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

TOLOL AM 25

1. Generic Name

Metoprolol Succinate Prolonged release and Amlodipine Tablets I.P.

2. Qualitative and quantitative composition

Each uncoated bilayered tablet contains:

Metoprolol Succinate I.P 23.75 mg

Equivalent to Metoprolol Tartrate…… 25.0 mg

(As Prolonged release form)

Amlodipine Besylate I.P.

Equivalent to Amlodipine……. 2.5 mg

Excipients…… q.s.

Colour: Ponceau 4R

Metoprolol Succinate Prolonged Release and Amlodipine Tablets are pink / white coloured circular slightly biconvexed uncoated, bilayered tablet and plain on both side. The excipients used are Hydroxy Propyl Methyl Cellulose, Microcrystalline Cellulose, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Talcum, Sodium Stearyl Fumarate, Lactose, Croscarmellose Sodium, Magnesium Stearate and Ponceau 4R.

3. Dosage form and strength

Dosage form: Uncoated Bilayered Tablet

Strength: Metoprolol Succinate 23.75 mg equivalent to Metoprolol Tartrate 25.0 mg and Amlodipine Besylate equivalent to Amlodipine 2.5 mg.

4. Clinical particulars

4.1 Therapeutic indication

For hypertension treatment

4.2 Posology and method of administration

Posology

Dose: As directed by physician

Method of administration

Tablet for oral administration.

4.3 Contraindications

Metoprolol Succinate

• Hypersensitivity to dihydropyridine derivatives, amlodipine, metoprolol, related derivatives, any other β-blockers or to any of the excipients.

• Severe hypotension.

• Shock (including cardiogenic shock).

• Obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis).

• Haemodynamically unstable heart failure after acute myocardial infarction.

• Second-or third-degree atrioventricular block

• Uncontrolled heart failure

• Clinically relevant sinus bradycardia (< 45-50 bpm)

• Sick sinus syndrome (unless a pacemaker is in situ).

• Prinzmetal's angina

• Myocardial infarction complicated by significant bradycardia, first degree heart block, systolic hypotension (less than 100mmHg) and/or severe heart failure and cardiogenic shock

Amlodipine Besilate

• Severe peripheral arterial disease

• Asthma and history of bronchospasm

• Untreated phaeochromocytoma

• Metabolic acidosis

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

• Hypotension

• Diabetes if associated with frequent episodes of hypoglycaemia

• Chronic obstructive pulmonary disease

• Severe hypotension.

• Shock (including cardiogenic shock).

• Obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis).

• Haemodynamically unstable heart failure after acute myocardial infarction.

• Cardiogenic shock

• Uncontrolled heart failure

• Sick sinus syndrome

• Second-or third-degree heart block

• Untreated phaeochromocytoma

• Metabolic acidosis

• Bradycardia (<45 bpm)

• Hypotension

• Severe peripheral arterial circulatory disturbances

4.4 Special warnings and precautions for use

Metoprolol Succinate

Abrupt cessation of therapy with a beta-blocker should be avoided especially in patients with ischaemic heart disease. When possible, metoprolol should be withdrawn gradually over a period of 10 days, the doses diminishing to 25mg for the last 6 days. If necessary, at the same time, initiating replacement therapy, to prevent exacerbation of angina pectoris. In addition, hypertension and arrhythmias may develop. When it has been decided to interrupt a beta-blockade in preparation for surgery, therapy should be discontinued for at least 24 hours. Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation, however the risk of hypertension may be increased as well. If treatment is continued, caution should be observed with the use of certain anaesthetic drugs. The patient may be protected against vagal reactions by intravenous administration of atropine. During its withdrawal the patient should be kept under close surveillance.

Although cardio selective beta blockers may have less effect on lung function than non-selective beta blockers these should be avoided in patients with reversible obstructive airways disease unless there are compelling clinical reasons for their use. Although metoprolol has proved safe in a large number of asthmatic patients, it is advisable to exercise care in the treatment of patients with chronic obstructive pulmonary disease. Therapy with a $beta_2$-stimulant may become necessary or current therapy require adjustment. Therefore, non-selective beta blockers should not be used for these patients, and $beta_1$-selective blockers only with the utmost care.

Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy with a beta blocker should be gradual.

Metoprolol Tartrate tablets 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 concomitant digoxin treatment is taking place, it must be borne in mind that both medicinal 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.

When a beta blocker is being taken, a serious, sometimes even life-threatening deterioration in cardiac function can occur, in particular in patients in whom the action of the heart is dependent on the presence of sympathetic system support. This is due less to an excessive beta-blocking effect and more to the fact that patients with marginal heart function tolerate poorly a reduction in sympathetic nervous system activity, even where this reduction is slight. This causes contractility to become weaker and the heart rate to reduce and slows down AV conduction. The consequence of this can be pulmonary oedema, AV block, and shock. Occasionally, an amlodipine Besylate g AV conduction disturbance can deteriorate, which can lead to AV block. In patients with a phaeochromocytoma, an alpha blocker should be given concomitantly.

Before a patient undergoes an operation, the anaesthetist must be informed that metoprolol is being taken. Acute initiation of high-dose metoprolol to patients undergoing non-cardiac surgery should be avoided, since it has been associated with bradycardia, hypotension and stroke including fatal outcome in patients with cardiovascular risk factors.

