SUMMARY OF PRODUCT CHARACTERISTICS

1.1 Proprietary name of a medicinal product

Tenoric

1.2 Approved generic name(s)

Atenolol & Chlortalidone Tablets BP

1.3 Qualitative and quantitative composition

Tenoric
Each film-coated tablet contains:
Atenolol EP..... 100mg
Chlortalidone EP..... 25mg

1.4 Dosage Form

Tablets

1.5 Clinical particulars

1. Therapeutic indication:

Hypertension

2. Route of administration

For oral use.

3. Contra-indications

Tenoric is contraindicated in patients with: sinus bradycardia; heart block greater than first degree; cardiogenic shock; overt cardiac failure; anuria; Hypotension; metabolic acidosis; severe peripheral arterial circulatory disturbances; sick sinus syndrome; hypersensitivity to this product or to sulfonamide derived drugs.

4. Warnings And Precautions

Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heartfailure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating

more severe failure. In patients who have congestive heart failure controlled by digitalis and/ordiuretics, Tenoric should be administered cautiously.
Both digitalis and atenolol slow AV conduction. In patients without a history of cardiac failure, continued depression of the myocardium with beta blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, Tenoric should be withdrawn.

Effects on ability to drive and use machines: Use is unlikely to result in any impairment of the ability of patients to drive or operate machinery. However, it should be taken into account that occasionally dizziness or fatigue may occur.

Usage in pregnancy and lactation: Usage in pregnancy and lactation Atenolol can cause fetal harm when administered to a pregnant woman. Atenolol crosses the placental barrier and appears in cord blood. Administration of atenolol, starting in the second trimester of pregnancy, has been associated with the birth of infants that are small for gestational age. No studies have been performed on the use of atenolol in the first trimester and the possibility of fetal injury cannot be excluded. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Thiazides cross the placental barrier and appear in cord blood. The use of chlortalidone and related drugs in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions, which have occurred in the adult. Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when atenolol is administered to a nursing woman. Clinically significant bradycardia has been reported in breast fed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

Usage in pediatrics: Safety and effectiveness in paediatric patients have not been established.

5. Interaction

The drug may potentiate the action of other antihypertensive agents used concomitantly. Patients treated with Tenoric plus a catecholamine depletor (e.g. reserpine) should be closely observed for evidence of hypotension and/or marked bradycardia, which may produce vertigo, syncope or postural hypotension. Concomitant therapy with dihydropyridines e.g. nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency. Calcium channel blockers may also have an additive effect when given with the drug. Digitalis glycosides, in association with betaadrenoceptor blocking drugs, may increase atrioventricular conduction time. Caution must be exercised when prescribing a betaadrenoceptor blocking drug with Class 1 antiarrhythmic agents such as disopyramide. Concomitant use of sympathomimetic agents, e.g. adrenaline, may counteract the effect of betaadrenoceptor blocking drugs. Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude the therapeutic effectiveness of norepinephrine. Thiazides may increase the responsiveness to tubocurarine. Concomitant use with insulin and oral antidiabetic drugs may lead to the intensification of the blood sugar lowering effects of these drugs. Concomitant use of prostaglandin synthase inhibiting drugs, e.g., indomethacin, ibuprofen, may decrease the hypotensive effects of beta-blockers. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Beta blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the betablocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of betablockers should be delayed for several days after clonidine administration has stopped. While taking beta blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.

6. Adverse Effects

The drug is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient. The adverse effects observed are essentially the same as those seen with the individual components.

Atenolol: The adverse effects include:

Cardiovascular - Bradycardia, cold extremities, postural hypotension, leg pain
Central nervous system/neuromuscular - Dizziness, vertigo, light-headedness, tiredness, fatigue, lethargy, drowsiness, depression, dreaming
Gastrointestinal - Diarrhea, nausea
Respiratory - Wheezing, dyspnea
The following adverse reactions have been reported in temporal relationship to the use of the drug: elevated liver enzymes and/or bilirubin, hallucinations, headache, impotence, Peyronie's disease, postural hypotension which may be associated with syncope, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbance, sick sinus syndrome, and dry mouth. The combination, like other beta-blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome, and Raynaud's phenomenon.

