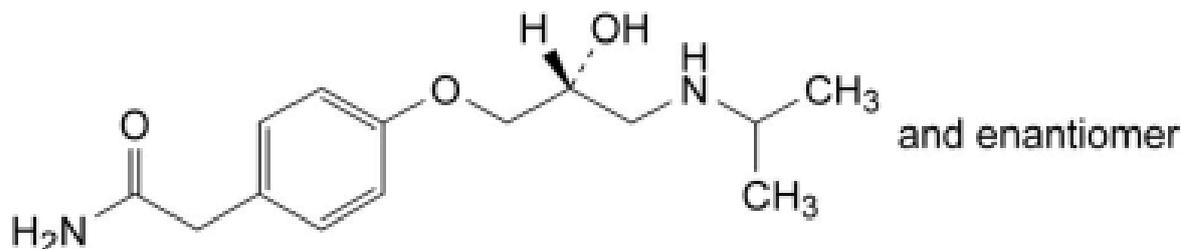


PRODUCT INFORMATION
ATENOLOL SANDOZ® 50mg FILM COATED TABLETS

NAME OF THE MEDICINE

Atenolol

Chemical name: (RS)-4-(2-hydroxy-3-isopropylaminopropoxy)phenyl]acetamide.



CAS [29122-68-7]

C₁₄H₂₂N₂O₃

MW: 266.3

DESCRIPTION

Atenolol is a white or almost white powder, sparingly soluble in water, soluble in ethanol, slightly soluble in methylene chloride and practically insoluble in ether.

The excipients in Atenolol Sandoz tablets include maize starch, sodium lauryl sulfate, heavy magnesium carbonate, magnesium stearate, gelatin, lactose, hypromellose, titanium dioxide and macrogol 4000.

PHARMACOLOGY

Beta-adrenoceptor blocking agent structurally related to propranolol and differing from it by substitution on the aromatic ring.

Pharmacology

Atenolol is a beta -adrenoceptor blocking agent which acts preferentially on beta-receptors in the heart. It has little intrinsic sympathomimetic activity and no membrane stabilising activity. It reduces raised blood pressure by an unknown mechanism and also inhibits exercise induced tachycardia and decreases plasma renin concentration. It causes slight airways obstruction but less than that seen with non selective beta-blockers. The inhibition of exercise induced tachycardia is correlated with blood levels but there is no correlation between plasma concentrations and antihypertensive effect.

The possible mechanism of the anti-anginal activity of atenolol appears to be due to a reduction in left ventricular work and oxygen utilisation resulting (mainly) from the decrease in heart rate and contractility.

The antiarrhythmic effect of atenolol is apparently due to its anti-sympathetic effect. There is no evidence that membrane stabilising activity or intrinsic sympathomimetic activity are necessary for antiarrhythmic efficacy. By its anti-sympathetic effect, atenolol depresses sinus node function, atrioventricular node function and prolongs atrial refractory periods. It has no direct effect on electrophysiological properties of the His-Purkinje system.

Selectivity decreases with increasing doses.

Atenolol is a racemic mixture and its activity resides in the S(-) enantiomer.

Atenolol is effective and well tolerated in most ethnic populations although the response may be less in Afro-Caribbean black patients.

Because of their negative inotropic effects, beta-adrenoreceptor blocking agents should be avoided in uncontrolled heart failure.

Pharmacokinetics

Although absorption of atenolol is variable and incomplete (40 to 60%), the virtual lack of hepatic metabolism results in relatively consistent systemic bioavailability compared to other beta-blockers. Blood levels in humans peak two to four hours after a single 100mg oral dose and are of the order of 0.4 to 0.9 microgram/mL. Blood levels are consistent and the levels after chronic oral administration are in good agreement with those predicted from single dose results. The medicine is distributed throughout the body tissues and less than 10% of the dose is metabolised, the minor urinary metabolite identified being a hydroxylated derivative. The main route of elimination is renal excretion. The plasma half-life, measured by blood level decay or urinary build-up is approximately seven to nine hours. In patients with impaired renal function, there is a progressive prolongation of the half-life. In patients with normal renal function, the therapeutic effect (i.e. control of raised blood pressure) lasts for at least 24 hours following a 50mg oral dose.

