Attachment 1

TGA Approval Date:

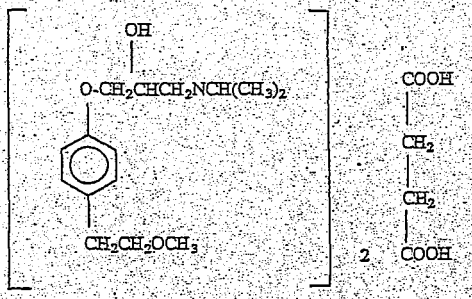
PRODUCT INFORMATION

TOPROL-XL™ Tablets

(Metoprolol Succinate)

NAME OF DRUG

The active ingredient in TOPROL-XL is metoprolol succinate. The chemical name for metoprolol succinate is di-(±)-1-(isopropylamine)-3-[*p*-(2-methoxyethyl)phenoxy]-2-propanol succinate. The molecular weight of metoprolol succinate is 652.8. Its structural formula is:



CAS number: 98418-47-4.

DESCRIPTION

Metoprolol succinate is a white, crystalline powder with a melting point of approximately 138°C. It is freely soluble in water, soluble in methanol, sparingly soluble in ethanol, slightly soluble in dichloromethane and 2-propanol, and practically insoluble in ethyl acetate, acetone, diethyl ether and heptane.

TOPROL-XL tablets contain metoprolol succinate. TOPROL-XL tablets also contain the inactive ingredients: ethylcellulose, hydroxypropylcellulose, hypromellose, microcrystalline cellulose, paraffin, macrogol 6000, silicon dioxide, sodium stearylfumarate and titanium dioxide.

PHARMACOLOGY

Metoprolol is a β_1-selective β-blocker, i.e. it blocks β_1-receptors at doses lower than those needed to block β_2-receptors.

Metoprolol is practically devoid of membrane stabilising activity and does not display partial agonist activity (i.e. intrinsic sympathomimetic activity = ISA) at doses required to produce β-blockade. The stimulant effect of catecholamines on the heart is reduced or inhibited by metoprolol. This leads to a decrease in heart rate, cardiac output, cardiac contractility and blood pressure.

Controlled release metoprolol succinate and the immediate release metoprolol tartrate are not bioequivalent. Controlled release metoprolol succinate gives an even plasma concentration

time profile and effect (β_1-blockade) over 24 hours in contrast to conventional tablet formulations of β_1-selective blockers including metoprolol tartrate formulations.

When given together with a β_2-agonist, metoprolol succinate in therapeutic doses interferes less than non-selective β-blockers with β_2-mediated bronchodilation (see PRECAUTIONS). When clinically necessary, metoprolol succinate, in combination with a β_2-agonist, may be given to patients with symptoms of obstructive pulmonary disease. Metoprolol succinate also interferes less with insulin release than non-selective β-blockers.

Pharmacokinetics

Absorption and Distribution

TOPROL-XL consists of several hundred beads of metoprolol succinate, each coated with a polymeric membrane which controls the rate of metoprolol release. After rapid disintegration within the gastrointestinal tract, metoprolol is continuously released for approximately 20 hours, and a stable metoprolol plasma concentration is achieved over a dosage interval of 24 hours. Approximately 12% of metoprolol is bound to human serum proteins.

Metabolism and Elimination

Metoprolol undergoes oxidative metabolism in the liver, primarily by CYP2D6. Due to polymorphism of CYP2D6, about 5-10% of Caucasians and a lower percentage of Asian and African populations are poor metabolisers of metoprolol. Such people experience higher plasma concentrations of metoprolol for a given dose. Because of these differences between individuals, gradual dose titration is important. Co-administration of drugs which inhibit CYP2D6 may increase plasma concentrations of metoprolol, particularly in extensive metabolisers (the majority of the population). Three main metabolites have been identified, although none have a beta-blocking effect of clinical importance.

Over 95% of an oral dose can be recovered in the urine. Only approximately 5% of the administered dose is excreted unchanged, with this figure rising to 30% in isolated cases.