Potential adverse effects

In addition, a variety of adverse effects not observed with atenolol but reported with other beta-adrenergic blocking agents should be considered potential adverse effects of atenolol.
Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, decreased performance on neuropsychometrics.
Cardiovascular: Intensification of AV block
Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis
Hematologic: Agranulocytosis
Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.
Miscellaneous: There have been reports of skin rashes and/or dry eyes associated with the use of betaadrenergic blocking drugs. The reported incidence is small, and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with atenolol. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to atenolol therapy with subsequent resolution or quiescence of the reaction.

Chlortalidone:

Cardiovascular - Orthostatic hypotension
Gastrointestinal - Anorexia, gastric irritation, vomiting, cramping, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis
CNS: Vertigo, paresthesia, xanthopsia
Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia;
Hypersensitivity: Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis).
Miscellaneous: Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness.

7. Dosage And Administration

Dosage must be individualized, Chlortalidone is usually given at a dose of 25 mg daily; the usual initial dose of atenolol is 50 mg daily.
Therefore, the initial dose should be one Tenoric 50 tablet given once a day. If an optimal response is not achieved, the dosage should be increased to one Tenoric 100 tablet given once a day.
When necessary, another antihypertensive agent may be added gradually beginning with 50 percent of the usual recommended starting dose to avoid an excessive fall in blood pressure. The lowest effective dose of Tenoric is recommended for patients with mild renal insufficiency. Since chlortalidone lose its diuretic effect when the creatinine clearance is <30ml/min, Tenoric should not be used in patients with creatinine clearance <30ml/min.

8. Overdosage

The symptoms of overdosage may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm. General treatment should include: 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 substitutes to treat hypotension and shock. The possible use of haemodialysis or haemoperfusion may be considered. Excessive bradycardia may be countered with atropine1-2mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10mg/hour depending on the 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 betaadrenoceptor 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 brochodilators. Excessive diuresis should be countered by maintaining normal fluid and electrolyte balance.

1.6 Pharmacological Properties

1.6.1 Pharmacodynamic properties

Atenolol

Atenolol is a beta -selective (cardioselective) beta- 1 adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. This preferential effect is not absolute, however, and at higher doses, atenolol inhibits beta -adrenoreceptors, chiefly located in the 2 bronchial and vascular musculature. In standard animal or human pharmacological tests, beta-adrenoreceptor blocking activity of atenolol has been demonstrated by: (1) reduction in resting and exercise heart rates and cardiac output, (2) reduction of systolic and diastolic blood pressure at rest and on exercise, (3) inhibition of isoproterenol induced tachycardia and (4) reduction in reflex orthostatic tachycardia. A significant beta-blocking effect of atenolol, as measured by reduction of exercise tachycardia, is apparent within one hour following administration of a single dose. This effect is maximal at about 2 to 4 hours and persists for at least 24 hours. The effect at 24 hours is dose related and also bears a linear relationship to the logarithm of plasma atenolol concentration. However, as has been shown for all beta blocking agents, the antihypertensive effect does not appear to be related to plasma level. In normal subjects, the beta -selectivity of atenolol has 1 been shown by its reduced ability to reverse the beta - 2 mediated vasodilating effect of isoproterenol as compared to equivalent beta-blocking doses of propranolol. In asthmatic patients, a dose of atenolol producing a greater effect on resting heart rate than propranolol resulted in much less increase in airway resistance. Atenolol produced a significantly smaller decrease of FEV than nonselective beta-blockers, such as 1 propranolol and unlike those agents did not inhibit bronchodilation in response to isoproterenol. Consistent with its negative chronotropic effect due to beta blockade of the SA node, atenolol increases sinus cycle length and sinus node recovery time. Conduction in the

