SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Atenolol 100mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains Atenolol 100mg.

For excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet.

Circular, white, flat tablet scored on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
1. The management of hypertension
2. The management of angina pectoris
3. The management of cardiac dysrhythmias
4. Myocardial infarction: Early intervention in the acute phase and long-term prophylaxis after recovery from myocardial infarction.

4.2 Posology and method of administration
For oral administration
The dose must always be adjusted to individual requirements of the patients, with the lowest possible starting dosage. The following are guidelines:

**Adults**

**Hypertension:**
One tablet daily. Most patients respond to 100mg daily given as a single dose. Some patients, however, will respond to 50mg given as a single daily dose. The effect will be fully established after one to two weeks. A further reduction in blood pressure may be achieved by combining Atenolol with other antihypertensive agents. For example, co-administration of Atenolol with a diuretic provides a highly effective and convenient antihypertensive therapy.

**Angina:**
Most patients with angina pectoris will respond to 100mg given orally once daily or 50mg given twice daily. It is unlikely that additional benefit will be gained by increasing the dose.

**Cardiac arrhythmias:**
A suitable initial dose of atenolol is 2.5 mg (5 ml) injected intravenously over a 2.5 minute period (i.e. 1 mg/minute). This may be repeated at 5 minute intervals, until a response is observed up to a maximum dosage of 10 mg. If atenolol is given by infusion, 0.15 mg/kg bodyweight may be administered over a 20 minute period. If required, the injection or infusion may be repeated every 12 hours. Having controlled the arrhythmias with intravenous Atenolol a suitable oral maintenance dosage is 50mg – 100mg daily, given as a single dose.

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

**Renal failure:**
Since atenolol is excreted via the kidneys, the 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 greater than 35ml/min/1.73m² (normal range is 100-150ml/min/1.73m²).

For patients with a creatinine clearance of 15-35 mL/minute/1.73m² (equivalent to serum creatinine of 300-600 micromol/L), the oral dose should be 50 mg daily and the intravenous dose should be 10 mg once every two days.

For patients with creatinine clearance of less than 15 mL/minute/1.73m² (equivalent to serum creatinine of greater than 600 micromol/L), the oral dose
should be 25 mg daily or 50 mg on alternate days and the intravenous dose should be 10mg once every four days.

Patients on haemodialysis should be given 50 mg Atenolol orally following each dialysis. Because of the possibility of marked falls in blood pressure, this should be carried out under hospital supervision.

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

**Children**
There is no paediatric experience with atenolol and for this reason it is not recommended for use in children.

### 4.3 Contraindications
1. Atenolol is contraindicated in patients with second degree or third degree heart block.

2. Atenolol should not be used in patients with severe bradycardia.

3. Uncontrolled or digitalis/diuretic-refractory heart failure.

4. Atenolol should not be used in patients with cardiogenic shock.

5. Atenolol should not be used in patients with sick sinus syndrome.

6. Atenolol should not be used in patients with untreated phaeochromocytoma.

7. Atenolol tablets should not be used in patients with hypersensivity to atenolol or to any other ingredients of the preparation.

8. Atenolol should not be used in patients with severe peripheral circulatory disturbances.

9. Atenolol should not be used in patients with metabolic acidosis.

10. Atenolol should not be used in patients with hypotension.
4.4 Special warning and precautions for use

Sudden withdrawal of Beta-adrenoceptor blocking agents in patients with ischaemic heart disease may result in the appearance of angina attacks of increased frequency or severity or deterioration in cardiac state. Atenolol therapy must not be withdrawn abruptly. The dosage should be reduced gradually over a period of 7–14 days and patients should be monitored during withdrawal.

Anaesthesia:
Care should be taken when using anaesthetic agents with Atenolol. The anaesthetist should be informed to ensure that the necessary precautions are taken.

If a beta-blocker is withdrawn prior to surgery it should be discontinued for at least 24 hours. 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 minimize the risk of myocardial depression. The patient may be protected against vagal reactions by intravenous administration of atropine (see section 4.5).