Pharmacokinetics in the elderly

The elderly shows no significant differences in the pharmacokinetics of metoprolol as compared with younger persons.

CLINICAL TRIALS

Three randomised, double-blind, placebo-controlled studies and one randomised, open crossover study had been conducted to establish the efficacy and safety of TOPROL-XL in patients with chronic heart failure.

The pivotal study, MERIT-HF (n=3991), was a survival study in patients with NYHA (New York Heart Association) functional class II-IV and decreased ejection fraction (≤ 0.40) on optimal standard therapy at enrolment. Patients were randomised to receive either TOPROL-XL (n=1990) or placebo (n=2001) once daily. The dose of TOPROL-XL was titrated during 6-8 weeks to the target of 200 mg. Treatment ranged from 0 to 622 days with a mean duration of one year.

Participants were predominantly male (76%), Caucasian (94%), previous (55%) or current (19%) smokers, aged 60-79 years (66%; mean age 64), with heart failure secondary to ischaemia (65%). Most had mild to moderate symptomatic heart failure at baseline: 41% in

NYHA Class II, 56% in Class III and 4% in Class IV. The mean ejection fraction was 0.28. About half the patients had a history of hypertension (44%) and/or myocardial infarction (48%). 25% had a history of diabetesm ellitus. 10-20% had peripheral oedema, jugular venous distension, pulmonary rales and/or hepatomegaly. 23% had a third heart sound, 34% had a heart murmur, 25% had an irregular heart beat and 16% were in atrial fibrillation. 90% of patients were on one or more diuretics, 89% on an angiotensin converting enzyme inhibitor, 7% on an angiotensin II-blocker, 63% on digitalis, 36% on long-acting nitrates, 54% on aspirin, 37% on an oral anticoagulant and 23% on a statin.

The following table summarises the results of the efficacy variables for TOPROL-XL compared to placebo:

Endpoint	Event rate per 100 patient-years		Relative Risk Reduction [95% Confidence Interval]	p-value
	TOPROL-XL N=1990	Placebo N=2001		
All-cause mortality	7.2	11.0	35% (19%; 47%)	0.0062*
All-cause mortality and all-cause hospitalisation#	31.9	38.7	19% (10%; 27%)	0.0001
All-cause mortality and hospitalisation due to worsening of heart failure#	15.5	22.2	31% (20%; 40%)	<0.0001
Death and heart transplant#	7.5	11.0	32% (16%; 45%)	0.0002
Cardiovascular mortality	6.4	10.3	38% (22%; 50%)	<0.0001
Sudden Death	1.5	2.9	41% (22%; 55%)	0.0002
Death from worsening heart failure	3.9	6.7	49% (21%; 67%)	0.0023
Cardiac death and non-fatal acute myocardial infarction#	6.9	11.4	39% (25%; 51%)	<0.0001
All-cause mortality, hospitalisation due to worsening heart failure and emergency room visit due to worsening heart failure#	15.8	23.0	32% (21%; 41%)	<0.0001

* Adjusted for interim analyses. Unadjusted p-value = 0.0001
# Time to first event

The numbers needed to treat (NNT) to achieve a reduction of 1 case of all cause mortality, cardiac death and non-fatal AMI, mortality from cardiovascular causes and from sudden death are as follows:

Endpoint	NNT (one year)
All cause mortality	27
Cardiac death & Non-fatal acute MI	24
Mortality from CV causes	26
Mortality from Sudden death	37

TOPROL-XL was generally well tolerated. Treatment was ceased due to adverse events in 10.3% of patients taking TOPROL-XL compared to 12.3% of those taking placebo. Compared to placebo, the overall rate of treatment withdrawal and withdrawal due to

worsening heart failure tended to be less with TOPROL-XL, but the difference did not reach statistical significance.

INDICATIONS

Stable, chronic heart failure as an adjunct to other heart failure therapy.