Beta-blockers mask some of the clinical signs of thyrotoxicosis. Therefore, Metoprolol should be administered with caution to patients having, or suspected of developing, thyrotoxicosis, and both thyroid and cardiac function should be monitored closely

Simultaneous administration of adrenaline (epinephrine), noradrenaline (norepinephrine) and β blockers may lead to increase in blood pressure and bradycardia.

Metoprolol may induce or aggravate bradycardia, symptoms of peripheral arterial circulatory disorders and anaphylactic shock. If the pulse rate decreases to less than 50-55 beats per minute at rest and the patient experiences symptoms related to the bradycardia, the dosage should be reduced.

Metoprolol may be administered when heart failure has been controlled. Digitalisation and/or diuretic therapy should also be considered for patients with a history of heart failure or patients known to have a poor cardiac reserve.

Metoprolol may reduce the effect of diabetes treatment and mask the symptoms of hypoglycaemia. The risk of a carbohydrate metabolism disorder or masking of the symptoms of hypoglycaemia is lower when using metoprolol prolonged release tablets than when using regular tablet forms for $beta_1$ selective beta blockers and significantly lower than when using nonselective beta blockers. In labile and insulin-dependent diabetes, it may be necessary to adjust the hypoglycaemic therapy.

In case of unstable or insulin dependent diabetes mellitus, it may be necessary to adjust the hypoglycaemic treatment (because of the likelihood of severe hypoglycaemic conditions).

In patients with significant hepatic dysfunction it may be necessary to adjust the dosage because metoprolol undergoes biotransformation in the liver. Patients with hepatic or renal insufficiency may need a lower dosage, and metoprolol is contraindicated in patients with hepatic or renal disease/failure. The elderly should be treated with caution, starting with a lower dosage but tolerance is usually good in the elderly. It may be necessary to use a lower strength formulation in elderly patients and patients with hepatic or renal impairment and an alternative product should be prescribed.

Patients with anamnestic ally known psoriasis should take beta-blockers only after careful consideration as the medicine may cause aggravation of psoriasis.

Beta blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions. Adrenaline (epinephrine) treatment does not always give the desired therapeutic effect in individuals receiving beta blockers.

Beta blockers may unmask myasthenia gravis.

In the presence of liver cirrhosis, the bioavailability of metoprolol may be increased, and dosage should be adjusted accordingly.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose mal-absorption should not take this medicine.

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.

Amlodipine Besylate

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

<u>Patients with cardiac failure</u>

Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of

pulmonary oedema was higher in the amlodipine treated group than in the placebo group. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Patients with hepatic impairment

The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Elderly patients

In the elderly increase of the dosage should take place with care.

Patients with renal impairment

Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

4.5 Drugs interactions

Metoprolol Succinate

- Anaesthetic drugs may attenuate reflex tachycardia and increase the risk of hypotension. Metoprolol therapy should be reported to the anaesthetist before the administration of a general anaesthetic. If possible, withdrawal of metoprolol should be completed at least 48 hours before anaesthesia. However, for some patients undergoing elective surgery, it may be desirable to employ a beta-blocker as premedication. By shielding the heart against the effect of stress, metoprolol may prevent excessive sympathetic stimulation which is liable to provoke such cardiac disturbance as arrhythmias or acute coronary insufficiency during induction and intubation. Anaesthetic agents causing myocardial depression, such as cyclopropane and trichloroethylene, are best avoided. In a patient under beta-blockade an anaesthetic with as little negative inotropic activity as possible (halothane/nitrous oxide) should be selected.

- It may be necessary to adjust the dose of the hypoglycaemic agent in labile or insulin-dependent diabetes. Beta-adrenergic blockade may prevent the appearance of signs of hypo-glycaemia (tachycardia).

- Like all beta-blockers, metoprolol should not be given in combination with calcium channel blockers i.e. verapamil and to a lesser extent diltiazem since this may cause bradycardia, hypotension, heart failure and asystole and may increase auriculoventricular conduction time. However, combinations of antihypertensive drugs may often be used with benefit to improve control of hypertension. Calcium blockers of the verapamil type should not be administered intravenously to patients receiving beta blockers.

- Care should also be taken when beta-blockers are given in combination with sympathetic ganglion blocking agents, other beta blockers or MAO inhibitors. Concomitant administration of tricyclic antidepressants, barbiturates and phenothiazines as well as other antihypertensive agents may increase the blood pressure lowering effect.

- Calcium channel blockers (such as dihydropyridine derivatives e.g. nifedipine) should not be given in combination with metoprolol because of the increased risk of hypotension and heart failure. In patients with latent cardiac insufficiency, treatment with beta-blocking agents may

lead to cardiac failure. Beta-blockers used in conjunction with clonidine increase the risk of "rebound hypertension". If combination treatment with clonidine is to be discontinued, metoprolol should be withdrawn several days before clonidine.

- The effects of metoprolol and other antihypertensive drugs on blood pressure are usually additive, and care should be taken to avoid hypotension.

- NSAIDs (especially indomethacin) may reduce the antihypertensive effects of beta-blockers possibly by inhibiting renal prostaglandin synthesis and/or causing sodium and fluid retention.

