SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

Antipressan Tablets 50 mg
Atenolol 50 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of Atenolol.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.
Orange, film coated tablets, engraved 1U1 or BERK 1U1 on one side and plain on the reverse.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Atenolol Tablets are indicated for the management of hypertension, angina pectoris, cardiac arrhythmias and for use in the acute phase following myocardial infarction.

4.2. Posology and Method of Administration

For oral administration.

Adults:

Hypertension: 50 - 100 mg daily as a single dose. A further reduction in blood pressure may be achieved by combining atenolol with other antihypertensive agents

Angina Pectoris: 50 mg twice daily or 100 mg daily as a single dose. It is unlikely that additional benefit will be gained by increasing the dose.

Cardiac arrhythmias: The initial dose of atenolol is 2.5 mg (5 ml) i.v. administered at 1 mg/minute. This may be repeated at 5 minute intervals until a response is observed (to a maximum of 10 mg of atenolol). If atenolol is given by infusion, 0.15mg/kg bodyweight may be given over a 20 minute period. The infusion may be repeated every 12 hours. Following control of the arrhythmias with i.v. atenolol, the maintenance dosage is oral atenolol 50 - 100 mg daily as a single dose.

Myocardial
Infarction: For suitable patients presenting within 12 hours of the onset of chest pain, atenolol 5-10 mg should be given immediately by slow i.v. injection (1 mg/minute) followed 15 minutes later, (provided no untoward effects were noted from the i.v. dose), by 50 mg atenolol orally. This should be followed by a further 50 mg orally 12 hours post-intravenous dose, and thereafter by 100 mg orally once daily. If bradycardia and/or hypotension requiring treatment, or any other untoward effects occur, atenolol should be discontinued.

Children: Atenolol is not recommended for use in children since no dosage etc, has been established.

The elderly: Dosage requirements may be reduced in elderly patients; particularly in those patients with impaired renal function.

Renal failure: Atenolol is excreted via the kidneys. Dosage adjustment should therefore be considered in patients with severe impairment of renal function.

No significant accumulation of atenolol occurs in patients who have a creatinine clearance greater than 35 ml/min/1.73 m\(^2\) (normal range is 100-150 ml/min/1.73m\(^2\)).

For patients with a creatinine clearance of 15-35 ml/min/1.73 m\(^2\) (equivalent to serum creatinine of 300-600 micromol/litre) the oral dose should be 50 mg daily.

For patients with a creatinine clearance of <15 ml/min/1.73m\(^2\) (equivalent to serum creatinine of >600 micromol/litre) the oral dose should be 25 mg daily or 50 mg on alternate days.

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

4.3. Contra-indications

Atenolol tablets are contra-indicated in patients with bradycardia, hypotension, known sensitivity to atenolol, cardiogenic shock, metabolic acidosis, severe peripheral arterial circulatory disturbances, second or third degree heart block, sick sinus syndrome, untreated phaeochromocytoma or uncontrolled heart failure.

4.4. Special Warnings and Precautions for Use

Anaesthesia: Caution should be exercised when using anaesthetics with atenolol. The anaesthetist should be informed and the anaesthetic used should have as little negative inotropic activity as possible. Combined use may lead to attenuation of the reflex tachycardia and an increased risk of hypotension. Anaesthetics causing myocardial depression should be avoided.

In patients with ischaemic heart disease, atenolol should not be withdrawn abruptly.
Although cardioselective beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers these should be avoided in patients with reversible obstructive airways disease, unless there are compelling clinical reasons for their use. If such reasons exist, atenolol can be used with caution. Occasionally, however, some increase in airways resistance may occur in asthmatic patients, although this can normally be reversed by the use of bronchodilators. The label will state - Do not take this medicine if you have a history of wheezing or asthma.

Although atenolol is contra-indicated in uncontrolled heart failure, it may be used in patients whose signs of heart failure have been controlled. Special care is required in patients whose cardiac reserve is poor.

