

# NEW ZEALAND DATASHEET

## Atehexal

*Atenolol, film coated tablets, 50 mg and 100 mg*

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### Presentation

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#### **50 mg**

White, 9 mm round, biconvex film coated tablets, scored on one side. Each tablet contains atenolol 50 mg.

#### **100 mg**

White, round, biconvex film coated tablets, scored on one side. Each tablet contains atenolol 100 mg.

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### Uses

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#### **Actions**

Atenolol is a beta-adrenoceptor blocking agent structurally related to propranolol and differing from it by substitution on the aromatic ring.

#### **Pharmacotherapeutic group**

C07AB03 - Beta blocking agents, selective, atenolol.

#### **Mechanism of action**

Atenolol is a beta-adrenoreceptor blocking medicine, which acts preferentially on beta receptors in the heart. Selectivity decreases with increasing dose. It has little intrinsic sympathomimetic activity and no membrane-stabilising activity. Atenolol is a racemic mixture and its activity resides in the S(-) enantiomer. 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.

#### **Pharmacodynamic effects**

The anti-arrhythmic 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 anti-arrhythmic 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.

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**

### **Absorption**

Although absorption of atenolol is variable and incomplete (40 to 60%) the virtual lack of hepatic metabolism results in a relatively consistent systemic bioavailability compared to other beta-blockers. Blood levels in humans peak 2 to 4 hours after a single 100 mg oral dose and are of the order of 0.4 to 0.9 mcg/ml. Blood levels are consistent and the levels after chronic oral administration are in good agreement with those predicted from single dose results.

### **Distribution**

The drug is distributed throughout the body tissues.

### **Biotransformation**

Less than 10% of the dose is metabolised, the minor urinary metabolite identified being a hydroxylated derivative.

### **Elimination**

The main route of elimination is renal excretion. The plasma half-life, measured by blood level decay or urinary build up, is approximately 7 to 9 hours. In patients with impaired renal function there is a progressive prolongation of the half-life.

### **Correlation with therapeutic activity**

In patients with normal renal function, the therapeutic effect (ie. control of raised blood pressure) lasts for at least 24 hours following a 50 mg oral dose.

## **Indications**

Control of hypertension.

Management of angina pectoris.

Control of cardiac dysrhythmias.

Myocardial infarction: early intervention in the acute phase and long term prophylaxis after recovery.

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## **Dosage and administration**

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### **Adults**

#### *Hypertension*

Most patients respond to 50 to 100 mg daily given orally in a single dose. The effect will be fully established after one to two weeks. A further reduction in blood pressure may be achieved by combining atenolol tablets with other antihypertensive agents.

#### *Angina*

Most patients with angina pectoris will respond to 100 mg daily given orally as a single or divided dose. It is unlikely that additional benefit will be gained by increasing the dose.

#### *Dysrhythmias*

Having controlled the dysrhythmias with intravenous atenolol, a suitable oral maintenance dosage is 50 to 100 mg daily, given as a single dose.

#### *Myocardial infarction*

Early intervention with atenolol in acute myocardial infarction reduces infarct size and decreases morbidity and mortality. Fewer patients with a threatened infarction progress to a frank infarction; the incidence of ventricular arrhythmias is decreased and marked pain relief may result in reduced need of opiate analgesics. Early mortality is decreased. Atenolol is an additional treatment to standard

coronary care.

For patients suitable for treatment with intravenous beta-blockade and presenting within 12 hours of the onset of chest pain, atenolol (5 to 10 mg) should be given immediately by slow intravenous injection (1 mg/minute) followed by atenolol (50 mg) orally about 15 minutes later, provided no untoward effects occur from the intravenous dose. This should be followed by 50 mg orally 12 hours after the intravenous dose and then 12 hours later by 100 mg orally to be given once daily. If bradycardia and/or hypotension, or any other untoward effects requiring treatment occur, atenolol should be discontinued.

For patients who present some days after suffering an acute myocardial infarction, an oral dose of 100 mg daily is recommended for long term prophylaxis.

#### *Renal dysfunction*

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 in patients who have a creatinine clearance >35 ml/min/1.73 meters squared body surface area (normal range is 100 to 150 ml/min/1.73 meters squared body surface area). For patients with a creatinine clearance of 15 to 35 mL/min/1.73 meters squared body surface area (equivalent to serum creatinine of 300 to 600 micromol/litre) the oral dose should be 50 mg daily and the intravenous dose should be 10 mg once every two days. For patients with a creatinine clearance of <15 ml/min/1.73 meters squared body surface area (equivalent to serum creatinine of 600 micromol/litre) the oral dose should be 25 mg daily or 50 mg on alternate days and the intravenous dose should be 10 mg once every four days.