INDICATIONS

All grades of hypertension, including hypertension of renal origin.

Frequent disabling angina without evidence of cardiac failure.

Cardiac arrhythmias (maintenance treatment of supraventricular and ventricular arrhythmias which have been controlled with intravenous atenolol, including those associated with acute myocardial infarction).

Myocardial infarction: late intervention (beta-blockers class effect).

CONTRAINDICATIONS

Bronchospasm. Beta-adrenergic blockade of the smooth muscle of bronchi and bronchioles may result in an increased airways resistance. These medicines also reduce the effectiveness of asthma treatment. This may be dangerous in susceptible patients. Therefore beta-blockers are contraindicated in any patient with a history of airways obstruction or tendency to bronchospasm. Use of cardioselective beta-blockers can also result in severe bronchospasm (see PRECAUTIONS, Allergic conditions).

Congestive heart failure

Allergic disorders (including allergic rhinitis) which may suggest a predisposition to bronchospasm

Right ventricular failure secondary to pulmonary hypertension

Significant right ventricular hypertrophy

Bradycardia (< 45 bpm)

Sick sinus syndrome

Second and third degree heart block

Shock (including cardiogenic and hypovolaemic shock)

Hypotension

Metabolic acidosis

Severe peripheral arterial circulatory disturbances

Untreated pheochromocytoma

Anaesthesia with agents that produce myocardial depression (e.g. ether, chloroform, cyclopropane)

Pregnancy and lactation (see PRECAUTIONS, Use in pregnancy and Use in lactation)

Known hypersensitivity to the active ingredient or any of the excipients.

PRECAUTIONS

Heart Failure

Beta-blockade depresses myocardial contractility and may precipitate cardiac failure in some patients with a history of cardiac failure, chronic myocardial insufficiency or unsuspected cardiomyopathy as may occur in chronic alcoholism. In patients without a history of cardiac failure, continuing depression of the myocardium may lead to cardiac failure. If signs of cardiac failure are present, the patient should be fully digitalised and/or given an ACE inhibitor or vasodilators with or without a diuretic and carefully monitored. If cardiac failure persists, the beta-blocker should be withdrawn (see *abrupt withdrawal of therapy*, below).

Note. Although congestive heart failure has been considered to be a contraindication to the use of beta-blockers, there is growing literature on the experimental use of beta-adrenergic blocking medicines in heart failure. As further trials are needed to identify which patients are most likely to respond to which medicines, beta-blockers should not normally be prescribed for heart failure outside of specialist centres.

Abrupt withdrawal of therapy

Atenolol, as with other beta-blockers, should not be withdrawn abruptly. The dosage should be withdrawn gradually over a period of 7-14 days, to facilitate a reduction in beta-blocker dosage. Patients should be followed during withdrawal, especially those with ischaemic heart disease. Care should be taken if beta-blockers have to be discontinued abruptly in patients with coronary artery disease. Severe exacerbation of angina and precipitation of myocardial infarction and ventricular arrhythmias have occurred following abrupt discontinuation of beta-blockade in patients with ischaemic heart disease. The drug may be reinstated temporarily if the angina worsens. If the drug must be withdrawn abruptly, close observation is required. In the perioperative period, beta-blockers should not be withdrawn unless indicated.

When a patient is scheduled for surgery, and a decision is made to discontinue beta-blocker therapy, this should be done at least 24 hours prior to the procedure. The risk-benefit assessment of stopping beta-blockade should be made for each patient. If treatment is continued, an anaesthetic with little negative inotropic activity should be selected to minimise

the risk of myocardial depression. The patient may be protected against vagal reactions by intravenous administration of atropine.