- Digitalis Glycosides and/or diuretics should be considered for patients with a previous history of heart failure or in patients known to have a poor cardiac reserve. Digitalis glycosides in association with beta-blockers may increase in auriculo-ventricular conduction time.

- The administration of adrenaline (epinephrine) or noradrenaline (norepinephrine) to patients undergoing beta-blockade can result in an increase in blood pressure and bradycardia, although this is less likely to occur with beta1-selective drugs. As beta-blockers may affect the peripheral circulation, care should be exercised when drugs with similar activity e.g. ergotamine are given concurrently. Concurrent use of moxisylyte may result in possible severe postural hypotension.

- The effect of adrenaline (epinephrine) in the treatment of anaphylactic reactions may be weakened in patients receiving beta blockers.

- Metoprolol will antagonise the beta1-effects of sympathomimetic agents but should have little influence on the bronchodilator effects of beta2-agonists at normal therapeutic doses.

- Enzyme inducing agents (e.g. rifampicin) may reduce plasma concentrations of metoprolol, whereas enzyme inhibitors (e.g. cimetidine, hydralazine and alcohol), selective serotonin reuptake inhibitors (SSRIs) as paroxetine, fluoxetine and sertraline, diphenhydramine, hydroxychloroquine, celecoxib, terbinafine may increase plasma concentrations of hepatically metabolized beta blockers.

- As with all beta-blockers particular caution is called for when metoprolol is administered together with prazosin for the first time as the co-administration of metoprolol and prazosin may produce a first dose hypotensive effect.

- Class 1 antiarrhythmic drugs, e.g. disopyramide, quinidine and amiodarone may have potentiating effects on atrial conduction time and induce negative inotropic effect. Concurrent use of propafenone may result in significant increases in plasma concentrations and half-life of metoprolol. Plasma propafenone concentrations are unaffected. Dosage reduction of metoprolol may be necessary.

- During concomitant ingestion of alcohol and metoprolol the concentration of blood alcohol may reach higher levels and may decrease more slowly. The concomitant ingestion of alcohol may enhance hypotensive effects.

- Metoprolol may impair the elimination of lidocaine.

- Prostaglandin synthetase inhibiting drugs may decrease the hypotensive effects of beta-blockers.

- Concurrent use of oestrogens may decrease the antihypertensive effect of beta-blockers because oestrogen induced fluid retention may lead to increased blood pressure.

- Concurrent use of xanthines, especially aminophylline or theophylline, may result in mutual inhibition of therapeutic effects.

- Xanthine clearance may also be decreased especially in patients with increased theophylline clearance induced by smoking.

- Concurrent use requires careful monitoring.

- Concurrent use of aldesleukin may result in an enhanced hypotensive effect.

- Concurrent use of alprostadil may result in an enhanced hypotensive effect.

- There is an increased risk of bradycardia following concomitant use of mefloquine with metoprolol.

- Concomitant use with anxiolytics and hypnotics may result in an enhanced hypotensive effect.

- Concomitant use with corticosteroids may result in antagonism of the hypotensive effect.

- The manufacturer of tropisetron advises caution in concomitant administration due to the risk of ventricular arrhythmias.

Amlodipine Besylate

Effects of other medicinal products on amlodipine

CYP3A4 inhibitors

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers

Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Dantrolene (infusion)

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with Hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicinal products

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

Tacrolimus

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) Inhibitors

MTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Cyclosporine

No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

Simvastatin

Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

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

Metoprolol Succinate

Pregnancy

It is recommended that metoprolol should not be administered during pregnancy or lactation unless it is considered that the benefit outweighs the possible risk to the foetus/infant. Should therapy with metoprolol be employed, special attention should be paid to the foetus, neonate and breast fed infant for any undesirable effects such as slowing of the heart rate.

Metoprolol has, however, been used in pregnancy associated hypertension under close supervision after 20 weeks' gestation. Although the drug crosses the placental barrier and is present in cord blood no evidence of foetal abnormalities has been reported. However, there is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period.

Beta blockers reduce placental perfusion and may cause foetal death and premature birth. Intrauterine growth retardation has been observed after long time treatment of pregnant women with mild to moderate hypertension. Beta blockers have been reported to cause bradycardia in the foetus and the newborn child, there are also reports of hypoglycaemia and hypotension in newborn children.

Animal experiments have shown neither teratogenic potential nor other adverse events on the embryo and/or foetus relevant to the safety assessment of the product. Treatment with metoprolol should be discontinued 48-72 hours before the calculated birth date. If this is not possible, the newborn child should be monitored for 24-48 hours' post-partum for signs and symptoms of beta blockade (e.g. cardiac and pulmonary complications).

Lactation

The concentration of metoprolol in breast milk is approximately three times higher than the one in the mother's plasma. 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). Cases of neonatal hypoglycaemia and bradycardia

have been described with beta-blockers with low plasma protein binding. Metoprolol is excreted in human milk. Even though the metoprolol concentration in milk is very low, breast-feeding should be discontinued during treatment with metoprolol. In case of treatment during breast feeding, infants should be monitored carefully for symptoms of beta blockade.

Amlodipine Besylate

Pregnancy

The safety of amlodipine in human pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses.

Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breast-feeding

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3-7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

Fertility

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility.