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

#### **Elderly**

Dosage requirements may be reduced especially in patients with impaired renal function.

#### **Children**

There is no experience with atenolol in children.

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## **Contraindications**

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Known hypersensitivity to atenolol, or to any of the inactive ingredients listed in [Further information](#).

#### **Asthma and other obstructive lung disorders**

Beta-adrenergic blockade of the smooth muscle of bronchi and bronchioles may result in an increased airway 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. If such therapy must be used, great caution should be exercised. Alternative therapy should be considered.

#### **Cardiovascular disease**

Uncontrolled congestive heart failure; right ventricular failure secondary to pulmonary hypertension; significant right ventricular hypertrophy; sick sinus syndrome; sinus bradycardia (less than 45 to 50 beats/minute); second and third degree atrio-ventricular block; shock (including cardiogenic and hypovolaemic shock); severe peripheral arterial circulatory disturbances; untreated phaeochromocytoma; hypotension.

#### **Other**

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

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

Metabolic acidosis.

Pregnancy and lactation.

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## Warnings and precautions

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### Cardiac 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 present, the patients 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.

Note: Although congestive heart failure has been considered to be a contraindication to the use of beta-blockers, there is a 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

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. Therefore, it is recommended that the dosage be reduced gradually over a period of about 8 to 14 days during which time the patient's progress should be reassessed. The medicine may be reinstated temporarily if the angina worsens. If the medicine must be withdrawn abruptly, close observation is required. In the peri-operative period, beta-blockers should not be withdrawn, unless indicated.

### Prinzmetal angina

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

### Peripheral circulation

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

### First degree heart block

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

### History of anaphylactic reaction

While taking beta-adrenoreceptor blocking agents, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reactions.

### 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 acute myocardial infarction**

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

- Systolic blood pressure less than 120 mmHg - systolic blood pressure less than 120 mmHg in combination with a heart rate greater than 90 beats/min has a particularly poor prognosis;
- First degree atrio-ventricular block - there is an increased incidence of cardiogenic shock (and need for inotropes), complete heart block and cardiovascular death in these patients, following atenolol administration.

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 such patients be digitalised before atenolol therapy is commenced.

### **Bradycardia**

If a treated patient develops symptoms which may be attributable to a slow heart rate, the dose may be reduced.

### **Anaesthesia and the peri-operative period**

Beta-blockade may have beneficial effects in decreasing the incidence of arrhythmias and myocardial ischaemia during anaesthesia and the post-operative period. It is currently recommended that maintenance of beta-blockade be continued peri-operatively. The anaesthetist must be made aware of beta-blockade because of the potential for interactions with other medication, 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 and trichloroethylene) were sometimes associated with severe circulatory depression in the presence of beta-blockade.

### **Diabetes**

Beta-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, 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.

### **Phaeochromocytoma**

In patients with this condition, an alpha-blocking agent (e.g. phentolamine / phenoxybenzamine) should be administered before the beta-blocker 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 drug practolol, a specific rash bearing a superficial resemblance to psoriasis was occasionally described. In a number of patients affected, this rash was associated with adverse effects on the eye (xerophthalmia and/or keratoconjunctivitis) of varying severity. This condition is called the oculomucocutaneous 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 considered.

More recently a putative association between Peyronie's disease (a fibrosing induration of the penis) and various beta-blockers has been suggested.

### **Allergic conditions**

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

### **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.

### **Renal disease**

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.

## ***Pregnancy and lactation***

### **Use in pregnancy**

Assigned Category C by the Australian Drug Evaluation Committee. This category includes medicines which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Beta-adrenergic blocking agents may cause pharmacological effects such as bradycardia in the foetus and newborn infant. During the final part of pregnancy and parturition, these agents should therefore only be given after weighing the needs of the mother against the risk to the foetus.

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

Atenolol diffuses across the placental barrier 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.

### **Use in lactation**

Residual atenolol may be present in breast milk at levels corresponding to 5.7 to 19.2% of the maternal dose. During breastfeeding, it is recommended to avoid atenolol in favour of antihypertensives with lower infant exposure.