Concomitant therapy with calcium antagonists

The concomitant use of beta-blockers and calcium antagonists with myocardial depressant and sinus node activity, e.g. verapamil and to a lesser extent diltiazem, may cause hypotension, bradycardia and asystole, particularly in patients with impaired ventricular function and/or sinoatrial or atrioventricular conduction abnormalities. Extreme caution is required if these medicines have to be used together.

Concomitant therapy with dihydropyridines, e.g. nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Antiarrhythmic medicines

Care should be taken when prescribing beta-blockers with antiarrhythmic medicines. Interactions have been reported during concomitant beta-blockers therapy with the class IA agents disopyramide and less frequently quinidine: class IB agents, tocainide, mexiletine and lignocaine: class IC agents, flecainide and propafenone (not available in Australia): the class III agent, amiodarone: and the class IV antiarrhythmic agents.

Peripheral circulation

Beta-blockade may impair the peripheral circulation and exacerbate the symptoms of peripheral vascular disease.

Prinzmetal angina

If this treatment is essential, it should only be undertaken in a coronary or intensive care unit. Atenolol as with other beta-blockers may increase the number and duration of angina attacks in patients with Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Atenolol is a beta1 selective beta-blocker; consequently, utmost caution must be exercised if its use is to be considered.

Euthyroid hyperthyroxinaemia

The effects of beta-blockers on thyroid hormone metabolism may result in elevations of serum free thyroxine (T₄) levels. In the absence of any signs or symptoms of hyperthyroidism, additional investigation is necessary before a diagnosis of thyrotoxicosis can be made.

Use in myocardial infarction

In addition to the contraindications listed (see CONTRAINDICATIONS), patients with the following conditions are not suitable for treatment with atenolol:

- *First degree atrioventricular block*: there is an increased incidence of cardiogenic shock (and need for inotropes), complete heart block and cardiovascular death in these patients following use of atenolol.
- Patients with atrial fibrillation following myocardial infarction who were treated with atenolol also had increased cardiovascular mortality compared with those not treated with atenolol. It is suggested that such patients be digitalised before atenolol therapy is commenced.
- *Systolic blood pressure less than 120mmHg*: systolic blood pressure less than 120mmHg in combination with a heart rate greater than 90 beats/minute has a particularly poor prognosis.

First degree heart block

Due to its negative effect on conduction time, caution must be exercised if atenolol is given to patient with first degree heart block.

Heart rate

Atenolol will reduce heart rate as a result of its pharmacological action. In the rare instances when a treated patient develops symptoms which may be attributable to a slow heart rate and the pulse rate drops to less than 50–55 bpm at rest, the dose should be reduced.

Anaesthesia and the perioperative period

Beta-blockade may have beneficial effects in decreasing the incidence of arrhythmias and myocardial ischaemia during anaesthesia and the postoperative period. It is currently recommended that maintenance beta-blockade be continued perioperatively. The anaesthetist must be made aware of beta-blockade because of the potential for interactions with other medicines, resulting in severe bradyarrhythmias and hypotension, the decreased reflex ability to compensate for blood loss, hypovolaemia and regional sympathetic blockade, and the increased propensity for vagal induced bradycardia. Incidents of protracted severe hypotension or difficulty restoring normal cardiac rhythm during anaesthesia have been reported. 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 beta-blockade.

Diabetes

Beta-blockers affect glucose metabolism and may mask the symptoms of hypoglycaemia, in particular, tachycardia.

In patients with insulin or non-insulin dependent diabetes, especially labile diabetes, or with a history of spontaneous hypoglycaemia, beta-blockade may result in the loss of diabetic control and delayed recovery from hypoglycaemia. The dose of insulin or oral hypoglycaemic agent may need adjustment.

Other metabolic effects

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

Use of catecholamine depleting agents

Concomitant use of medicines such as reserpine and guanethidine requires careful monitoring since the added effect of beta-blockade may produce an excessive reduction of the resting sympathetic nervous tone.

Phaeochromocytoma

As with other beta-blocker, in patients with this condition, an alpha-blocker should be given concomitantly to avoid exacerbation of hypertension.

