1.3 PRODUCT INFORMATION

1.3.1 Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT:

ATENOLOL TABLETS BP 100 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:
Each Film coated tablet contains:
Atenolol BP 100 mg
Excipients Q.S.
Colour: Sunset Yellow FCF

QUANTITATIVE DECLARATION:

Sr. No	Name of Raw Material	Spec.	Label claim / tab	Qty per tablet (mg)	% Over age	Qty per tablet with Overages	Std. Qty for 2.0 Lac
1.	*Atenolol	BP	100 MG	100.00 MG	0 %	100.00 MG	20.00 KG
2.	** Lactose	BP		114.00 MG	3 %	117.42 MG	23.484 KG
3.	**Maize Starch	BP		94.00 MG	8 %	101.52 MG	20.304 KG
4.	** Microcrystalline Cellulose	BP		45.00 MG	2 %	45.90 MG	9.180 KG
5.	Maize Starch (F/P)	BP		35.00 MG		35.00 MG	7.000 KG
	Purified Water	BP					Q.S
6.	Purified Talc	BP		7.000 MG		7.000 MG	1.400 KG
7.	Magnesium Stearate	BP		4.000 MG		4.000 MG	0.800 KG
8.	Colloidal Silicon Dioxide	BP		3.000 MG		3.000 MG	0.600 KG
9.	Sodium Starch Glycolate	BP		5.000 MG		5.000 MG	1.000 KG
10.	Croscarmellose Sodium	BP		5.000 MG		5.000 MG	1.000 KG
11.	Maize Starch	BP		8.000 MG		8.000 MG	1.600 KG
	Avg. wt. of tablet		**Total**	**420.0 MG**		**420.0 MG**	**84.00 KG**

Note: * Compensate the qty. of Actives with Lactose to maintain the average weight.

**** compensate of overages of microcrystalline cellulose, lactose and maize starch to loss on drying.**

3. PHARMACEUTICAL FORM

Tablet
An orange colored, round shaped, biconvex, film coated tablet having break-line on one side & Plain on other 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

Posology
Adults
Hypertension:
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.
Dysrhythmias:
Having controlled the dysrhythmias with intravenous Atenolol a suitable maintenance dosage is 50mg - 100mg daily, given as a single dose.
Myocardial infarction:
15 minutes after the administration of the intravenous dose an oral dose of 50mg may be given 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 to be given once daily for up to ten days. If bradycardia and/or hypotension requiring treatment, or any other untoward effects occur, Atenolol should be discontinued.
Renal failure:
Atenolol is excreted via the kidneys, dosage adjustment should therefore be considered in patients with severe impairment of renal function. As a guide, for patients with a serum creatinine of 300- 600µMol/Litre, the Atenolol oral dose should be 50mg daily or 100mg once every two days, for patients with a serum creatinine of >600µMol/Litre, the oral dose of Atenolol should be 50mg on alternate days or 100mg once every four days.
Patients on haemodialysis should be given 50mg 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.
Paediatric population
There is no paediatric experience with atenolol and for this reason it is not recommended for use in children.
Method of administration
For oral administration.

4.3 Contraindications:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Atenolol is contraindicated in patients with second-degree or third-degree heart block.
- Atenolol should not be used in patients with severe bradycardia.
- Uncontrolled or digitalis/diuretic-refractory heart failure.
- Atenolol should not be used in patients with cardiogenic shock.
- Atenolol should not be used in patients with sick sinus syndrome.
- Atenolol should not be used in patients with untreated pheochromocytoma.
- Atenolol should not be used in patients with severe peripheral circulatory disturbances.
- Atenolol should not be used in patients with metabolic acidosis.
- Atenolol should not be used in patients with hypotension.

4.4 Special Warnings and Precautions for Use

Sudden withdrawal of Beta-adrenoceptors blocking agents in patients with ischemic 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.
Anesthesia:
Care should be taken when using anaesthetics agents with Atenolol. The anesthetist 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 anaesthetics 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 cardio selectivity, 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.
The initial treatment of severe malignant hypertension should be so designed as to avoid sudden reduction in diastolic blood pressure with impairment of auto regulatory 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$_1$ selective beta adrenoceptors 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 hypoglycemic or hyperglycemic 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, and disopyramide), beta- adrenoceptors stimulants such as isoprenaline, or verapamil or alpha- adrenoceptors 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 hypoglycemic or hyperglycemic actions and may decrease or increase the patient's 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 Fertility, pregnancy and lactation

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. 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.
Breast-feeding:
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 (≥ 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: Thrombocytopenia, purpura.
Metabolism and nutrition disorders:
Not known: Hypoglycaemia or hyperglycaemia (see section 4.4).
Endocrine disorders:
The signs and symptoms of thyrotoxicosis may be masked by atenolol treatment.
Psychiatric disorders:
Uncommon: Sleep disturbances.
Rare: Mood changes, depression, 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.
Not known: Vasospasm.
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, pruritus, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes.
Not known: Hypersensitivity reaction, including angioedema, pruritus and urticaria.
Musculoskeletal and connective tissue disorders:
Not known: Muscle fatigue, lupus-like syndrome.
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.
Management:
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; and 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 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: C07AB03.
Beta-adrenergic blocking agents (hereafter called Beta-blockers) compete with Beta-adrenergic agonists for available Beta receptor sites. Unselective Beta- blockers inhibit the $Beta_1$ receptors (located chiefly in cardiac muscle) and $Beta_2$ receptors (located chiefly in the bronchial and vascular musculature), inhibiting the chronotropic, inotropic and vasodilator responses to Beta-adrenergic stimulation. Atenolol is cardio selective and preferentially inhibits $Beta_1$ adrenoceptors. $Beta_1$ selectivity has been confirmed by the inability of Atenolol to reverse the $Beta_2$ 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 metabolized to a significant extent in man.
Elimination
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

Lactose
Maize Starch
Microcrystalline Cellulose
Sodium lauryl Sulphate
Purified Water
Purified Talc
Magnesium Stearate
Colloidal Silicon Dioxide
Sodium Starch Glycolate
Croscarmellose Sodium

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

Store at temperature below 30°C in a dry place. Protect from light.

6.6 Nature and Contents of Container

Blister Packs of 2 X 14 Tablets

6.5 Special Precautions for Disposal of a used medicinal product or waste materials derived from such medicinal product and Other Handling of the Product

No special requirements

7. APPLICANT/HOLDER OF CERTIFICATE OG PRODUCT REGISTRATION

MULTICHRIS PHARM & CHEMICAL COMPANY LTD.
13 Qudus Folawoyi Ehi Crescent, Off Ashirigbon Street Isolo, Lagos, Nigeria..

8. DRUG PRODUCT MANUFACTURER

RELAX BIOTECH PVT. LTD.
862/1, G.I.D.C., Makarpura, Vadodara - 390010, INDIA.

9. NAFDAC REGISTRATION NUMBER(S)

B4-7530