Although contraindicated in uncontrolled heart failure (see section 4.3), atenolol may be used with caution in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.

Beta-blockers, even those with apparent cardioselectivity, should not be used in patients with asthma or a history of obstructive airways disease, unless no alternative treatment is available. In such cases the risk of inducing bronchospasm should be appreciated and appropriate precautions taken.

Special labelling requirement:
If you have ever had asthma or wheezing, you should not take this medicine unless you have discussed these symptoms with the prescribing doctor.

The initial treatment of severe malignant hypertension should be so designed as to avoid sudden reduction in diastolic blood pressure with impairment of autoregulatory mechanisms.

Patients with psoriasis should take beta-blockers only after careful consideration.

Beta-blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions. Such patients may be unresponsive to the usual doses of adrenaline (epinephrine) used to treat the allergic reactions.

Atenolol 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 beta<sub>1</sub> selective beta adrenoceptor
blocking drug; consequently its use may be considered although utmost caution must be exercised.

Although contra-indicated in severe peripheral arterial circulatory disturbances, atenolol may also aggravate less severe peripheral arterial circulatory disturbances.

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

Beta-blockers may have hypoglycaemic or hyperglycaemic actions and may decrease or increase patient requirements for insulin or oral antidiabetic agents. May mask the symptoms of hypoglycaemia, in particular tachycardia (see section 4.5).

The signs of thyrotoxicosis may be masked by atenolol treatment.

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

Should be used with caution in the elderly, starting with a lower dose (see section 4.2).

Since atenolol is excreted via the kidneys, the dosage should be reduced in patients with a creatinine clearance of less than 35ml/minute (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Anaesthetics, General:
Caution should be exercised when using anaesthetic agents with atenolol. The anaesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible. Use of beta-blockers with anaesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided (see section 4.4).

Anti-arrhythmics:
There is increased myocardial depression when beta-blockers are given with anti-arrhythmics (e.g. lidocaine, procainamide, flecainide, disopyramide), beta-adrenoceptor stimulants such as isoprenaline, or verapamil or alpha-adrenoceptor stimulants such as noradrenaline, adrenaline (which reverse the hypotensive effects and increase the vasoconstrictor activities). Amiodarone also increases the risk of bradycardia and atrioventricular block.
Amiodarone has a long-half life, and there is potential for drug interactions to occur for several weeks after treatment with amiodarone has been stopped.

**Antidiabetics:**
Beta-blockers may also have hypoglycaemic or hyperglycaemic actions and may decrease or increase the patients' requirements for insulin or oral antidiabetic agents. Symptoms of hypoglycaemia, particularly tachycardia, may be masked (see sections 4.4 and 4.8).

**Antihypertensives (see also calcium-channel blockers and clonidine):**
There is an enhanced hypotensive effect when beta-blockers are given with other antihypertensive drugs (e.g. angiotensin-converting enzyme inhibitors, angiotensin-II antagonists, alpha blockers, vasodilators such as minoxidil, hydralazine, diazoxide or sodium nitroprusside, diuretics, nitrates, methyldopa, moxonidine) or other drugs with blood pressure lowering potential (e.g. aldesleukin, alprostadil, general anaesthetics, anxiolytics, baclofen, hypnotics, levodopa, phenothiazines, monoamine oxidase inhibitors, moxisylyte, tizanidine).

There is an increased risk of first-dose hypotension in patients treated with beta-blockers when post-synaptic alpha blockers such as prazosin are introduced.

**Calcium-channel blockers:**
Combined use of beta-blockers and calcium channel blockers with negative inotropic effects, e.g. verapamil and diltiazem, can lead to an exaggeration of these effects particularly in patients with impaired ventricular function and/or sinoatrial or atrioventricular conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-blocker nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

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

**Clonidine:**
Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co-administered, the beta-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped.

**Digoxin:**
Digitalis glycosides, in association with beta-blockers, may increase atrioventricular conduction time. There is an increased risk of bradycardia and atrioventricular block with concurrent use.
Ergot alkaloids:
Concurrent use of ergot alkaloids such as ergotamine and methysergide with beta-blockers may result in increased peripheral vasoconstriction.