CONTRAINDICATIONS

- Predisposition to bronchospasm

  β-adrenergic blockade of the smooth muscle of bronchi and bronchioles may result in an increased airways resistance. These drugs also reduce the effectiveness of asthma treatment. This may be dangerous in susceptible patients.

  Therefore, β-blockers are contraindicated in any patient with a history of airways obstruction or a tendency to bronchospasm. Use of cardioselective β-blockers can also result in severe bronchospasm. If such therapy must be used, great caution should be exercised. Alternative therapy should be considered.
- Allergic disorders (including allergic rhinitis) which may suggest a predisposition to bronchospasm
- Right ventricular failure secondary to pulmonary hypertension
- Significant right ventricular hypertrophy
- Second and third degree atrioventricular block
- Shock (including cardiogenic and hypovolaemic shock)
- Unstable decompensated congestive heart failure (pulmonary oedema, hypoperfusion or hypotension).
- Continuous or intermittent inotropic therapy acting through β-receptor agonism
- Clinically relevant sinus bradycardia (less than 45-50 beats/minute)
- Non-compensated congestive heart failure (see PRECAUTIONS)
- Sick-sinus syndrome
- Severe peripheral arterial circulatory disorders
- Suspected acute myocardial infarction with a heart rate of < 45 beats/minute, a P-R interval of > 0.24 seconds or a systolic blood pressure of < 100 mmHg, and/or moderate to severe non-compensated heart failure
- Hypotension
- Untreated phaeochromocytoma (see PRECAUTIONS)
- Hypersensitivity to any component of TOPROL-XL and related derivatives. Cross-sensitivity between β-blockers can occur.

PRECAUTIONS

Symptomatic cardiac failure

β-blockers should not be used in patients with unstabilised heart failure. This condition should first be stabilised with appropriate treatment (e.g. angiotensin-converting enzyme

inhibitors, digoxin, diuretics). If cardiac failure persists, TOPROL-XL should be discontinued gradually (see PRECAUTIONS - Abrupt Withdrawal).

Bronchospasm

Where TOPROL-XL is prescribed for patients known to be suffering from asthma, an inhaled β_2-agonist should be administered. The dosage of β_2-agonists may require adjustment (increase), however the risk of TOPROL-XL interfering with β_2-receptors is less than with conventional tablet formulations of β_1-selective blockers.

Concomitant therapy with calcium antagonists

The concomitant use of calcium antagonists with myocardial suppressant and sinus node activity (e.g. verapamil and to a lesser extent diltiazem) and β-blockers may cause bradycardia, hypotension and asystole. Extreme caution is required if these drugs have to be used together (see INTERACTIONS WITH OTHER DRUGS).

Anti-arrhythmic drugs

Care should be taken when prescribing β-blockers with antiarrhythmic drugs as they may enhance the negative inotropic and chronotropic effects (see INTERACTIONS WITH OTHER DRUGS).

Diabetes

TOPROL-XL should be used with caution in patients with diabetes mellitus, especially those who are receiving insulin or oral hypoglycaemic agents. Diabetic patients should be warned that β-blockers affect glucose metabolism and may mask some important premonitory signs of acute hypoglycaemia, such as tachycardia.

In patients with insulin or non-insulin dependent diabetes, especially labile diabetes, or with a history of spontaneous hypoglycaemia, β-blockade may result in the loss of diabetic control and delayed recovery from hypoglycaemia. The dose of insulin or oral hypoglycaemic agent may need to be adjusted. Diabetic patients receiving TOPROL-XL should be monitored to ensure diabetes control is maintained.

Other metabolic effects

Beta adrenoreceptors are involved in the regulation of lipid as well as carbohydrate metabolism. Some drugs affect the lipid profile adversely although the long-term clinical significance of this change is unknown and the effect appears to be less for drugs with intrinsic sympathomimetic activity.

