Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Atenolol Actavis 50 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Atenolol Actavis 50 mg film-coated tablet contains 50 mg atenolol

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White, round, biconvex film-coated tablet scored and with AH engraved on one side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of:
- Hypertension
- Chronic stable angina pectoris
- Supraventricular arrhythmias:
  - paroxysmal supraventricular tachycardia (in therapeutic or prophylactic treatment)
  - atrial fibrillation and atrial flutter: in case of inadequate response to maximum dosages of cardiac glycosides; in cases where cardiac glycosides may be contraindicated or may be associated with an unfavorable risk/benefit ratio
- Ventricular arrhythmias:
  - ventricular extrasystoles (prophylactic or therapeutic treatment), if the extrasystoles are the result of increased sympathetic activity
  - ventricular tachycardias and ventricular fibrillation (prophylactic treatment), especially when the ventricular abnormality is the result of elevated sympathetic activity
- Secondary prevention after acute myocardial infarction

4.2 Posology and method of administration

For oral administration.

Posology

The dosage should be determined on an individual basis. It is recommended to start with the lowest possible dosage so that heart failure, bradycardia and bronchial symptoms are noticed timely. This is especially important in elderly. Further adaptation should be done gradually (e.g., once a week) under controlled conditions or based on the clinical effect.

Adults:

Hypertension: A starting dose of 25 mg is recommended. The usual maintenance dosage in hypertension is one tablet (50-100 mg) daily. The maximum effect will be reached after 1-2 weeks. If further improvement of the blood pressure is desired, atenolol may be combined with another anti-hypertensive e.g., a diuretic.

Angina pectoris: 50-100 mg daily, depending on the clinical effect, in order to obtain a heartbeat in rest of 55-60 beats per minute. Increasing the dose above 100 mg daily does not generally lead to an increased antianginous effect. If desired the dosage of 100 mg daily can be divided in two dosages.

Arrhythmias: Initially controlled intravenously. A suitable oral maintenance dosage is 50-100 mg daily, given as a single dose.

Secondary prevention after myocardial infarction: Initially controlled intravenously, followed by 50 mg orally about 10 minutes after the intravenous dose provided no adverse effects occur. This should be followed by a further 50 mg orally 12 hours later. Maintenance dose 100 mg daily in 1-2 dosages for 6 days or until discharge from hospital.

The Elderly: Dosage requirements may be reduced, especially in patients with impaired renal function. Dosage should be titrated according to clinical effect.

Children and adolescents under 18 years of age: The use of atenolol is not recommended in children or adolescents under 18 years of age.

Impaired renal function: Atenolol is excreted via the kidneys, therefore the dosage will need to be adjusted in severe renal conditions.

GFR (mL/min/1.73 m^2 BSA)	**Recommended daily dose atenolol (mg/day)**
>35	No dose adjustment necessary
15-35	25-50 (or 50-100 every second day)
<15	25-50 every second day

In haemodialysis a 50 mg tablet is administered after each dialysis. The administration should be done in hospital since sudden decrease of the arterial pressure may occur.

Decreased hepatic function: No dose adjustment is necessary.

4.3 Contraindications

- Second or third degree heart block
- Cardiogenic shock
- Uncontrolled heart failure
- Sick sinus syndrome (including sino-atrial block)
- Untreated phaeochromocytoma
- Metabolic acidosis
- Bradycardia (less than 45-50 beats per minute)
- Hypotension
- Hypersensitivity to the active substance(s) or any of the excipients listed in section 6.1
- Severe peripheral circulatory disturbances
- Concomitant use of floctafenine
- Concomitant intravenous use of verapamil or diltiazem
- Severe asthma and severe chronic obstructive pulmonary disease such as airway obstructions

4.4 Special warnings and precautions for use

Ischaemic heart disease: Especially in patients with ischaemic heart disease, treatment should not be discontinued suddenly. The dosage should be gradually reduced, i.e. over 1-2 weeks, if necessary at the same time initiating replacement therapy, to prevent exacerbation of angina pectoris. In addition, hypertension and arrhythmias may develop. Furthermore, there is a risk of myocardial infarction and sudden death.

Untreated congestive heart disease: Atenolol should not be used in patients with untreated congestive heart failure. The condition should be stabilised first.

Surgery: When a patient is scheduled for surgery, and it has been decided to interrupt beta-blockade, therapy should be discontinued for at least 24 hours. Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation, however the risk of hypotension may be increased as well.
If treatment is continued, caution should be observed with the use of certain anaesthetic drugs. The patient may be protected against vagal reactions by intravenous administration of atropine.

Peripheral Circulatory Disease: In patients with peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), atenolol should be used with great caution as aggravation of these disorders may occur. Severe peripheral circulatory disorders are a contra-indication (see section 4.3).

Heart rate disorders: Atenolol may induce bradycardia. If the pulse rate decreases to less than 50-55 beats per minute at rest and the patient experiences symptoms related to the bradycardia, the dosage should be reduced.

Respiratory disorders: In patients with chronic obstructive pulmonary disorders, airway obstructions may be aggravated. Therefore, atenolol should only be used for these patients with the utmost care.