Eye and skin reactions

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

During long term treatment with the beta-blocking medicine practolol, a specific rash bearing a superficial resemblance to psoriasis was occasionally described. In a number of patients affected, this rash was accompanied by adverse effects on the eye (xerophthalmia and/or

keratoconjunctivitis) of varying severity. This condition is called the oculomuocutaneous syndrome or practolol syndrome. In a few patients, these eye changes occurred independently of a skin rash. On rare occasions, serious otitis media, sclerosing peritonitis, pericarditis and pleurisy have been reported. Although the practolol syndrome has not been observed in patients taking other beta-blockers, the possibility of such side effects occurring should be borne in mind.

Atenolol should only be given to patients with psoriasis after careful consideration, as psoriasis may be aggravated.

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

Allergic conditions

Beta-blockers should be avoided if there is a risk of bronchospasm. Atenolol may cause a more severe reaction to a variety of allergens when given to patients with a history of anaphylactic reaction to such allergens. Such patients may be unresponsive to the usual doses of adrenaline (epinephrine) used to treat the allergic reactions.

Atenolol may cause a hypersensitivity reaction including angioedema and urticaria.

Atenolol may cause an increase in airways resistance in asthmatic patients. If increased airways resistance does occur, atenolol should be discontinued and bronchodilator therapy (e.g. salbutamol) administered if necessary.

Hyperthyroidism

Because beta-blockers may mask the clinical signs of developing or continuing hyperthyroidism, resulting in symptomatic improvement without any change in thyroid hormone status, special care should be exercised in those patients who are hyperthyroid and are also receiving beta-blockers.

Clonidine

Concurrent use of beta-blockers and clonidine should be avoided because of the risk of adverse interaction and severe withdrawal symptoms. If administered concomitantly, the clonidine should not be discontinued until several days after the withdrawal of the beta-blocker.

Significant cardiomegaly

Impaired renal function

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

Effect on the ability to drive or operate machinery

While it is unlikely that atenolol will impair these abilities, it should be taken into account that occasionally dizziness or fatigue may occur.

Use in pregnancy (Category C)

Beta-adrenergic blocking agents may cause pharmacological effects such as bradycardia in the foetus and new born infant. Therefore, during the later stages of pregnancy and parturition, these medicines should only be given after weighing the needs of the mother against the risk to the foetus.

Atenolol crosses the placental barrier and appears in the cord blood. In pregnant women and under steady state conditions, maternal and foetal blood levels of atenolol are approximately equal.

No studies have been performed on the use of atenolol in the first trimester and the possibility of foetal injury cannot be excluded. Atenolol has been used under close supervision for the treatment of hypertension in the third trimester. Administration of atenolol for longer periods to pregnant women in the management of mild to moderate hypertension has been associated with intrauterine growth retardation.

The use of atenolol in women who are, or may become, pregnant requires that the anticipated benefit be weighed against the possible risks, particularly in the first and second trimesters., since beta-blockers, in general, have been associated with a decrease in placental perfusion which may result in intra-uterine deaths, immature and premature deliveries.

Atenolol has been shown to produce a dose related increase in embryo/foetal resorptions in rats at doses equal to or greater than 50mg/kg. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25mg/kg.

Use in lactation

There is significant accumulation of atenolol in breast milk. Caution should be exercised when atenolol is administered to breastfeeding women and the infant should be regularly assessed for signs of beta-blockade.

Use in the elderly

Atenolol should be used with caution in the elderly, starting with a lesser dose.

INTERACTIONS WITH OTHER MEDICINES

Calcium antagonists with myocardial depressant effects, such as Verapamil (see PRECAUTIONS, Concomitant therapy with calcium antagonists).

Care should be taken in prescribing a beta-adrenoceptor blocking medicine with antiarrhythmic medicines (see PRECAUTIONS, Antiarrhythmic medicines).

Insulin and oral hypoglycaemics (see PRECAUTIONS, Diabetes).

Anaesthetics such as ether, chloroform and cyclopropane are contraindicated with atenolol (see PRECAUTIONS, Anaesthesia and the perioperative period).