Conduction disorders

Very rarely a pre-existing A-V conduction disorder of moderate degree may become aggravated (possibly leading to A-V block). TOPROL-XL should be administered with caution to patients with first degree A-V block (see CONTRAINDICATIONS).

Peripheral vascular disease

β-blockade may impair the peripheral circulation and exacerbate the symptoms of peripheral vascular disease (see CONTRAINDICATIONS).

Bradycardia

If patients develop increasing bradycardia, TOPROL-XL should be given in lower doses or gradually withdrawn.

Prinzmetal angina

There is a risk of exacerbating coronary artery spasm if patients with Prinzmetal or variant angina are treated with a β-blocker. If this treatment is essential, it should only be undertaken in a Coronary or Intensive Care Unit.

Effects on the thyroid

The effects of β-blockers on thyroid hormone metabolism may result in elevations of serum free thyroxine (T_4) levels. In the absence of any signs or symptoms of hyperthyroidism, additional investigation is necessary before a diagnosis of thyrotoxicosis can be made.

Phaeochromocytoma

Where TOPROL-XL is prescribed for a patient known to be suffering from phaeochromocytoma, an α-blocker should be given concomitantly to avoid exacerbation of hypertension.

Effects on the eye and skin

Various skin rashes and conjunctival xerosis have been reported with β-blocking agents. Cross-reactions may occur between β-blockers, therefore substitutions within the group may not necessarily preclude occurrence of symptoms.

During long-term treatment with the β-blocking drug practolol a specific rash bearing a superficial resemblance to psoriasis was occasionally described. In a number of the patients affected, this rash was accompanied by adverse effects on the eye (xerophthalmia and/or keratoconjunctivitis) of varying severity. This condition is called the oculomucocutaneous or practolol syndrome. On a few rare occasions, serious otitis media, sclerosing peritonitis and pleurisy have been reported as part of this syndrome.

The oculomucocutaneous syndrome as reported with practolol has not been reported with metoprolol. However, dry eyes and skin rash have been reported with metoprolol. If such symptoms occur, discontinuation of metoprolol should be considered.

Recently, an association between Peyronie's disease (a fibrosing induration of the penis) and various β-blockers has been suggested but is not proven.

General anaesthesia

Prior to surgery the anaesthetist should be informed that the patient is receiving TOPROL-XL because of the potential for interactions with other drugs, resulting in severe bradyarrhythmias and hypotension, decreased reflex ability to compensate for blood loss, hypovolaemia and regional sympathetic blockade, and decreased propensity for vagal-induced bradycardia (see INTERACTIONS WITH OTHER DRUGS). It is not recommended to stop β-blocker treatment in patients undergoing surgery.

If it is thought necessary to withdraw β-blocker therapy before surgery, this should be done gradually and completed about 48 hours before surgery. (See Abrupt Withdrawal below)

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Effects on ability to drive or use machinery

TOPROL-XL may occasionally cause dizziness, visual disturbances or fatigue (see ADVERSE REACTIONS), hence patients should know how they react to TOPROL-XL before they drive or use machinery, particularly when starting or changing treatment.

Abrupt withdrawal

Abrupt withdrawal of β-blockade is hazardous, especially in high risk patients, and should not be done. If there is a need to discontinue treatment with TOPROL-XL, this should be done gradually over at least two weeks with the dose reduced by half in each step, down to a final dose of half a 23.75 mg tablet. The final dose should be taken for at least four days before discontinuation. Close observation of the patient is required during the withdrawal phase. If symptoms occur, a slower withdrawal rate is recommended. Sudden withdrawal of β-blockade may aggravate chronic heart failure and also increase the risk of myocardial infarction and sudden death.

Allergic conditions

Allergic reactions may be exaggerated by β-blockade (e.g. allergic rhinitis during the pollen season and allergic reactions to bee and wasp stings). β-blockers should be avoided if there is a risk of bronchospasm.

In patients taking β-blockers, anaphylactic shock assumes a more severe form and may be resistant to usual doses of adrenaline. Whenever possible, β-blockers should be avoided in patients who are at increased risk of anaphylaxis.