Heart block: Due to its negative effect on conduction time, atenolol should only be given with caution to patients with first degree heart block.

Renal impairment: In patients with impaired renal function, the dose should be adjusted to reduced glomerular filtration rate (see section 4.2).

Elderly: The elderly should be treated with caution, starting with a lower dosage (see section 4.2).

Prinzmetal's anginal: Atenolol may increase the number and duration of anginal attacks in patients with Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. For these patients atenolol should only be used with the utmost care.

Psoriasis: Patients with anamnestically known psoriasis should take atenolol only after careful consideration.

Allergies: Atenolol may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions. Atenolol may reduce the efficacy of the usual dose of adrenaline (epinephrine) used to treat allergic reactions.

Hypersensitivity: Atenolol may cause a hypersensitivity reaction including angio-oedema and urticaria (see section 4.8).

Hypoglycaemia: The symptoms of hypoglycaemia may be masked by atenolol, in particular tachycardia. Diabetic patients should be warned that this 'warning sign' may not occur. Insulin sensitivity may be reduced in patients treated with atenolol.

Diabetic patients: Treatment should be initiated with a glycaemia monitoring.

Thyrotoxicosis: Beta-blockade may mask cardiovascular signs of thyrotoxicosis.

Treated phaeochromocytoma: Atenolol should be used with blood pressure monitoring in patients with treated phaeochromocytoma.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations contra-indicated:

Floctafenine:
Beta-adrenergic blocking agents may impede the compensatory cardiovascular reactions associated with hypotension or shock that may be induced by floctafenine.

Calcium antagonists of the verapamil or diltiazem type:
Negative influence on the contractility and AV-conduction.

Concomitant use not recommended:

Digitalis glycosides:
Association with atenolol may increase the atrioventricular conduction time and decrease heart rate. Concomitant use can increase the risk of bradycardia.

Monoamineoxidase inhibitors (except MAO-B inhibitors)

Clonidine:
Beta-blockers increase the risk of rebound hypertension. 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.

Sultopride:
Atenolol should not be concomitantly administered with sultopride since there is an increased risk of ventricular arrhythmias, e.g. torsades de pointes.

Use with caution:

Class I anti-arrhythmic drugs (e.g. disopyramide, quinidine) and amiodaron:
May have potentiating effect on atrial-conduction time and induce a negative inotropic effect.

Insulin and oral antidiabetic drugs:
May intensify the blood sugar lowering effects of these drugs (especially non-selective beta-blockers).
Beta-adrenergic blockade may prevent the appearance of signs of hypoglycaemia (tachycardia).

Anaesthetic drugs:
Attenuation of the reflex tachycardia and increase the risk of hypotension.
Continuation of beta-blockades reduces the risk of arrhythmia during induction and intubation. The anaesthesiologist should be informed when the patient is receiving a beta-blocking agent.
Anaesthetic agents causing myocardial depression, such as cyclopropane and trichlorethylene, lidocaine, procainamide and beta-adrenoceptor stimulants such as noradrenaline (norepinephrine) are best avoided.

Baclofen:
Causes an increased antihypertensive activity.

Contrast media, iodinated:
Atenolol may impede the compensatory cardiovascular reactions associated with hypotension or shock induced by iodated contrast products.

Amiodaron:
Combination with atenolol may result in additive depressant effects on conduction and negative inotropic effects, especially in patients with underlying sinus node dysfunction or atrioventricular node dysfunction.

Take into account:

Calcium antagonists; dihydropyridine derivates such as nifedipine:
The risk of hypotension may be increased. In patients with latent cardiac insufficiency, treatment with atenolol may lead to cardiac failure.

Prostaglandin synthetase inhibiting drugs (like NSAID's):
May decrease the hypotensive effects of atenolol.

Sympathicomimetic agents (e.g. adrenaline (epinephrine)):
May counteract the effect of atenolol.

Concomitant administration of tricyclic antidepressants, barbiturates and phenothiazines as well as other antihypertensive agents:
May increase the blood pressure lowering effect and/or risk of bradycardia.

Ampicillin:
May reduce the bioavailability of atenolol. Therefore the physician should watch for evidence of altered atenolol response especially when large doses of ampicillin are administered concomitantly.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of atenolol in pregnant women to determine its potential harmfulness. Atenolol crosses the placental barrier and appears in the cord blood.
Animal studies showed no teratogenicity or foetotoxic effects after systemic administration in the therapeutic dose range.
Administration of atenolol in pregnancy has been associated with reduced foetal growth.
On the basis of its pharmacological properties, adverse effects may occur in the foetus and newborn infant, if used in the second and third trimesters (especially hypoglycaemia, hypotension and bradycardia). Beta-blockers reduce placental perfusion. Because of lack of experience, administration of atenolol during pregnancy is not recommended.

Breastfeeding
Atenolol is secreted into breast milk reaching higher concentration than in plasma. A risk to the suckling child cannot be excluded (beta-blockade). Therefore, breastfeeding should be discontinued during treatment with atenolol.