Mefloquine:
There is increased risk of bradycardia when mefloquine is given with beta-blockers.

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

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

Alcohol:
The hypotensive effects of beta-blockers are enhanced when given with alcohol.

4.6 Pregnancy and lactation

Atenolol should not be given during pregnancy and lactation unless it is considered essential by the physician.

Pregnancy:
Atenolol crosses the placental barrier and appears in the cord blood. No studies have been performed on the use of atenolol in the first trimester and the possibility of foetal injury cannot be excluded. Animal studies do not suggest a teratogenic effect with the drug. Atenolol has been used under close supervision for the treatment of hypertension in the third trimester. Administration of atenolol to pregnant women in the management of mild to moderate hypertension has been associated with intra-uterine 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.

Lactation:
There is significant accumulation of atenolol in breast milk.

Neonates born to mothers who are receiving atenolol at parturition or breast-feeding may be at risk of hypoglycaemia and bradycardia.

Caution should be exercised when atenolol is administered during pregnancy or to a woman who is breast-feeding.
4.7 Effects on ability to drive and use machines

Atenolol may occasionally produce drowsiness, dizziness, light-headedness, blurred vision. Patients should observe caution while driving or performing other tasks requiring alertness.

4.8 Undesirable Effects

Atenolol is generally well-tolerated, side effects associated with it are infrequent and generally mild.

Adverse events reported are usually attributable to the pharmacological actions of atenolol.

The following events, listed by body system, have been reported with the following frequencies: very common \( \geq 1/10 \); common \( \geq 1/100 \) to \( < 1/10 \); uncommon \( \geq 1/1,000 \) to \( < 1/100 \); rare \( \geq 1/10,000 \) to \( < 1/1,000 \); very rare \( < 1 \) in 10,000; not known (cannot be estimated from the available data).

**Blood and lymphatic system disorders:**
Rare: Thrombocytopenia, purpura

**Metabolism and nutrition disorders:**
Not known: Hypoglycaemia or hyperglycaemia (see section 4.4)

**Psychiatric disorders:**
Uncommon: Sleep disturbances
Rare: Mood changes, nightmares, confusion, psychoses and hallucinations.

**Nervous system disorders:**
Rare: Dizziness, headache, paraesthesia
Not known: Lethargy

**Eye disorders:**
Rare: Visual disturbances, dry eyes, sore eyes, conjunctivitis. The reported incidence is small and in most cases symptoms have cleared when treatment is withdrawn.

**Cardiac disorders:**
Common: Bradycardia
Rare: Heart failure deterioration, precipitation of heart block.
Vascular disorders:  
Common: Peripheral vasoconstriction with coldness of extremities.  
Rare: Postural hypotension which may be associated with syncope.  
Exacerbation of intermittent claudication, Raynaud’s phenomenon.

Respiratory, thoracic and mediastinal disorders:  
Rare: Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints.  
Not known: Dyspnoea

Gastrointestinal disorders:  
Common: Gastrointestinal disturbances including nausea and vomiting, diarrhoea, constipation and abdominal cramping.  
Rare: Dry mouth

Hepato-biliary disorders:  
Uncommon: Elevations of transaminase levels.  
Rare: Hepatic toxicity including intrahepatic cholestasis.

Skin and subcutaneous tissue disorders:  
Rare: Alopecia, pruritis, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes.  
Not known: Hypersensitivity reaction, including angioedema, pruritis and urticaria.

Musculoskeletal and connective tissue disorders:  
Not known: Muscle fatigue

Reproductive system and breast disorders:  
Rare: Impotence

General disorders and administration site conditions:  
Common: Fatigue  
Not known: Malaise

Investigations:  
Very rare: An increase in antinuclear antibodies has been observed, however the clinical relevance of this is not clear.

Discontinuation of atenolol should be considered if, according to clinical judgment, the well-being of the patient is adversely affected by any of the above reactions. Cessation of therapy with a beta-blocker should be gradual.
4.9 **Overdose**

*Symptoms:* Patients may develop severe and occasionally fatal cardiovascular depression. Effects can include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

*Treatment:* Close supervision; 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.