Hyperthyroidism

Because β-blockers may mask the clinical signs of developing or continuing hyperthyroidism resulting in symptomatic improvement without any change in thyroid status, special care should be exercised in hyperthyroid patients who are also receiving β-blockers. Where TOPROL-XL is administered to patients having, or suspected of developing thyrotoxicosis, both thyroid and cardiac function should be closely monitored.

Effects on the heart rate

If the patient develops increasing bradycardia (heart rate less than 50 to 55 beats/minute), the dosage of TOPROL-XL should be gradually reduced or treatment gradually withdrawn (see CONTRAINDICATIONS).

Impaired renal function

In patients with severe renal disease haemodynamic changes following β-blockade may impair renal function further. β-blockers which are excreted mainly by the kidney may require dose adjustment in patients with renal failure.

Impaired hepatic function

Metoprolol is mainly eliminated by hepatic metabolism (see Pharmacokinetics). Therefore, liver cirrhosis may increase the systemic bioavailability of metoprolol and reduce its total clearance, leading to increased plasma levels.

Use in children

The safety and efficacy of metoprolol in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In rats at dietary doses of up to 800 mg/kg/day (36 times the maximum recommended clinical dose (MRCD) on a mg/m^2 basis) for 18 months, there was no increase in the incidence of neoplasms. The only histologic changes that appeared to be drug related were an increased incidence of focal accumulation of foamy macrophages in pulmonary alveoli and an increased incidence of biliary hyperplasia.

In a 21-month study in CD-1 mice at dietary doses of up to 750 mg/kg/day (17 times the MRCD on a mg/m^2 basis), benign lung tumours (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumours, nor in the overall incidence of tumours.

Metoprolol tartrate was not mutagenic in a bacterial assay, nor did it induce chromosomal damage in Chinese hamsters (bone marrow micronucleus and chromosome aberration assays) or in mice (dominant lethal assay).

In rats dosed with 500 mg/kg/day (23 times the MRCD on a mg/m^2 basis), there was a slight decrease in insemination rate (75% cf. 95% in untreated controls) with signs of maternal toxicity. There was no evidence of impaired fertility at 50 mg/kg/day (2.3 times the MRCD).

USE IN PREGNANCY Category C

As with most drugs, TOPROL-XL should not be given during pregnancy unless its use is considered essential. As with all antihypertensive agents, β-blockers may cause side effects (e.g. reduced placental perfusion and bradycardia) in the foetus and newborn. During the late stages of pregnancy these drugs should only be given after weighing the needs of the mother against the risk to the foetus.

The lowest possible dose should be used and discontinuation of treatment should be considered at least 2 to 3 days before delivery to avoid increased uterine contractility and effects of β-blockade in the newborn (e.g. bradycardia, hypoglycaemia).

Metoprolol tartrate was shown to increase foetal loss in rabbits at 25 mg/kg/day PO (2 times the MRCD on a mg/m^2 basis), and increase still births and decrease neonatal survival in rats at 500 mg/kg/day PO (23 times the MRCD on a mg/m^2 basis). These studies revealed no evidence of teratogenicity.

USE IN LACTATION

As with most drugs, TOPROL-XL should not be given during lactation unless its use is considered essential. As with all antihypertensive agents, β-blockers may cause side effects (e.g. bradycardia), in the breast-fed infant. The amount of metoprolol ingested via breast-milk seems to be negligible, in regard to β-blocking effect in the infant, if the mother is treated with metoprolol in doses within the normal therapeutic range.

Postnatal growth was not affected in lactating rats dosed with metoprolol tartrate at up to 500 mg/kg/day PO (23 times the MRCD on a mg/m^2 basis).

INTERACTIONS WITH OTHER DRUGS

CYP2D6 Inhibitors

Coadministration of drugs which inhibit CYP2D6 such as quinidine, fluoxetine and paroxetine may cause increased exposure to metoprolol and consequent increased pharmacological effects.