4.7 Effects on ability to drive and use machines

There are no studies on the effect of this medicine on the ability to drive. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

The following undesirable effects have been observed during treatment with atenolol with the following frequencies:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders:
Rare: Purpura, thrombocytopenia.

Endocrine disorders:
Not known: Beta-blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia.

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

Nervous system disorders:
Rare: Dizziness, headache, paraesthesia.

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, Raynaud's phenomenon (in susceptible patients).

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.

Hepatobiliary disorders:
Rare: Hepatic toxicity including intrahepatic cholestasis.

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

Musculoskeletal and connective tissue disorders:
Not known: Lupus-like syndrome.

Reproductive system and breast disorders:
Rare: Impotence.

General disorders and administration site conditions:
Common: Fatigue.

Investigations:
Uncommon: Elevations of transaminase levels.
Very rare: An increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear.

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. In all cases cessation of therapy should be gradual.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

4.9 Overdose

Symptoms
The most important effects are on the heart. Bradycardia, hypotension, pulmonary oedema, syncope and cardiogenic shock may develop. First or second degree AV block may occur and rarely arrhythmias.

Treatment
After ingestion of an overdose or in the case of hypersensitivity, the patient should be kept under close supervision and treated in an intensive care ward.

Activated charcoal and a laxative should be used to prevent absorption of any drug still present in the gastrointestinal tract (within one hour). Plasma or plasma substitutes can be used to treat hypotension or shock. The use of haemodialysis or haemoperfusion may be considered.

Excessive bradycardia can be treated with atropine 1-2 mg intravenously and or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously and if required, this may be repeated or followed by an intravenous infusion of glucagon 1-10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute 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 therefore be increased if necessary to achieve the required response according to the clinical condition of the patient. Bronchospasm can usually be reversed by bronchodilators.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective
ATC code: CO7A B03

Atenolol is a beta-adrenoceptor blocking agent which is cardioselective, its principal action being on beta-adrenergic receptors in the heart. It is without intrinsic sympathomimetic and membrane stabilising activities and as with other beta-blockers, has negative inotropic effects (and is therefore contraindicated in uncontrolled heart failure). Its mode of action in the treatment of hypertension is unclear. It is probably the action of atenolol in reducing cardiac rate and contractility which makes it effective in eliminating or reducing the symptoms of patients with angina. It is unlikely that any additional ancillary properties possessed by S (-) atenolol, in comparison with the racemic mixture, will give rise to different therapeutic effects.

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

Atenolol is effective for at least 24 hours after a single oral dose. The drug facilitates compliance by its acceptability to patients and simplicity of dosing. The narrow dose range and early patient response ensure that the effect of the drug in individual patients is quickly demonstrated. Atenolol is compatible with diuretics, other hypotensive agents and antianginals (see section 4.5). Since it acts preferentially on beta-receptors in the heart, atenolol may, with care, be used successfully in the treatment of patients with respiratory disease, who cannot tolerate non-selective beta-blockers.

Human studies have shown that a negligible amount of atenolol crosses the blood brain barrier. Early intervention in

acute myocardial infarction reduces infarct size and may decrease morbidity and mortality. Fewer patients with a threatened infarction progress to 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.

5.2 Pharmacokinetic properties

Absorption: The oral bioavailability is about 50 to 60%. The bioavailability is decreased by 20% when taken with food. Peak plasma concentrations are found 2−4 hours after repeated oral administration. There is a linear relationship between dosage and plasma concentration. The inter-subject variability in AUC and C_{max} is about 30-40%.

Distribution: The volume of distribution is 50 to 75 L. Only small amounts are reported to cross the blood-brain barrier and plasma-protein binding is minimal (less than 5%).
(Women: it crosses the placenta and is distributed into breast milk where concentrations higher than those in maternal plasma have been achieved).

Metabolism: Atenolol undergoes little or no hepatic metabolism.

Elimination: Most of an absorbed dose (85-100%) is excreted unchanged via the urine. The clearance is about 6 L/h and the half-life is about 6 to 9 hours. In elderly patients, clearance is decreased and elimination half-life increased. The clearance is correlated to renal function and the elimination is prolonged in patients with renal impairment. Impaired liver function does not influence the pharmacokinetics of atenolol.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose, microcrystalline Type 101 (E460)
Maize starch
Crospovidone Type A (E1202)
Calcium hydrogen phosphate dihydrate (E341)
Colloidal anhydrous silica
Magnesium stearate (E572)
Hydrogenated vegetable oil
Sodium laurilsulfate

Film-coat
Titanium dioxide (E171)
Hypromellose 5cP
Propylene glycol (E1520)
Talc (E553b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister pack (PVC /Aluminium) with push-through foil.
Tablet container (HDPE) with plastic cap (HDPE) or plastic screw cap (PP).

Pack sizes:
Blisters (PVC/Al):
Atenolol Actavis 50 mg film-coated tablets: 20, 30, 50, 90 and 100 film-coated tablets

Tablet container (HDPE) with plastic screw cap (PP):
Atenolol Actavis 50 mg film-coated tablets: 20, 30, 100, 250 and 500 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1380/105/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 31st October 2013

10 DATE OF REVISION OF THE TEXT

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