Caution must be exercised in patients with first degree heart block as atenolol has a negative effect on conduction time.

Reduction of heart rate is one of the pharmacological actions of atenolol. In the rare instances when symptoms may be attributable to a slow heart rate, the dose should be reduced.

Atenolol may modify the tachycardia of hypoglycaemia.

Atenolol may mask the signs of thyrotoxicosis.

Beta-adrenergic blocking agents may increase the incidence and length of angina attacks in cases of Prinzmetal's angina, due to unopposed alpha receptor mediated coronary artery vasoconstriction. Because of the beta₁ selectivity of atenolol its use may be possible, but extreme caution is required.

Although atenolol is contra-indicated in severe peripheral arterial circulatory disturbances (see section 4.3.) it may also aggravate less severe peripheral arterial circulatory disturbances.

As with other beta-adrenergic blocking drugs, 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. These patients may not respond to the usual doses of adrenaline used to treat such allergic reactions.

4.5. Interactions with other Medicaments and other forms of Interaction

Caution should be exercised with the concurrent administration of atenolol and antiarrhythmic agents, e.g. disopyramide.

Similarly, concurrent administration of atenolol and calcium channel blockers with negative inotropic effects, e.g. verapamil or diltiazem, can lead to an exaggeration of these effects, particularly in patients with impaired ventricular function or abnormal conduction status. Severe hypotension, bradycardia and cardiac failure may occur. Neither the atenolol nor the calcium channel blocker should be administered intravenously within 48 hours of stopping the other.

Care should be exercised in changing patients to atenolol from clonidine. If given concurrently, clonidine should be continued for several days after withdrawal of atenolol. If replacing clonidine with beta-adrenoceptor blocking drugs, the introduction of such drugs should be delayed until several days after withdrawal of clonidine.

If administered with dihydropyridines e.g. nifedipine, the risk of hypotension may be increased, and cardiac failure may occur in patients with latent cardiac insufficiency.
Concomitant administration with digitalis glycosides may increase atrio-ventricular conduction time.

The hypotensive effects of beta-adrenoceptor blocking drugs may be decreased if prostaglandin synthetase inhibiting drugs e.g. ibuprofen or indomethacin, are co-administered.

Concurrent administration of sympathomimetic agents e.g. adrenaline, may counteract the affect of beta-adrenoceptor blocking agents.

Concomitant use with insulin and oral antidiabetic agent drugs may lead to the intensification of the blood sugar lowering effects of these drugs.

4.6. Pregnancy and Lactation

**Pregnancy:**

Atenolol crossed the placental barrier and appears in the blood cord. 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 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-adrenoeceptor blocking drugs, 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. Caution should be exercised when atenolol is administered to a nursing woman.

4.7. Effects on Ability to Drive and Use Machines

Atenolol would not normally be expected to affect the ability to drive or to use machines, however, it should be noted that occasionally dizziness or fatigue may occur.

4.8. Undesirable Effects

As with other beta-blocking agents, side effects reported are usually attributable to the pharmacological actions of the drug. The following adverse effects, listed by body system, have been reported:

Cardiovascular: Bradycardia, coldness in the extremities, deterioration of heart failure, postural hypotension which may be associated with syncope. In susceptible patients precipitation of heart block, intermittent claudication or Raynaud's phenomenon may occur.
CNS: Headache, dizziness, confusion, mood changes, nightmares, sleep disturbances, psychoses and hallucinations.

Respiratory: Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints.

Gastrointestinal: Dry mouth, gastrointestinal disturbances. Elevations of transaminase levels have been seen infrequently, rare cases of hepatic toxicity including intrahepatic cholestasis have been reported.

Haematological: Purpura, thrombocytopenia.

Neurological: Paraesthesia.

Reproductive: Impotence.

Integumentary: Reversible alopecia, dry eyes, skin rashes, psoriasiform skin reactions and worsening of psoriasis.

Other: Fatigue, visual disturbances, an increase in ANA (antinuclear antibodies) although the clinical significance of this is unclear.