Concomitant administration of the CYP2D6 inhibitor quinidine has been shown to substantially increase systemic exposure of both enantiomers of metoprolol. In healthy subjects with CYP2D6 extensive metaboliser phenotype, coadministration of quinidine 100 mg and immediate release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. These increases in plasma concentration are ~~This increase is~~ highly likely to be associated with exaggerated pharmacological effects and decrease in the cardioselectivity of metoprolol.. Interactions with hydroxychloroquine and diphenhydramine, although smaller, could still be clinically significant.

Other anti-hypertensive agents

Metoprolol enhances the effects of other antihypertensive drugs. Particular care is required when initiating administration of a β-blocker and prazosin together.

Sympathetic ganglion blocking agents, other β-blockers or monoamine oxidase (MAO) inhibitors

Patients receiving concomitant treatment with sympathetic ganglion blocking agents, other β-blockers (including eye drops), or monoamine oxidase (MAO) inhibitors should be kept under close surveillance.

Clonidine

Concurrent use of β-blockers and clonidine should be avoided because of the risk of adverse interaction and severe withdrawal symptoms.

If concomitant treatment with clonidine is to be discontinued, the β-blocker medication should be withdrawn several days before the gradual withdrawal of clonidine. The rebound hypertension associated with clonidine withdrawal can be exacerbated by the presence of a β-blocker. If both drugs are withdrawn simultaneously, a marked rise in blood pressure and/or arrhythmias may result.

If replacing clonidine by β-blocker therapy, the introduction of β-blockers should be delayed for several days after clonidine administration has stopped.

Calcium antagonists

If TOPROL-XL is given with calcium antagonists of the verapamil and diltiazem type the patient should be monitored for possible negative inotropic and chronotropic effects. Calcium antagonists of the phenylalkylamine type (e.g. verapamil) should not be given by intravenous administration to patients treated with metoprolol because there is a risk of cardiac arrest in

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this situation. Patients taking oral calcium antagonists of this type in combination with metoprolol should be closely monitored.

The combination of β-blockers with dihydropyridine calcium channel blockers with a weak myocardial depressant effect (e.g. felodipine, nifedipine) can be administered together with caution. In case excess hypotension develops, the calcium antagonist should be stopped or the dosage reduced.

Antiarrhythmic agents

When metoprolol is given together with antiarrhythmic agents, the patients should be monitored for possible negative inotropic and chronotropic effects. The negative inotropic and negative chronotropic effects of antiarrhythmic agents of the quinidine type and amiodarone may be enhanced by β-blockers. Interactions have been reported during concomitant β-blocker therapy with the Class IA agents disopyramide, and less frequently quinidine; class IB agents, tocainide, mexiletine and lignocaine; the Class IC agent flecainide; the Class III agent amiodarone; and the Class IV antiarrhythmic agents (e.g. verapamil).

Anaesthetics

In patients receiving β-blocker therapy, inhalation anaesthetics enhance the cardiodepressant effect (see PRECAUTIONS). Metoprolol may also reduce the clearance of other drugs (e.g. lignocaine).

Modern inhalational anaesthetic agents are generally well tolerated, although older agents (ether, cyclopropane, methoxyflurane, trichlorethylene) were sometimes associated with severe circulatory depression in the presence of β-blockage.

Liver enzyme effects

Enzyme-inducing and enzyme-inhibiting substances may exert an influence on the plasma level of metoprolol. The plasma concentration of metoprolol is lowered by rifampicin and may be raised by cimetidine, alcohol, hydralazin, and selective serotonin re-uptake inhibitors (SSRIs) e.g. paroxetine, fluoxetine, and sertraline, quinidine, verapamil and diphenhydramine..

Prostaglandin synthetase inhibiting agents

Concomitant treatment with indomethacin or other prostaglandin synthetase inhibiting agents may decrease the antihypertensive effect of β-blockers.

