reported adverse reactions during treatment is fatigue. Gangrene (in patients with severe peripheral circulatory disorder), thrombocytopenia and agranulocytosis may occur very rarely (less than 1 case per 10,000 patients).The following undesirable effects have been reported during the course of clinical studies or have been reported after routine use. In many cases, a link with the use of metoprolol (tartrate) has not been firmly established.

	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Very rare (< 1/10,000)
Blood and lymphatic system disorders					Thrombocyt openia, leukopenia
Endocrine disorders				Deterioration of latent diabetes mellitus.	
Metabolism and nutrition disorders			Weight gain.		
Psychiatric disorders			Depression, concentration problems, drowsiness or insomnia, nightmares.	Nervousness, anxiety.	Forgetfulnes s or memory impairment, confusion, hallucination s, personality changes (e.g.

					mood changes).
Nervous system disorders		Dizziness, headache.	Paresthesia.		
Eye disorders				Visual disturbances, dry or irritated eyes, conjunctivitis.	
Ear and labyrinth disorders					Tinnitus, hearing problems.
Cardiac disorders		Bradycardia, balance disturbances (very rarely with associated syncope), palpitations.	Temporary exacerbation of symptoms of heart failure, first-degree atrioventricular block, precordial pain.	Functional heart symptoms, heart arrhythmia, conductivity disturbances.	
Vascular disorders	Pronounced blood pressure drop and orthostatic hypotension, very rarely with syncope.	Cold hands and feet.			Necrosis in patients with severe peripheral vascular disorders prior to treatment, exacerbation of claudicatio intermittens or Raynaud's syndrome.
Respiratory, thoracic and mediastinal disorders		Functional dyspnea.	Bronchospasms.	Rhinitis.	
Gastrointestinal disorders		Nausea, abdominal pain, diarrhoea, constipation.	Vomiting.	Dryness of mouth.	Taste disturbances.
Hepatobiliary disorders				Abnormal LFT values.	Hepatitis.
Skin and subcutaneous tissue disorders			Rash (psoriasislike urticaria and dystrophic	Hair loss.	Light hypersensitivity reactions, exacerbation

			cutaneous lesions), increased perspiration.		of psoriasis, new psoriasis manifestation, psoriasis-like dermatological changes.
Musculoskeletal and connective tissue disorders			Muscle spasms.		Arthralgia, muscle weakness.
Reproductive system and breast disorders				Impotence and other sexual dysfunctions, induratio penis plastica (Peyronie's syndrome).	
General disorders and administration site conditions	Fatigue.		Oedema.		

4.9 Overdose

Toxicity:

7.5 g to an adult resulted in a lethal intoxication. 100 mg to a 5-year-old did not result in any symptoms after gastric lavage. 450 mg to a 12-year-old and 1.4 g to an adult resulted in moderate intoxication. 2.5 g to an adult resulted in a serious intoxication and

7.5 g to an adult resulted in a very serious intoxication.

Symptoms:

An overdose of metoprolol may cause severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, asystole, QT-prolongation (isolated cases), poor peripheral perfusion, bronchospasms, loss of consciousness (even coma), nausea, vomiting or cyanosis. Respiratory depression, apnea, fatigue, fine tremor, seizures, sweating, paraesthesias, possible oesophageal spasm, hypoglycaemia (especially in children) or hyperglycaemia, hyperkalaemia, renal effects, transient symptoms of myasthenia.

In certain cases, especially among children and adolescents, CNS-symptoms and respiratory depression may predominate.

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. The effects of massive overdose may persist for several days, despite declining plasma concentrations.

Management:

Patients should be admitted to hospital and, generally, should be managed in an intensive care setting, with continuous monitoring of cardiac function, blood gases, and blood biochemistry. Emergency supportive measures such as artificial ventilation or cardiac pacing should be instituted if appropriate. Even apparently well patients who have taken a small overdose should be closely observed for signs of poisoning for at least 4 hours.

Active charcoal, gastric lavage if necessary. NOTE! Atropine (0.25-0.5 mg i.v. to adults, 10-20 micrograms/kg to children) should be administered prior to gastric lavage (due to the risk of vagal stimulation). Intubation and assisted ventilation should occur based on a very wide indication. Adequate volume substitution. Glucose infusion. ECG monitoring. Atropine sulphate may be administered (0.5 - 2.0 mg intravenously) for blocking the vagus nerve. This can be repeated.