4.7 Effects on ability to drive and use machines

Metoprolol Succinate

As with all beta-blockers, metoprolol can affect patient's ability to drive and operate machinery. It should be taken into account that occasionally dizziness and fatigue may occur. Patient should be warned accordingly. If affected, patients should not drive or operate machinery.

Amlodipine Besylate

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

Metoprolol Succinate

Frequency estimates: 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); not known (cannot be estimated from the available data)

System Organ Class	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)	Not known (cannot be estimated from the

						available data)
Blood and lymphatic system disorders					Thrombocytopenia, agranulocytosis	
Psychiatric disorders				Depression, nightmares, Nervousness, anxiety, impotence	Hallucinations, personality disorder, Amnesia / memory impairment	
Nervous system disorders		Dizziness, headache		Alertness decreased, somnolence or insomnia, paraesthesia		
Eye disorders					Visual disturbance (e.g. blurred vision, dry eyes and/or eye irritation	
Ear and labyrinth disorders					Tinnitus, and, in doses exceeding those recommended, "hearing disorders (eg. hypoacusis or deafness)	
Cardiac disorders		Bradycardia		Heart failure, cardiac arrhythmias, palpitation	Cardiac conduction disorders, precordial pain	Increase in exAmlodipine g Besylate g intermittent claudication
Vascular disorders		Orthostatic hypotension (occasiona		Oedema, Raynaud's phenomenon	Gangrene in patients with pre-exAmlodipine g Besylate g	

		lly with syncope)			severe peripheral circulatory disorders	
Respiratory, thoracic and mediastinal disorders		Exertional dyspnoea		Bronchospam (which may occur in patients without a history of obstructive lung disease)	Rhinitis	
Gastrointestinal disorders		Nausea and vomiting, abdominal pain		Diarrhoea or constipation	Dry mouth	Retroperitoneal fibrosis *
Hepatobiliary disorders						Hepatitis
Skin and subcutaneous tissue disorders				Skin rash (in the form of urticaria, psoriasiform and dystrophic skin lesions)	Photosensitivity, hyperhidrosis, alopecia, worsening of psoriasis	Occurrence of antinuclear antibodies (not associated with SLE)
Musculoskeletal and connective tissue disorders				Muscle cramps	Arthritis	
Reproductive system and breast disorders					Disturbances of Libido and potency	Peyronie's disease *
General disorders and administrat		Fatigue			Dysgeusia (Taste disturbances)	

ion site conditions						
Investigations					Weight increase, liver function test abnormal	

* (relationship to Metoprolol has not been definitely established).

Beta-blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia.

Post Marketing Experience

The following adverse reactions have been reported during post-approval use of metoprolol: confusional state, an increase in blood triglycerides and a decrease in high density lipoprotein (HDL). Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency.

Amlodipine Besylate

Summary of the safety profile

The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

Tabulated list of adverse reactions

The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: 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); not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very rare	Leukocytopenia, thrombocytopenia
Immune system disorders	Very rare	Allergic reactions
Metabolism and nutrition disorders	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Depression, mood changes (including anxiety), insomnia
	Rare	Confusion
Nervous system disorders	Common	Somnolence, dizziness, headache (especially at the beginning of the treatment)

	Uncommon	Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia
	Very rare	Hypertonia, peripheral neuropathy
Eye disorders	Common	Visual disturbance (including diplopia)
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Common	Palpitations
	Uncommon	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
	Very rare	Myocardial infarction
Vascular disorders	Common	Flushing
	Uncommon	Hypotension
	Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	Uncommon	Cough, rhinitis
Gastrointestinal disorders	Common	Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation)
	Uncommon	Vomiting, dry mouth
	Very rare	Pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders	Very rare	Hepatitis, jaundice, hepatic enzyme increased*
Skin and subcutaneous tissue disorders	Uncommon	Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria
	Very rare	Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity

	Not known	Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Common	Ankle swelling, muscle cramps
	Uncommon	Arthralgia, myalgia, back pain
Renal and urinary disorders	Uncommon	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	Uncommon	Impotence, gynaecomastia
General disorders and administration site conditions	Very common	Oedema
	Common	Fatigue, asthenia
	Uncommon	Chest pain, pain, malaise
Investigations	Uncommon	Weight increased, weight decreased

*mostly consistent with cholestasis

Exceptional cases of extrapyramidal syndrome have been reported.

4.9 Overdose

Metoprolol Succinate

Poisoning due to an overdose of metoprolol may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness, coma, nausea, vomiting, cyanosis, hypoglycaemia and, occasionally, hyperkalaemia. The first manifestations usually appear 20 minutes to two hours after drug ingestion.

After ingestion of an overdose or in case of hypersensitivity, the patient should be kept under close supervision and be treated in an intensive- care ward. Absorption of any drug material still present in the gastrointestinal tract can be prevented by induction of vomiting, gastric lavage, administration of activated charcoal and a laxative. Artificial respiration may be required.