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.

4.9. Overdose

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

Patients should be kept under close supervision and treated in an intensive care ward. Gastric lavage, activated charcoal and a laxative should be used to prevent absorption of any drug still present in the gastrointestinal tract. Hypotension and shock can be treated by plasma or plasma substitutes. Use of haemodialysis or haemoperfusion may be considered.

Excessive bradycardia should respond to 1 - 2 mg atropine given intravenously and/or a cardiac pacemaker. This may be followed, as necessary, by a bolus dose of glucagon 10 mg intravenously. This may be repeated, if required, or followed by an intravenous infusion of glucagon 1 - 10 mg/hour depending on patient response. If there is no response or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute by intravenous infusion may be administered. Dobutamine can 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-adrenoceptor blockade if a large overdose has been taken. Dosage should be adjusted according to the clinical condition of the patient.

Bronchospasm can usually be reversed by bronchodilators.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic Properties

ATC Code: CO7A B03 beta blocking agents, plain, selective.

Atenolol is a cardioselective beta-adrenoceptor blocking drug. Selectivity decreases with increasing dosage. Atenolol has no membrane stabilising action or intrinsic sympathomimetic activity and as with other beta-adrenoceptor blocking drugs, has negative inotropic effects and so is contra-indicated in uncontrolled heart failure.

As with other beta-adrenoceptor blocking drugs, the mode of action of atenolol 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.

Different therapeutic effects between S(-)-atenolol and the racemic mixture are unlikely to occur.

For most ethnic populations atenolol is effective and well tolerated although the response may be less in black patients.

Atenolol is compatible with diuretics, other antihypertensive agents and antianginal agents (see section 4.5.)

Early intervention with atenolol in acute myocardial infarction reduces infarct size and decreases 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 for opiate analgesics. Early mortality is decreased. Atenolol is an additional treatment to standard coronary care.

5.2 Pharmacokinetic Properties

Atenolol is incompletely absorbed from the gastro-intestinal tract. It is almost entirely eliminated from the body unchanged in the urine. First pass metabolism does not occur.

Peak plasma levels occur between 2 and 4 hours after dosing. Following an oral dose of 100 mg, mean peak plasma levels are about 0.6 mg/ml. Atenolol blood levels are consistent with little variability in peak plasma levels. The plasma half-life is 6 - 8 hours but this may increase in patients with severe kidney impairment since the kidney is the major route of elimination.

Atenolol has low lipid solubility. Its concentration in brain tissue is low and plasma-protein binding is minimal.

Atenolol crosses the placenta and it is excreted in breast milk.

5.3 Preclinical Safety Data

Preclinical information has not been included because the safety profile of atenolol has been established after many years of clinical use. Please refer to Section 4.
6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Tablets contain:
- Lactose monohydrate
- Microcrystalline cellulose (E460)
- Croscarmellose sodium
- Magnesium stearate (E572)
- Colloidal anhydrous silica

Coating contains:
- Hypermellose (E464)
- Polyethylene glycol
- Sunset yellow (E110)
- Titanium dioxide (E171)
- Quinoline yellow (E104)
- Ponceau red (E124)
- Carnauba wax

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

24 months

6.4. Special Precautions for Storage

Do not store above 25°C. Store in the original package.

6.5. Nature and Contents of Container

HDPE containers with LDPE lids in packs of 100, 250, 500 or 1000 tablets.

PVdC coated PVC film with hard temper aluminium foil blister strips in packs of 28 tablets.

Not all pack sizes may be marketed.

6.6. Instruction for Use/Handling

Not applicable

Administrative Data
7. **MARKETING AUTHORISATION HOLDER**

TEVA UK Limited
Eastbourne BN22 9AG

8. **MARKETING AUTHORISATION NUMBER**

PL 0289/0733

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION**

07 March 2006

10. **DATE OF (PARTIAL) REVISION OF THE TEXT**

March 2006

POM