In case of severe hypotension, bradycardia or in risk of heart failure, the patient could be given a beta-1 agonist (e.g. prenalterol or isoprenaline) intravenously at intervals of 2-5 minutes or as continuous infusion until achieving the desired effect. If a selective beta-1 agonist is unavailable, dopamine may be used.

If the desired effect is not achieved, another sympathomimetic agent may be used, e.g. dobutamine or noradrenaline.

The patient may also be given 1-10 mg glucagon. It may be necessary to use a pacemaker. A beta-2 agonist may be administered intravenously to prevent bronchospasms in the patient, the patients should be monitored for evidence of cardiac arrhythmias during and after administration of the bronchodilator.

Note! The doses required for managing overdoses are much higher than the therapeutic doses usually applied as the beta blocker has blocked the beta receptors.

Note! In case of cardiac arrest after overdosage with a beta-blocker, cardiopulmonary resuscitation during several hours may be required.

5 Pharmacological properties

5.1 Mechanism of Action

Metoprolol is a beta-1 selective beta blocker.

It has a relatively greater blocking effect on beta receptors (i.e. those mediating adrenergic stimulation of heart rate and contractility and release of the fatty acids from fat stores) than on beta receptors which are chiefly involved in broncho and vasodilation.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blockers, selective. ATCcode: C 07 AB 02.

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.

If required, metoprolol may be administered concomitantly with a beta-2 agonist to patients with symptoms of obstructive pulmonary disease.

5.3 Pharmacokinetic properties

Absorption and distribution:

Metoprolol is completely absorbed after an oral dose, peak plasma concentrations occurring 1.5 – 2 hours after dosing. Due to a pronounced first passage metabolism for metoprolol, the bioavailability of a single oral dose is approx. 50 %. Concomitant intake of food increases bioavailability to approximately 70% Only a small fraction of metoprolol (approx. 5-10 %) binds to plasma proteins. Metoprolol crosses the placenta, and is found in breast milk.

Biotransformation and elimination:

Metoprolol is metabolised by hepatic oxidation. The three known main metabolite s 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 individua ls, 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.

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.

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.

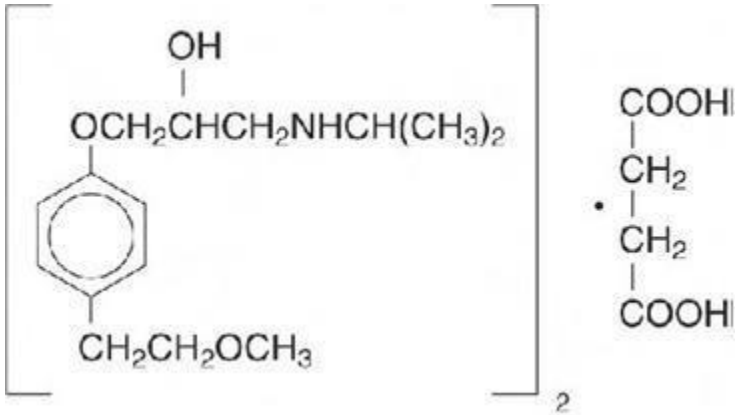
6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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

7 Description

Metoprolol Succinate is a beta1-selective (cardioselective) adrenoceptor blocking agent, for oral administration. Its chemical name is (±) 1-(isopropylamino)-3-[p-(2-methoxyet hyl) phenoxy]-2-propanol succinate (2:1) (salt) having molecular weight of 652.81. Its empirical formula is $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$ with structural formula of



TOLOL XR 12.5

Tolol XR 12.5 is pink coloured round biconvex film coated tablets plain on both sides. The excipients used are Polyvinyl Pyrrolidone K30, Isopropyl Alcohol, Carbopol, Microcrystalline Cellulose, Hydroxy Propyl Methyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Poly Ethylene Glycol, Titanium Dioxide, Red Oxide of Iron.

TOLOL XR 25

Tolol XR 25 is white to off-white coloured round biconvex film coated tablets plain on both sides. The excipients used are Polyvinyl Pyrrolidone K30, Isopropyl Alcohol, Carbopol, Microcrystalline Cellulose, Hydroxy Propyl Methyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Poly Ethylene Glycol, Titanium Dioxide.