Bradycardia or extensive vagal reactions should be treated by administering atropine or methyl atropine. Hypotension and shock should be treated with plasma/plasma substitutes and, if necessary, catecholamines. The beta-blocking effect can be counteracted by slow intravenous administration of isoprenaline hydrochloride, starting with a dose of approximately 5 micrograms/minute, or dobutamine, starting with a dose of 2.5micrograms/minute, until required effect has been obtained. In refractory cases isoprenaline can be combined with dopamine. If this does not produce the desired effect either, intravenous administration of 8-10mg glucagon may be considered. If required the injection should be repeated within one hour, to be followed – if required – by an i.v. infusion of glucagon at an administration rate of 1-3mg/hour. Administration of calcium ions or the use of a cardiac pacemaker may also be considered. In patients intoxicated with hydrophilic beta-blocking agents haemodialysis or haemoperfusion may be considered.

Amlodipine Besylate

In humans experience with intentional overdose is limited.

Symptoms

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment

Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Metoprolol Succinate

Pharmacotherapeutic category: Beta blocking agents, selective, ATC code: C07AB02

Metoprolol tartrate is a cardioselective beta-adrenergic blocking agent. It has a relatively greater blocking effect on $beta_1$-receptors (i.e. those mediating adrenergic stimulation of heart rate and contractility and release of free fatty acids from fat stores) than on $beta_2$-receptors, which are chiefly involved in broncho and vasodilation.

Amlodipine Besylate

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects. ATC Code: C08CA01.

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions.

1) Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

2) The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

5.2 Pharmacodynamic properties

Metoprolol Succinate

Metoprolol tartrate is a cardioselective beta-adrenergic blocking agent. It has a relatively greater blocking effect on $beta_1$-receptors (ie those mediating adrenergic stimulation of heart rate and contractility and release of free fatty acids from fat stores) than on $beta_2$-receptors, which are chiefly involved in broncho and vasodilation.

Amlodipine Besylate

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1 mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Use in patients with coronary artery disease (CAD)

The effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multi-centre, randomized, double-blind, placebo-controlled study of 1997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these patients, 663 were treated with amlodipine 5-10 mg, 673 patients were treated with enalapril 10-20 mg, and 655 patients were treated with placebo, in addition to standard care of statins, beta-blockers, diuretics and aspirin, for 2 years. The key efficacy results are presented in Table 1. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

Table 1. Incidence of significant clinical outcomes for CAMELOT

	Cardiovascular event rates, No. (%)			Amlodipine vs. Placebo	
Outcomes	Amlodipine	Placebo	Enalapril	Hazard Ratio (95% CI)	*P* Value
Primary Endpoint					
Adverse cardiovascular events	110 (16.6)	151 (23.1)	136 (20.2)	0.69 (0.54-0.88)	.003
Individual Components					
Coronary revascularization	78 (11.8)	103 (15.7)	95 (14.1)	0.73 (0.54-0.98)	.03

Hospitalization for angina	51 (7.7)	84 (12.8)	86 (12.8)	0.58 (0.41-0.82)	.002
Nonfatal MI	14 (2.1)	19 (2.9)	11 (1.6)	0.73 (0.37-1.46)	.37
Stroke or TIA	6 (0.9)	12 (1.8)	8 (1.2)	0.50 (0.19-1.32)	.15
Cardiovascular death	5 (0.8)	2 (0.3)	5 (0.7)	2.46 (0.48-12.7)	.27
Hospitalization for CHF	3 (0.5)	5 (0.8)	4 (0.6)	0.59 (0.14-2.47)	.46
Resuscitated cardiac arrest	0	4 (0.6)	1 (0.1)	NA	.04
New-onset peripheral vascular disease	5 (0.8)	2 (0.3)	8 (1.2)	2.6 (0.50-13.4)	.24
Abbreviations: CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack.					

Use in patients with heart failure

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that Amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that Amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo controlled study (PRAISE-2) of Amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, Amlodipine had no effect on total cardiovascular mortality. In this same population Amlodipine was associated with increased reports of pulmonary oedema.

Treatment to prevent heart attack trial (ALLHAT)

A randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrolment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%),

left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy. RR 0.96 95% CI [0.89-1.02] p=0.20.

Use in children (aged 6 years and older)

In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5 mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood has also not been established.

5.3 Pharmacokinetic properties

Metoprolol Succinate

Absorption

Metoprolol is readily and completely absorbed from the gastrointestinal tract. Metoprolol is absorbed fully after oral administration. Within the therapeutic dosage range, the plasma concentrations increase in a linear manner in relation to dosage. Peak plasma levels are achieved after approx. 1.5–2 hours. Even though the plasma profile displays a broader interindividual variability, this appears to be easily reproducible on an individual basis. Due to the extensive first-pass effect, bioavailability after a single oral dose is approx. 50%. After repeated administration, the systemic availability of the dose increases to approx. 70%. After oral intake with food, the systemic availability of an oral dose increases by [SIC] approx. 30–40%.

Distribution

Peak plasma concentrations occur about 1½ hours after a single oral dose. Peak plasma metoprolol concentrations at steady state with usual doses have been reported as 20-340ng/ ml. Metoprolol is widely distributed, it crosses the blood brain barrier, the placenta. It is slightly bound to plasma protein. The medicinal product is approx. 5–10% bound to plasma proteins.