Alcohol

Metoprolol may modify the pharmacokinetic behaviour of alcohol when taken together. The plasma level of metoprolol may be raised by alcohol.

Oral antidiabetic agents

The dosages of oral antidiabetics may need to be adjusted in patients receiving β-blockers. (see PRECAUTIONS).

Warfarin

A limited number of reports have demonstrated a rise in AUC and concentration of warfarin when taken with another β-blocker. This could potentially increase the anti-coagulant effect of warfarin.

Catecholamine-depleting agents

Concomitant use of catecholamine-depleting drugs such as reserpine, mono amine oxidase (MAO) inhibitors and guanethidine have an additive effect when given with β-blocking agents. Patients treated with TOPROL-XL plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension, ~~requires careful monitoring~~ since the added effect of a β-blocker may produce an excessive reduction of the resting sympathetic nervous tone.

ADVERSE REACTIONS

TOPROL-XL is well tolerated and adverse reactions have generally been mild and reversible. The following events have been reported as adverse events in clinical trials or reported from routine use, mostly with conventional metoprolol (metoprolol tartrate). In many cases a relationship with metoprolol has not been established.

The following definitions of frequency are used: very common ≥ 10%; common 1 - 9.9%; uncommon 0.1 - 0.9%; rare 0.01 - 0.09%; very rare < 0.01%.

Cardiovascular

Common:	Bradycardia, postural disorders (very rarely with syncope), cold hands and feet (Raynaud's phenomenon), palpitations.
Uncommon:	Transient deterioration of heart failure symptoms, A-V block I, oedema, precordial pain.
Rare:	Disturbances of cardiac conduction, cardiac arrhythmias.
Very rare:	Gangrene in patients with pre-existing severe peripheral circulatory disorders.

Central nervous system

Very common:	Fatigue
Common:	Dizziness, headache.
Uncommon:	Paraesthesia, muscle cramps.

Gastrointestinal

Common:	Nausea, diarrhoea, constipation, abdominal pain.
Uncommon:	Vomiting
Rare:	Dry mouth

Haematologic

Very rare:	Thrombocytopenia

Hepatic

Rare:	Liver function test abnormalities
Very Rare:	Hepatitis

Metabolic

Uncommon:	Weight gain

Psychiatric

Uncommon:	Depression, impaired concentration, somnolence or insomnia, nightmares.
Rare:	Nervousness, anxiety, impotence / sexual dysfunction.
Very rare:	Amnesia / memory impairment, confusion, hallucinations.

Respiratory

Common:	Dyspnoea on exertion
Uncommon:	Bronchospasm (which may also occur in patients without a history of obstructive lung disease)
Rare:	Rhinitis

Sense organs

Rare:	Disturbances of vision, dry and/or irritated eyes, conjunctivitis.
Very rare:	Tinnitus, taste disturbances.

Skin

Uncommon:	Rash (in the form of urticaria, psoriasiform and dystrophic skin lesions), increased sweating.
Rare:	Loss of hair
Very rare:	Photosensitivity reactions, aggravated psoriasis.

Miscellaneous

Very rare:	Arthralgia

DOSAGE AND ADMINISTRATION

TOPROL-XL has not been established to be clinically equivalent to immediate release forms of metoprolol, and should not be used for treatment of conditions other than stable, chronic heart failure.

TOPROL-XL ~~(metoprolol succinate)~~ is recommended for once daily treatment and is preferably taken together with the morning meal. The tablets may be broken in half. TOPROL-XL tablets should be swallowed with liquid and should not be chewed or crushed.

The dose of TOPROL-XL should be individu lly adjusted in patients with chronic heart failure stabilised on other heart failure treatment.