TOLOL XR 50

Tolol XR 50 is orange coloured round biconvex film coated tablets plain on both sides. The excipients used are Polyvinyl Pyrrolidone K30, Isopropyl Alcohol, Carbopol, Microcrystalline Cellulose, Hydroxy Propyl Methyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Poly Ethylene Glycol, Titanium Dioxide, Lake Of Sunset Yellow.

TOLOL XR 100

Tolol XR 100 is blue coloured round biconvex film coated tablets plain on both sides. The excipients used are Polyvinyl Pyrrolidone K30, Isopropyl Alcohol, Carbopol, Microcrystalline Cellulose, Hydroxy Propyl Methyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Poly Ethylene Glycol, Titanium Dioxide, Lake Of Brilliant Blue.

8 Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

Tolol XR 12.5 is available in blister strips of 10 tablets Tolol XR 25 is available in blister pack of 10 tablets Tolol XR 50 is available in blister pack of 10 tablets Tolol XR 100 is available in blister strips of 10 tablets

8.4 Storage and handing instructions

Store at a temperature not exceeding 30°C. Protected from light and moisture.

9 Patient Counselling Information

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harmthem, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

9.1 What Tolol XR is and what it is used for

Tolol XR contains metoprolol tartrate, which belongs to a group of medicines called beta-blockers. Metoprolol tartrate reduces the effect of the stress hormones on the heart in connection with physical and mental exertion. This results in the heart beating slower (pulse rate is reduced).

It is used to treat:high blood pressure

- angina pectoris (pain in the chest caused by lack of oxygen in the heart)
- irregular heart rhythm (arrhythmia). In adults. It is used to prevent:
- migraine
- heart damage, heart death or further heart attacks after a heart attack. in adults.

9.2 What you need to know before you take Tolol XR

Do not take Tolol XR if: You

- are a lergic to metoprolol, other betablockers or any of the other ingredients of this medicine.
- have heart conduction problems (serious AV-block or sinoatrial block)
- suffer from sick sinus syndrome
- have untreated heart failure, are receiving treatment to increase heart contractions or are in shock caused by heart problems
- suffer from severely blocked blood vessels, including blood circulation problems (which may cause your fingers and toes to tingle or turn pale or blue)
- have a slow heart rate (less than 50 beats/ min)
- have low blood pressure
- suffer from increased acidity of the blood (metabolic acidosis)
- have severe asthma or COPD (chronic obstructive pulmonary disease)
- are receiving other blood pressure lowering medicines such as verapamil and diltiazam by intravenous injection. See also "Other medicines and Metoprolol"
- are using antiarrrhythmics such as disopyramide. See also "Other medicines and Metoprolol"
- have untreated high blood pressure due to tumour of the adrenal medulla (phaechromocytoma).

Warnings and precautions

Talk to your doctor or pharmacist before taking Tolol XR if you:

- have asthma
- have diabetes me litus (low blood sugar levels may be hidden by this medicine)
- have high blood pressure due to tumour of the adrenal medulla (treated phaeochromocytoma)
- are having treatment to reduce a lergic reactions. Metoprolol may increase your hypersensitivity to the substances you are allergic to and increase the severity of a lergic reactions • have an overactive thyroid, (symptoms such as increased heart rate, sweating, tremor, anxiety, increased appetite or weight loss may be hidden by this medicine)
- have or have suffered from skin rashes ca led psoriasis

• suffer from blood circulation problems (in the fingers, toes, arms and legs)

• suffer from a heart conduction disorder (AV block)

• have a type of chest pain ca led Prinzmetal's angina.

• have heart failure and one of the following:

• had a heart attack or angina attack in the last 28 days

• reduced kidney or liver function

• are under 40 years old or over 80 years old

• diseases of the heart valves

• enlarged heart muscle

• had heart surgery in the last 4 months

• have unstable heart failure.

If are going to have an anaesthetic, please tell your doctor or dentist that you are taking Metoprolol.

Children and adolescents

There is limited data on the use of metoprolol in children and adolescents, therefore the use of metoprolol is not recommended.