Biotransformation

Metoprolol is metabolised through oxidation in the liver mainly by the CYP2D6 isoenzyme. Even though three main metabolites have been identified, none of them has a clinically significant beta-blocking effect. Generally, 95% of an oral dose is found in the urine. Only 5% of the dose is excreted unmodified via the kidneys; in isolated cases, this figure can reach as high as 30%. The elimination half-life of metoprolol averages 3.5 hours (with extremes of 1 and 9 hours). Total clearance is approx. 1 litre/minute. It is extensively metabolised in the liver; O-dealkylation followed by oxidation and aliphatic hydroxylation. The rate of hydroxylation to alpha-hydroxymetoprolol is reported to be determined by genetic polymorphism; the half-

life of metoprolol in fast hydroxylators is stated to be 3-4 hours, whereas in poor hydroxylators it is about 7 hours.

Elimination

The metabolites are excreted in the urine together with only small amounts of unchanged metoprolol. Metoprolol is excreted in breast milk.

Special population

Elderly:

In comparison with administration to younger patients, the pharmacokinetics of metoprolol when administered to older patients shows no significant differences.

Renal impairment:

Renal dysfunction has barely any effect on the bioavailability of metoprolol. However, the excretion of metabolites is reduced. In patients with a glomerular filtration rate of less than 5 ml/minute, a significant accumulation of metabolites has been observed. This accumulation of metabolites, however, produces no increase in the beta blockade.

Hepatic impairment:

The pharmacokinetics of metoprolol are influenced only minimally by reduced hepatic function. However, in patients with serious hepatic cirrhosis and a portacaval shunt, the bioavailability of metoprolol can increase, and the total clearance can be reduced. Patients with portacaval anastomosis had a total clearance of approx. 0.3 litres/minute and AUC values that were 6 times higher than those found in healthy persons.

Severe angina pectoris

Intrinsic sympathomimetic activity (ISA) may be a disadvantage for the patient with severe angina pectoris. There are however no indications that the efficacy in hypertensives is influenced by this characteristic. In exceptional cases, however, very high dosages can cause the ISA to predominate over the beta-adrenergic blocking capacity so that restriction of the maximum dosage is indicated.

Respiratory impairment

It has not been proven that beta-blockers with ISA give a lower risk for bronchospasm or enhancement of pre-existing bronchospastic complaints.

Amlodipine Besylate

Absorption, distribution, plasma protein binding***:*** After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

The bioavailability of amlodipine is not affected by food intake.

Biotransformation/elimination

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Hepatic impairment

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

Elderly population

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

Paediatric population

A population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

6. Nonclinical properties

6.1 Animal Toxicology

Metoprolol Succinate

There are no preclinical data of relevance to the prescriber.

Amlodipine Besylate

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

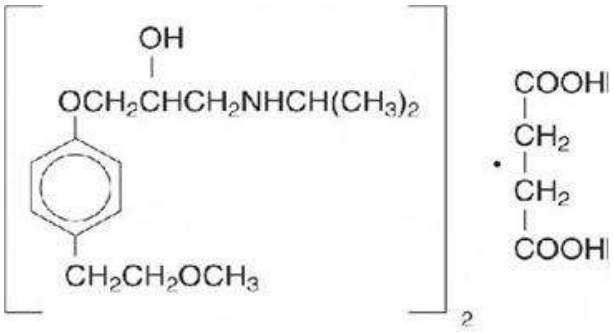
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

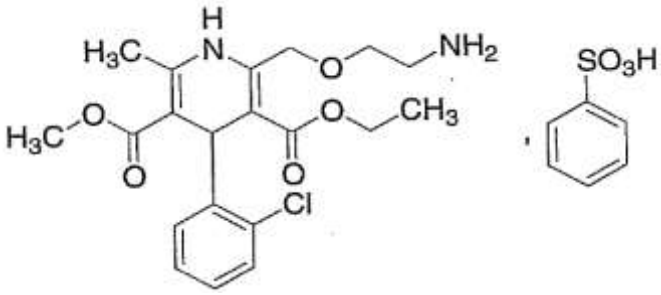
*Based on patient weight of 50 kg

7. Description

Metoprolol Succinate is a beta1-selective (cardioselective) adrenoceptor blocking agent, for oral administration. Its chemical name is (±) 1-(isopropylamino)-3-[p-(2-methoxyethyl) 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



Amlodipine Besylate is Antihypertensive agent. Its chemical name is 3-ethyl5-methyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzene sulphonate having molecular weight of 567.1. Its empirical formula is $C_{26}H_{31}ClN_2O_8S$ with structural formula of



TOLOL AM 25

Metoprolol Succinate Prolonged release and Amlodipine Tablets are pink/white coloured circular slightly biconvexed uncoated, bilayered tablet and plain on both side. The excipients used are Hydroxy Propyl Methyl Cellulose, Microcrystalline Cellulose, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Talcum, Sodium Stearyl Fumarate, Lactose, Croscarmellose Sodium, Magnesium Stearate and Ponceau 4R.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not Stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

TOLOL AM 25 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

Package leaflet: Information for the user

TOLOL AM 25

Metoprolol Succinate & Amlodipine

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 harm them, even if their signs of illness are the same as yours.

- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet?

9.1 What TOLOL AM 25 is and what it is used for

TOLOL AM 25 is combination of active substance Amlodipine (belongs to a group of medicines called calcium antagonists) and Metoprolol Succinate (belongs to a group of medicines called beta blockers).

TOLOL AM 25 is used for treatment of hypertension.