Maintenance of a clear airway and adequate ventilation is mandatory in patients who are unconscious. Excessive bradycardia and hypotension may be countered by atropine intravenously and/or a cardiac pacemaker.

Cardiogenic shock unresponsive to atropine may be treated with intravenous glucagon. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine by intravenous infusion may be given. 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 blocker blockade if a large overdose has been taken. The dose of dobutamine should there be increased if necessary to achieve the required response according to clinical condition of the patient.

Bronchospasm can usually be reversed by bronchodilators.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Beta-adrenergic blocking agents (hereafter called Beta-blockers) compete with Beta-adrenergic agonists for available Beta receptor sites. Unselective Beta-blockers inhibit both the Beta₁ receptors (located chiefly in cardiac muscle) and Beta₂ receptors (located chiefly in the bronchial and vascular musculature), inhibiting the chronotropic, inotropic and vasodilator responses to Beta-adrenergic stimulation. Atenolol is cardioselective and preferentially inhibits Beta₁ adrenoceptors. Beta₁ selectivity has been confirmed by the inability of Atenolol to reverse the Beta₂ mediated vasodilating effects of Epinephrine or Isoproterenol. This contrasts with the effect of nonselective Beta-blockers which completely reverse the vasodilating effects of Epinephrine.
Atenolol does not have membrane stabilising effects, little direct myocardial depressant activity and little or no intrinsic sympathomimetic activity.

Clinical response to Beta-blockade includes slowing of sinus heart rate, depressed AV conduction, decreased cardiac output at rest and on exercise, reduction of systolic blood pressure on exercise, reduction of both supine and standing blood pressure, inhibition of Isoproterenol-induced tachycardia and reduction of reflex orthostatic tachycardia.

5.2 Pharmacokinetic properties

Absorption: Atenolol is consistently absorbed when administered orally; with approximately 50 - 60% of the dose administered being absorbed. After an oral dose of 100mg a mean peak serum level of 880ng/ml was reached in approximately 3 hours, declining to approximately 63ng/ml in 24 hours.

Distribution: Atenolol is widely distributed throughout the body, but only a small amount of the drug reaches the brain, Atenolol is not significantly bound to serum proteins.

In pregnancy, atenolol readily crosses the placenta, the umbilical and maternal serum being approximately equal at birth.

Metabolism: Metabolism of atenolol in man is minimal. In animal studies a hydroxylated compound with minor Beta-blocking activity, has been identified as a minor metabolite of Atenolol, but Atenolol does not appear to be metabolised to a significant extent in man.

Excretion: Atenolol is excreted unchanged, mainly through the kidneys. About 40 - 50% of a single oral dose is excreted in the urine of healthy subjects. The elimination half-life of Atenolol is approximately 6 - 7 hours.

In renal dysfunction, the elimination of Atenolol is closely related to the glomerular filtration rate, although important accumulation probably only occurs if the glomerular filtration is less than 30ml/minute.
5.3 Preclinical safety data
No further data is presented given the well-known pre-clinical and clinical profile of Atenolol.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Gelatin
Heavy Magnesium Carbonate
Magnesium Stearate
Microcrystalline Cellulose
Maize Starch
Sodium Lauryl Sulphate
Talc
Purified Water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Do not store above 25ºC.
Keep the container tightly closed (bottles & tablet containers).
Store in the original package (blisters).
6.5 Nature and contents of container

a) Amber glass bottles with closures of LD-polyethylene.

b) Polypropylene tablet container with polyethylene cap.

c) Blister strips made of clear PVC plastic foil 250micrometer thick and aluminium foil, hard-tempered, 20micrometer thick, laminated against 30g PVC.

Pack sizes 28, 100, 250 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Strides Pharma UK Ltd
Unit 4 Metro Centre
Tolpits Lane
Watford
Hertfordshire
WD18 9SS
Trading as: Co-pharma

8 MARKETING AUTHORISATION NUMBER(S)

PL 13606/0139

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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