Other medicines and Tolol XR

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Tolol XR tablets can affect how some other medicines work, and some medicines an also affect how metoprolol work. If Tolol XR tablets are to be combined with the medicines listed below, you must consult your doctor before taking this medicine:

<u>The following combination with metoprolol should be avoided</u>:

• Barbituric acid derivatives e.g. phenobarbital (used to treat epilepsy)

• Propafenone, quinidine, verapamil, diltiazem, nifedipine and amlodipine (used to treat cardiovascular disease)

<u>The following combinations with metoprolol may require dose adjustment</u>:

• Amiodarone, disopyramide (for irregular heart rhythm)

• Indomethacin, sulindac, diclofenac and foctafenine (medicines used to reduce inflammation, fever and pain)

• Fluoxetine, paroxetine and bupropion (medicines used to treat depression)

• Thioridazine (antipsychotic)

• Ritonavir (antiretroviral)

• Diphenhydramine (antihistamine)

• Hydroxychloroquine, mefloquine (used in malaria)

• Terbinafine (for fungal infection of skin)

• Cimetidine (for ulcers)

• Digitalis glycosides such as digoxin (used in heart failure)

- Epinephrine (medicine used in acute shock and severe allergic reaction)
- Phenylpropanolamine (used to reduce swelling of the nasal mucosa)
- Other beta blockers e.g. eye drops
- Monoamine oxidase inhibitors (MAOIs) (used to treat depression and Parkinson's disease)
- Clonidine, guanfacin, moxonidine, methyldopa, rilmenidine (blood pressure lowering medicines) • Ergotamine (used in migraine)
- Nitrates such as nitroglycerine (used in angina)
- General anaesthetics
- Insulin and oral antidiabetic (for reducing blood sugar level) medicines
- Prazosine, tamsulosin, terazosine, doxazosine (alpha blockers, used to treat high blood pressure and benign prostatic hyperplasia)
- Lidocaine (local anaesthetic)
- Rifampicine (used to treat tuberculosis)
- Antacids (used for stomach upsets).

Tolol XR with alcohol

You are advised to avoid alcohol whilst taking this medicine. Alcohol may increase the blood pressure lowering effect of Metoprolol.

Pregnancy, breast-feeding and fertility

Tolol XR is not recommended during pregnancy or breastfeeding. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Tolol XR may make you feel tired and dizzy. Make sure you are not affected before you drive or operate machinery.

9.3 How to take Tolol XR

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Tolol XR should be taken without food and on an empty stomach. Tolol XR tablets can be divided into equal doses.

The recommended dose is:

- **High blood pressure:**

Initially 100 mg daily.

- **Angina pectoris:**

Usually 50-100 mg twice daily.

- **Irregular heart beats (arrhythmia):**

100-200 mg daily.

- **Preventive therapy after a heart attack:**

The usual maintenance dose is 100 mg twice daily.

- **Prevention of migraine:**

50-100 mg twice daily.

If you take more Tolol XR than you should

If you have accidentally taken more than the prescribed dose, contact your nearest casualty department or tell your doctor or pharmacist at once. Depending on the extent of the overdose, this can lead to excessive reduction in blood pressure and a decrease in heart rate. As a consequence of the failure of heart function, this can even lead to cardiac arrest, heart muscle weakness and shock. Other symptoms include problems in breathing, constriction of the muscles in the respiratory tract, vomiting, disturbances of consciousness and even occasionally generalized seizures.

If you forget to take Tolol XR

If you forget to take a dose, take it as soon as you remember, unless it is nearly time for your next dose. Then go on as before. Do not take a double dose to make up for a forgotten dose.

If you stop taking Tolol XR

Do not suddenly stop taking Tolol XR as this may cause worsening of heart failure and increase the risk of heart attack. Only change the dose or stop the treatment in consultation with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop treatment and contact a doctor at once if you have:

- an a lergic reaction such as itchy skin rash, flushing, swe ling of the face, lips, tongue or throat, or difficulty breathing or swallowing.

This is a very serious but rare side effect. You may need urgent medical attention or hospitalisation.

Tell your doctor if you notice any of the following side effects or notice any other effects not listed:

Very common (may affect more than 1 in 10 people):

- feeling faint on standing due to low blood pressure, tiredness.