9.2 What you need to know before you take TOLOL AM 25

Do not take TOLOL AM 25

 are allergic to Metoprolol Succinate and Amlodipine or any other ingredients of this medicine

 suffer with heart conduction or rhythm problems

 have severe or uncontrolled heart failure

 are in shock caused by heart problems

 suffer with 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 or have suffered a heart attack which has been complicated by a significantly slow heart rate

 suffer from a tight, painful feeling in the chest in periods of rest (Prinzmetal's angina)

 have or have had breathing difficulties or asthma including COPD (Chronic Obstructive Pulmonary Disease causing cough, wheezing or breathlessness, phlegm or increase in chest infections)

 suffer with untreated phaeochromocytoma (high blood pressure due to a tumour near the kidney)

 suffer from increased acidity of the blood (metabolic acidosis)

 have low blood pressure

 suffer with diabetes associated with frequent episodes of low blood sugar (hypoglycaemia)

 have liver or kidney disease or failure

 are given other medicines for blood pressure by injection especially verapamil, diltiazem or disopyramide

Warnings and precautions

 Talk to your doctor or pharmacist before using TOLOL AM 25 if you:

 have a history of allergic reactions, for example to insect stings, foods or other substances,

 have diabetes mellitus (low blood sugar levels may be hidden by this medicine)

 have controlled heart failure.

 Recent heart attack

 have a slow heart rate or blood vessel disorder.

 suffer from treated phaeochromocytoma (high blood pressure due to tumour near the kidney)

 have or have suffered from psoriasis (severe skin rashes)

 have liver cirrhosis

 are elderly

 have myasthenia gravis.

 If you suffer from dry eyes

 Severe increase in blood pressure (Hypertensive crisis)

Anaesthetics and surgery

If you are going to have an operation or an anaesthetic, please tell your doctor or dentist that you are taking TOLOL AM 25, as your heart beat might slow down too much.

Taking other medicines

Do not take TOLOL AM 25 if you are already taking:

 Monoamine oxidase inhibitors (MAOIs) for depression

 other blood pressure lowering medicines such as verapamil, nifedipine and diltiazem

 Disopyramide or quinidine (to treat irregular heartbeat (arrhythmia)

Children

Do not give this medicine to children.

Other medicines and TOLOL AM 25

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

TOLOL AM 25 may affect or be affected by other medicines, such as:

 Ketoconazole, itraconazole (anti-fungal medicines)

 Ritonavir, indinavir, nelfinavir (so called protease inhibitors used to treat HIV)

 Rifampicin, erythromycin, clarithromycin (antibiotics)

 Hypericum perforatum (St. John's Wort)

 Verapamil, diltiazem (heart medicines)

 Dantrolene (infusion for severe body temperature abnormalities)

 Tacrolimus, sirolimus, temsirolimus, and everolimus (medicines used to alter the way your immune system works)

 Simvastatin (cholesterol lowering medicine)

 Cyclosporine (an immunosuppressant)

 Medicines used to treat stomach ulcers such as cimetidine

 Medicines used to treat high blood pressure such as hydralazine, clonidine or prazosin

 Medicines used to treat irregular heart rhythm such as amiodarone and propafenone

 Medicines used to treat depression such as tricyclic or SSRI antidepressants

 Medicines used to treat epilepsy such as barbiturates

 Medicines used to treat mental illness such as phenothiazines

 Anaesthetics such as cyclopropane or trichloroethylene

 Medicines used to treat some cancers, particularly cancer of the kidney such as aldesleukin

 Medicines used to treat erectile dysfunction such as alprostadil

 Anxiolytics or hypnotics (e.g. temazepam, nitrazepam, diazepam)

 Indomethacin or celecoxib (Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

 Oestrogens such as a contraceptive pill or hormone replacement therapy

 Corticosteroids (e.g. hydrocortisone, prednisolone)

 Other beta-blockers e.g. eye drops.

 Adrenaline (epinephrine) or noradrenaline (norepinephrine), used in anaphylactic shock or other sympathomimetic

 Medicines used to treat diabetes

 Lidocaine (a local anaesthetic)

 Moxisylyte (used in Raynaud's syndrome)

 Medicines used to treat malaria such as mefloquine

 Medicines used to prevent nausea and vomiting such as tropisetron

 Medicines used to treat asthma such as xanthines such as aminophylline or theophylline

 Medicines to treat migraines such as ergotamine

 Medicines used to treat heart conditions such as cardiac glycosides e.g. digoxin

 Medicines used to treat rheumatoid arthritis such as hydroxychloroquine

 Diphenhydramine (sedative antihistamine).

TOLOL AM 25 may lower your blood pressure even more if you are already taking other medicines to treat your high blood pressure.

TOLOL AM 25 with food and drink

Grapefruit juice and grapefruit should not be consumed by people who are taking TOLOL AM 25. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active ingredient amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of TOLOL AM 25.

TOLOL AM 25 and alcohol

You are advised to avoid alcohol whilst taking this medicine. Alcohol may increase the blood pressure lowering effect of TOLOL AM 25.

Pregnancy and breast-feeding

TOLOL AM 25 tablets are not recommended during pregnancy or breast-feeding. If you are pregnant or breastfeeding, 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 AM 25 tablets may make you feel tired and dizzy. If affected, patients should not drive or operate machinery.