Catecholamine depleting medicines such as reserpine or guanethidine (see PRECAUTIONS, Use of catecholamine depleting agents).

Clonidine (see PRECAUTIONS, Clonidine)

Digitalis/digitalis glycosides and β -blockers are commonly used together, although there have been reports of excessive bradycardia when beta-blockers are used to treat digitalis intoxication.

Concomitant use of sympathomimetic agents, e.g. adrenaline (epinephrine), may counteract the effect of beta-blockers.

Concomitant use of prostaglandin synthetase inhibiting medicines, e.g. ibuprofen and indomethacin, may decrease the hypotensive effects of beta-blockers.

Concomitant use of baclofen may increase the antihypertensive effect making dose adjustments necessary.

ADVERSE EFFECTS

Clinical trial data

Adverse effects reported in clinical trials of atenolol are mainly attributable to pharmacological actions. The adverse reactions listed below have been observed in patients in clinical trials who have received dosages of about 100mg/day. It is not possible to give percentage incidences for each reaction, but if all mild and transient reactions are included as well as more serious ones, up to 10% of patients may experience some form of adverse reaction.

Frequency of possible side effects listed below is

More common reactions

Gastrointestinal. Disturbances including indigestion, constipation, dry mouth

Nervous System. Fatigue, dizziness.

Respiratory Wheezing, bronchospasm (see CONTRAINDICATIONS)

Less common reactions

Biochemical. Increases in AST, blood urea and serum creatine have been reported.

Cardiovascular. Bradycardia, left ventricular insufficiency, postural hypotension (which may be associated with syncope), intermittent claudication may occur if already present, Raynaud's phenomenon, cold extremities, deterioration in heart failure, heart block.

Dermatological. Rash, alopecia, psoriasiform skin reaction, exacerbation of psoriasis.

Gastrointestinal. Diarrhoea.

Hepatic. Elevations of transaminase levels have been seen infrequently, rare cases of hepatic toxicity including intrahepatic cholestasis have been reported.

Genitourinary. Impotence.

Musculoskeletal. Ataxia.

Nervous system. Vivid dreams, paraesthesiae, tinnitus, vertigo, malaise, headache, insomnia, mood changes, nightmares, confusion.

Ocular. Dry eyes, visual disturbances.

Psychiatric. Hallucinations, depression, psychoses.

Respiratory. Asthma, dyspnoea, nasal congestion.

Haematological. Thrombocytopenia, purpura. An increase in ANA (Antinuclear Antibodies) has been observed, however, the clinical relevance of this is not clear.

Severe or life-threatening reactions

Myocardial insufficiency may require treatment with digitalis and diuretics. Bradycardia may respond to atropine. Bronchospasm may be reversed with a beta₂-stimulant. Hypotension, if severe, may require use of a vasopressor.

Post-marketing experience

The frequency of possible side effects listed below is defined as:

Very common ($\geq 1/10$), common ($\geq 1/100, < 1/10$), uncommon ($\geq 1/1.000, < 1/100$), rare ($\geq 1/10.000, < 1/1.000$), very rare ($< 1/10.000$), not known (frequency cannot be estimated from the available data).

Blood and lymphatic system disorders:

Rare: Thrombocytopenia, purpura

Psychiatric disorders:

Uncommon: sleep disturbances

Rare: mood changes, nightmares, confusion, psychoses and hallucinations

Nervous system disorders:

Rare: dizziness, headache, paresthesia

Eye disorders:

Rare: dry eyes, visual disturbances

Cardiac disorders:

Common: bradycardia

Rare: heart failure deterioration, precipitation of heart block

Vascular disorders:

Common: cold extremities

Rare: postural hypotension which may be associated with syncope, intermittent claudication may be increased if already present, in susceptible patients
Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders:

Rare: bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints

Gastrointestinal disorders:

Common: gastrointestinal disturbances

Rare: dry mouth

Not known: constipation

Hepatobiliary disorders:

Uncommon: elevations of transaminase levels

Rare: hepatic toxicity including intrahepatic cholestasis

Skin and subcutaneous tissue disorders:

Rare: alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rash

Not known: hypersensitivity reactions, including angioedema and urticaria

Reproductive system and breast disorders:

Rare: impotence

General disorders and administration site conditions:

Common: fatigue

Investigations:

Very rare: an increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear

DOSAGE AND ADMINISTRATION

Adults

Hypertension. Therapy should be initiated with Atenolol Sandoz 50mg daily. This may be increased each week in daily doses of 50mg up to a maximum of 200mg. Where patients are controlled on daily doses of 50 to 100mg this may be given once daily. Doses above 100mg daily should be given on a divided basis. Where necessary, a further reduction in blood pressure may be achieved by combining Atenolol Sandoz with other antihypertensive agents. Patients can be transferred to Atenolol Sandoz from other antihypertensive treatments with the exception of clonidine (see PRECAUTIONS Clonidine).

Angina pectoris. Therapy should be initiated with Atenolol Sandoz 50mg daily. This may be increased if required to 100mg daily given as a single or divided dose. It is unlikely that additional benefit will be gained by increasing the dose.

Cardiac dysrhythmias. 50mg to 100mg daily (for controlled cardiac dysrhythmias).

Acute myocardial infarction. Data from other beta-blocker trial suggest that there is a significant reduction in mortality and a reduced incidence of nonfatal re-infarction if the beta-blocker is continued for one to three years. Hence, maintenance oral therapy of Atenolol Sandoz 50mg daily is recommended for one to three years following myocardial infarction, beginning after early intervention with intravenous atenolol, or immediately in those patients who present more than 12 hours after suffering an acute myocardial infarction.

Impaired renal function.

Since atenolol is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of atenolol occurs at a creatine clearance greater than 35 mL/minute/1.73m² (normal range is 100 to 150 mL/minute/1.73m²). For patients with a creatine clearance of 15 to 35 mL/minute/1.73m² (equivalent to serum creatinine of 300 to 600 micromol/L), the oral dose should be 50mg daily or 100mg on alternate days. For patients with a creatinine clearance less than 15 mL/minute/1.73m² (equivalent to serum creatinine greater than 600 micromol/L), the oral dose should be 50mg on alternate days or 100mg every fourth day.

Elderly

Similarly, dosage requirements in the elderly may need to be reduced, especially in patients with impaired renal function.

Patients on haemodialysis should be given 50mg orally after each dialysis: this should be done under hospital supervision as marked falls in blood pressure can occur.

Children

There is no experience with atenolol in children.

OVERDOSAGE

Symptoms

The symptoms of overdosage may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

Treatment

General treatment should include: close supervision, treatment in an intensive care ward; the use of gastric lavage; activated charcoal and a laxative to prevent absorption of any medicine still present in the gastrointestinal tract; the use of plasma or plasma substitutes to treat hypotension and shock. The possible uses of haemodialysis or haemoperfusion may be considered.

Severe bradycardia. Atropine 1 to 2mg intravenously may be used to induce vagal blockade. If bradycardia persists, intravenous isoprenaline (25 microgram initially) or orciprenaline (0.5mg given by slow intravenous injection) may be given. In refractory cases, the use of a cardiac pacemaker may be considered.

Hypotension. Severe hypotension should respond to a sympathomimetic amine such as noradrenaline. In refractory cases, the use of glucagon hydrochloride should be considered. Dobutamine, because of its positive inotropic effect could also be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta-blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

Bronchospasm Therapy with a beta₂-stimulant such as salbutamol or terbutaline or therapy with aminophylline may be considered.

Acute cardiac failure. Conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases, the use of intravenous isoprenaline, followed if necessary by glucagon hydrochloride or intravenous aminophylline, should be considered.

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS

Atenolol Sandoz 50mg tablets: white, round, biconvex film-coated tablet with one-sided score notch. They are available in blister packs of 30 per pack.

Store below 25°C. Protect from light and moisture.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):
27/08/2004

Date of most recent amendment: 02/12/2015