Common (may affect up to 1 in 10 people):

- slow heart rate,
- difficulties in maintaining balance (very rare with fainting),
- cold hands and feet,
- palpitation,
- dizziness,
- headache,
- feeling sick,
- diarrhoea,
- constipation,

- stomach pain,
- shortness of breath with strenuous physical activity.

Uncommon (may affect up to 1 in 100 people):

- chest pain,
- weight gain,
- depression
- concentration problems
- inability to sleep (insomnia)
- drowsiness
- nightmares
- tingling in the skin,
- temporary worsening of symptoms of heart failure
- disturbances in the conduction of the heart
- spasmodic contraction of the smooth muscle of the bronchi (causing shortness breath),
- vomiting
- rashes
- increased sweating
- fluid retention
- muscle cramps

Rare (may affect up to 1 in 1,000 people):

- worsening of diabetes,
- nervousness,
- anxiety,
- visual disturbances,
- dry or irritated eyes,
- conjunctivitis,
- impotence, other sexual dysfunctions,
- Peyronie's syndrome (bending of penis on erection),
- irregular heart beat,
- heart conduction disturbances,
- dry mouth,
- runny nose,
- hair loss,
- changes in liver function tests.

Very rare (may affect up to 1 in 10,000 people):

- changes in blood cells, forgetfulness, memory impairment

- confusion,
- hallucinations,
- personality changes e.g. mood changes,
- ringing in the ears (tinnitus),
- hearing problems,
- taste changes,
- inflammation of the liver (hepatitis),
- sensitivity to light,
- worsening or new psoriasis, psoriasis like changes
- muscle weakness,
- joint pain,
- tissue death in patients with severe circulation disturbances

9.5 How to store Tolol XR

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister, carton and bottle label after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

9.6 Contents of the pack and other information

TOLOL XR 12.5

The active ingredient is Metoprolol Succinate I.P 11.88 mg equivalent to Metoprolol Tartrate 12.5 mg

The excipients used are Polyvinyl Pyrrolidone K30, Isopropyl Alcohol, Carbopol, Microcrystalline Cellulose, Hydroxy Propyl Methyl Cellulose, Colloidal Silicon

Dioxide, Magnesium Stearate, Poly Ethylene Glycol, Titanium Dioxide, Red Oxide of Iron.

TOLOL XR 25

The active ingredient is Metoprolol Succinate I.P 23.75 mg equivalent to Metoprolol Tartrate 25 mg

The excipients used are Polyvinyl Pyrrolidone K30, Isopropyl Alcohol, Carbopol, Microcrystalline Cellulose, Hydroxy Propyl Methyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Poly Ethylene Glycol, Titanium Dioxide.

TOLOL XR 50

The active ingredient is Metoprolol Succinate I.P 47.5 mg equivalent to Metoprolol Tartrate 50 mg

The excipients used are Polyvinyl Pyrrolidone K30, Isopropyl Alcohol, Carbopol, Microcrystalline Cellulose, Hydroxy Propyl Methyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Poly Ethylene Glycol, Titanium Dioxide, Lake Of Sunset Yellow.

TOLOL XR 100

The active ingredient is Metoprolol Succinate I.P 95 mg equivalent to Metoprolol Tartrate 100 mg

The excipients used are Polyvinyl Pyrrolidone K30, Isopropyl Alcohol, Carbopol, Microcrystalline Cellulose, Hydroxy Propyl Methyl Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Poly Ethylene Glycol, Titanium Dioxide, Lake Of Brilliant Blue.

10. Details of manufacturer

TOLOL XR 12.5/25/50/100

Manufactured by:

TORRENT PHARMACEUTICALS LTD.

32 No. Middle Camp, NH-10,

East District, Gangtok, Sikkim-737 135

OR

Uni Medicolabs

Plot No. 21 & 22, Phannacity, Selaqui, Dehradun.

11. Manufacture Licence no:

TOLOL XR 12.5/25/50/100

Mfg Licence No.: M/563/2010 issued on 06.12.2021

OR

TOLOL XR 25/100

Mfg. Licence No. 65/UA/2015 issued on 06.01.2021

TOLOL XR 50

Mfg. Licence No. 65/UA/2015 issued on 22.02.2020

12. Date of revision

Oct 2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/TOLOL XR 12.5, 25, 50, 100 mg/Oct 22/02/PI