9.3 How to take TOLOL AM 25 tablets

Always take tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Dose: As suggested by Physician

If you take more TOLOL AM 25 tablets 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.

Symptoms of overdose are low blood pressure (fatigue and dizziness), slow pulse, heart conduction problems, shortness of breath, unconsciousness, coma, cardiac arrest, feeling and being sick, blue colouring of the skin, low blood sugar levels and high levels of potassium in the blood.

If you forget to take TOLOL AM 25 tablets

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 AM 25 tablets

Do not suddenly stop taking TOLOL AM 25 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 the following symptoms of an:

• Allergic reaction such as itching, difficulty breathing or swelling of the face, lips, throat or tongue. Visit your doctor immediately if you experience any of the following side effects after taking this medicine.

 Sudden wheeziness, chest pain, shortness of breath or difficulty in breathing

 Swelling of eyelids, face or lips

 Swelling of the tongue and throat which causes great difficulty breathing

 Severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes (Stevens Johnson Syndrome, toxic epidermal necrolysis) or other allergic reactions

 Heart attack, abnormal heart beat

 Inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell

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

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

 Tiredness

 Dizziness

 Headache

 A slow heart rate

 Feeling faint on standing due to low blood pressure

 Shortness of breath with or without strenuous physical activity

 Feeling or being sick

 Stomach pain

 Visual disturbances, double vision

 Muscle cramps

 Ankle swelling

Other side effects that have been reported include the following list. If any of these get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Uncommon: may affect up to 1 in 100 people

 Mood changes, anxiety, depression, sleeplessness

 Trembling, taste abnormalities, fainting

 Numbness or tingling sensation in your limbs, loss of pain sensation

 Ringing in the ears
 Low blood pressure
 Sneezing/running nose caused by inflammation of the lining of the nose (rhinitis)
 Cough
 Dry mouth, vomiting (being sick)
 Hair loss, increased sweating, itchy skin, red patches on skin, skin discolouration
 Disorder in passing urine, increased need to urinate at night, increased number of times of Passing urine
 Inability to obtain an erection, discomfort or enlargement of the breasts in men
 Pain, feeling unwell
 Joint or muscle pain, back pain
 Weight increase or decrease

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

 Depression
 Nightmares
 Nervousness
 Anxiety
 Sexual dysfunction or reduced sex drive
 Inability to think clearly
 Sleepiness or difficulty in sleeping
 Tingling or 'pins and needles'
 Difficulty breathing
 Heart failure
 Irregular heart rate
 Palpitation
 Water retention causing swelling
 Raynaud's phenomenon (causing pain, numbness, coldness and blueness of the fingers)
 Diarrhoea or constipation
 Skin rash
 Muscle cramps

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

 Changes in the results of blood tests
 Effects on blood clotting causing easy or unexplained bruising
 Changes in personality

 Confusion

 Hallucinations

 Visual disturbances

 Dry or irritated eyes

 Ringing in the ears

 Loss of hearing with high doses

 Heart conduction problems

 Chest pain

 Gangrene in patients with severe poor circulation

 Runny nose

 Dry mouth

 Weight gain sensitivity to light

 Increased sweating

 Hair loss

 Worsening or new psoriasis

 Joint inflammation (arthritis)

 Disturbances of sexual desire and performance

 Changes in liver function tests

 Taste disorders

 Excess sugar in blood (hyperglycaemia)

 A disorder of the nerves which can cause muscular weakness, tingling or numbness

 Swelling of the gums

 Abdominal bloating (gastritis)

 Abnormal liver function, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), liver enzyme increase which may have an effect on some medical tests

 Increased muscle tension

 Inflammation of blood vessels, often with skin rash

 Sensitivity to light

 Disorders combining rigidity, tremor, and/or movement disorders

Not known (frequency cannot be estimated from the available data):

 Worsening or development of limping

 Hepatitis (symptoms include fever, sickness and yellowing of the skin or whites of the eyes)

 Peyronie's syndrome (bending of the penis)

 Symptoms of high levels of the thyroid hormone or low blood sugar may be hidden

 Increase in blood fats or decrease in cholesterol

 Retroperitoneal fibrosis (symptoms include lower back pain, high blood pressure)

 Occurrence of antinuclear antibodies not associated with systemic lupus erythematosus (SLE).

9.5 How to store TOLOL AM 25

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

9.6 Contents of the pack and other information

TOLOL AM 25

The active ingredient is Metoprolol Succinate 23.75 mg equivalent to Metoprolol Tartrate 25 mg and Amlodipine Besylate 2.5 mg. The excipients used are Hydroxy Propyl Methyl Cellulose, Microcrystalline Cellulose, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Talcum, Sodium Stearyl Fumarate, Lactose, Croscarmellose Sodium, Magnesium Stearate and Ponceau 4R.

10. Details of manufacturer by

Tristar Formulations Private Limited.

Plot No. A-116 & A-117, 27th Cross, PIPDIC Industrial Estate,

Mettupalayam, Puducherry – 605009

11. Details of permission or licence number with date

Mfg Lic No. 04 13 1106 issued on 12.02.2018

12. Date of revision

MAY 2020

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/TOLOL AM 25 and 2.5 mg/MAY 20/03/PI