It is recommended that patients be titrated from an initial low dose in accordance with the following titration schedule:

Titration schedule

TOPROL-XL	Treatment Regimen
Initial dose: TOPROL-XL 23.75	½ or 1 tablet daily for 2 weeks*
TOPROL-XL 47.5	1 tablet daily for 2 weeks
TOPROL-XL 95	1 tablet daily for 2 weeks
TOPROL-XL 190 or highest tolerated dose	Continued#

*Patients with moderate to severe heart failure (NYHA III-IV): It is recommended that these patients start treatment with a half a TOPROL-XL 23.75 tablet od for one week, then take a full TOPROL-XL 23.75 tablet od for the second week.

#Maintenance dose: During long term treatment the aim should be to reach TOPROL-XL 190 od (or the highest tolerated dose).

The patient should be carefully evaluated at each dose level with regard to tolerability. If the patient experiences hypotension a decreased dose of concomitant heart failure medication may be necessary. Initial hypotension does not necessarily mean that the dose cannot be tolerated during chronic treatment but the patient should be kept at the lower dose until their blood pressure has stabilised.

Some patients may experience an initial, usually transient, worsening of the symptoms and signs of heart failure when starting treatment with TOPROL-XL. If this occurs, the patient should be monitored very closely and the dose of TOPROL-XL should be reduced if symptoms continue to worsen. TOPROL-XL should not be ceased abruptly due to the risk of rebound hypertension and tachycardia. If treatment is to be discontinued, it should be reduced gradually (see PRECAUTIONS).

Impaired renal and hepatic function

Dose adjustment is not needed in patients with impaired renal function.

Dose adjustment is normally not needed in patients suffering from liver cirrhosis because metoprolol is low protein binding (5-10%). When there are signs of serious impairment of liver function (e.g. patients who have had a shunt operation), a dose reduction should be considered.

Elderly

Dose adjustment is not needed in the elderly.

Children

There is limited experience with TOPROL-XL treatment in children.

OVERDOSAGE

Symptoms

Overdosage of TOPROL-XL may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness/coma, convulsions, nausea, vomiting, and cyanosis.

Concomitant ingestion of alcohol, antihypertensives, quinidine or barbiturates may aggravate the patient's condition. The first manifestations of overdose may be observed 20 minutes to 2 hours after the drug is ingested.

Management

Induction of vomiting or gastric lavage. In the presence of severe hypotension, bradycardia, and impending heart failure, administer a β_1-agonist (e.g. isoprenaline) intravenously at 2-5 minute intervals or as continuous infusion until the desired effect is achieved. Where a selective β_1-agonist is not available, dopamine or atropine sulphate i.v. may be used in order to block the vagus nerve. If a satisfactory effect is not achieved, other sympathomimetic agents, such as dobutamine may be used, or noradrenaline may be given.

Glucagon in a dose of 1-10 mg can also be administered. Glucagon activates the adenylcyclase system independently of the β-receptor, augmenting the contractility in the presence of β-blockade. A pacemaker may be necessary.

To combat bronchospasm, a β_2-agonist can be given intravenously.

Observe that the dosage of drugs (antidotes) needed to treat overdose of β-blockade are much higher than normally recommended therapeutic dosages. This is because β-receptors are occupied by the β-blocker.

PRESENTATION

All TOPROL-XL tablets are white to off white in colour and have the following appearance:

TOPROL-XL 23.75 tablets (23.75 mg) are oval-shaped with one side marked with "A/β" and a breakline on both sides.

TOPROL-XL 47.5 tablets (47.5 mg) are circular-shaped with one side marked with "A/mO" and a breakline on the other side.

TOPROL-XL 95 tablets (95 mg) are circular-shaped with one side marked with "A/mS" and a breakline on the other side.

TOPROL-XL 190 tablets (190 mg) are oval-shaped with one side marked with "A/mY" and a breakline on the same side.

TOPROL-XL tablets are available as:

Calendar blister packs: 15 tablets (TOPROL-XL 23.75, 47.5 & 95) and 30 tablets (TOPROL-XL 95 & 190)

POISON SCHEDULE OF THE DRUG S4

STORAGE Store below 30°C

NAME AND ADDRESS OF ~~MANUFACTURER/DISTRIBUTOR~~ SPONSOR

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