## ***Effects on ability to drive and use machines***

This medicine is presumed to be safe or unlikely to produce an effect. The use of atenolol is unlikely to result in any impairment of the patient to drive or operate machinery. However, it should be taken into account that occasionally dizziness or fatigue may occur.

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## Adverse effects

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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 100 mg/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.

### More common

*Gastrointestinal:* dry mouth, gastrointestinal disturbance including indigestion, constipation.

*Nervous system:* fatigue, dizziness.

*Respiratory:* wheezing, bronchospasm (refer to Contraindications).

### Less common

*Biochemical abnormalities:* increases in AST or SGOT, blood urea and serum creatinine.

*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 reactions, exacerbation of psoriasis.

*Gastrointestinal:* diarrhoea.

*Hepatobiliary:* elevations of transaminase levels have been seen infrequently; rare cases of hepatic toxicity including intrahepatic cholestasis.

*Genito-urinary:* impotence.

*Musculo-skeletal:* ataxia.

*Nervous system:* vivid dreams, confusion, headache, mood changes, nightmares, paraesthesiae, tinnitus, vertigo, malaise, insomnia.

*Ocular:* dry eyes, visual disturbances.

*Psychiatric:* hallucinations, depression, psychoses.

*Respiratory:* asthma, dyspnoea, nasal congestion.

*Haemopoietic:* thrombocytopenia, purpura; an increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear.

### Serious 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.

Discontinuance of the drug should be considered if, according to clinical judgement, the well-being of the patient is adversely affected by any of the above reactions.

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## Interactions

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### ***Medicines and other pharmacologically active substances***

#### **Anaesthetics**

Anaesthetics, such as methoxyflurane, are contraindicated with atenolol (refer to [Warnings and precautions - Anaesthesia and peri-operative period](#)).

#### **Antiarrhythmic agents**

Care should be taken when prescribing beta-blockers with antiarrhythmic drugs. Class IA antiarrhythmic agents (e.g. disopyramide) and the Class III agent amiodarone may have potentiating effect on atrial conduction time and induce negative inotropic effect. This is seen less frequently with quinidine; Class IB agents, tocainide, mexiletine and lignocaine; Class IC agents, flecainide and propafenone; and the Class IV antiarrhythmic agents.

#### **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 sino-atrial or atrio-ventricular conduction abnormalities. Extreme caution is required if these medicines are to be used together.

The dihydropyridine calcium antagonists (e.g. nifedipine) have a weaker myocardial depressant effect and can be administered cautiously with beta-blockers. If excessive hypotension develops, the calcium antagonist should be stopped or the dosage reduced.

#### **Cardiac glycosides**

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

#### **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.

#### **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, clonidine treatment should not be discontinued until several days after the withdrawal of the beta-blocker.

#### **Insulin and oral hypoglycaemics**

Refer to [Warnings and precautions - Diabetes](#).

#### **Prostaglandin synthetase inhibitors**

Concomitant use of prostaglandin synthetase inhibiting drugs (e.g. ibuprofen, indomethacin) may decrease the hypotensive effects of beta adrenoreceptor blocking medicines.

#### **Sympathomimetic agents**

Concomitant use of sympathomimetic agents such as adrenaline or epinephrine may counteract the effect of beta-adrenoreceptor blocking medicines.

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## Overdosage

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### ***Signs and symptoms***

Overdosage has not been reported with atenolol but in overdosage with other beta-blocking agents, severe bradycardia and hypotension are commonly found. Acute heart failure and bronchospasm may also occur.

### ***Management***

General treatment should include close supervised treatment in an intensive care ward, the use of gastric lavage activated charcoal and a laxative to prevent absorption of any drug 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 2 mg intravenously may be used to induce vagal blockade. If bradycardia persists an inotrope, such as intravenous isoprenaline (25 mcg initially) or orciprenaline (0.5 mg 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.

### **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.

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## Pharmaceutical precautions

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### ***Instructions for use/handling***

Nil.

### ***Incompatibilities***

None known.

### ***Special precautions for storage***

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

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## Medicine classification

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Prescription Medicine.

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## **Package quantities**

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Packs of 30 tablets in cartoned blister strips.

Not all pack sizes and/or strengths may be currently marketed.

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## **Further information**

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### ***List of excipients***

Magnesium carbonate, maize starch, hydroxypropylmethylcellulose, magnesium stearate, sodium laurylsulphate, gelatin, propylene glycol.

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## **Name and address**

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## **Date of preparation**

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