AV node is also prolonged. Atenolol is devoid of membrane stabilizing activity, and increasing the dose well beyond that producing beta blockade does not further depress myocardial contractility. Several studies have demonstrated a moderate (approximately 10%) increase in stroke volume at rest and exercise. Atenolol given as a single daily dose, was an effective antihypertensive agent providing 24-hour reduction of blood pressure. Atenolol has been studied in combination with thiazide-type diuretics and the blood pressure effects of the combination are approximately additive. Atenolol is also compatible with methyldopa, hydralazine and prazosin, the combination resulting in a larger fall in blood pressure than with the single agents. The dose range of atenolol is narrow, and increasing the dose beyond 100 mg once daily is not associated with increased antihypertensive effect. The mechanisms of the antihypertensive effects of beta-blocking agents have not been established. Several mechanisms have been proposed and include: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output, (2) a central effect leading to reduced sympathetic outflow to the periphery and (3) suppression of renin activity. The results from long-term studies have not shown any diminution of the antihypertensive efficacy of atenolol with prolonged use.

Chlortalidone

Chlortalidone is a monosulfonamyl diuretic. It is an oral diuretic with prolonged action and low toxicity. The diuretic effect of the drug occurs within 2 hours of an oral dose. It produces diuresis with greatly increased excretion of sodium and chloride. Natriuresis is accompanied by some loss of potassium. The diuretic effects of chlortalidone lead to decreased extracellular fluid volume, plasma volume, cardiac output, total exchangeable sodium, glomerular filtration rate, and renal plasma flow. The mechanism by which chlortalidone reduces blood pressure is not fully known but may be related to the excretion and redistribution of body sodium. The site of action appears to be the cortical diluting segment of the ascending limb of Henle's loop of the nephron.

1.6.2 Pharmacokinetic properties

Atenolol

Absorption of an oral dose is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract,

the remainder being excreted unchanged in the feces. Peak blood levels are reached between 2 and 4 hours after ingestion. It has very low lipid solubility. Atenolol undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Only a small amount (6-16%) is bound to proteins in the plasma. This kinetic profile results in relatively consistent plasma drug levels with about a fourfold interpatient variation. Only small amounts are reported to cross the blood brain barrier. The elimination half-life of atenolol is approximately 6 to 7 hours and there is no alteration of the kinetic profile of the drug by chronic administration. Following doses of 50 mg or 100 mg, both beta-blocking and antihypertensive effects persist for at least 24 hours. When renal function is impaired, elimination of atenolol is closely related to the glomerular filtration rate; but significant accumulation does not occur until the creatinine clearance falls below 35 ml/min/1.73m2.

Chlortalidone

Chlortalidone is erratically absorbed from the gastrointestinal tract. Absorption of chlortalidone following oral dosing is consistent but incomplete (Approximately 60%) with peak plasma concentrations occurring about 12 hours after dosing. It has a prolonged elimination half life from plasma and blood of 40 to 60 hours and is highly bound to red blood cells; the receptor to which it is bound has been identified as carbonic anhydrase. Plasma protein binding is high (approximately 75%). Chlortalidone is mainly excreted unchanged in the urine. It crosses the placental barrier and is distributed into breast milk. Co-administration of chlortalidone and atenolol has little effect on the pharmacokinetics of either. The combination is effective for at least 24 hours after a single oral daily dose. This simplicity of dosing facilitates compliance by its acceptability to patients.

1.6.3 Preclinical safety data

1.7 PHARMACEUTICAL PARTICULARS

i) Incompatibilities

None

ii) Shelf life

36 months.

iii) Storage

Store below 30°C
Keep out of reach of children

iv) Nature and composition of container

Blister strip of 14 tablets

v) List of excipients:

Heavy Magnesium Carbonate BP/EP,
Sodium Starch Glycollate BP/EP
Sodium Lauryl Suphate BP/EP
Colloidal Anhydrous Silica BP/EP
Mazie Starch BP/EP
Purified Water BP/EP
Dried Maize Starch
Magnesium Stearate BP/EP (Veg grade)
Titanium Dioxide BP/EP
Ferric Oxide Red USP-NF
Macrogol 6000 BP/EP

1.8 APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

Ipca Pharma Nig Ltd.
No, 3, llupeju Bye Pass,
(Olajire House) llupeju Lagos,
ipcaharma@yahoo.com

1.9 DRUG PRODUCT MANUFACTURER

Ipca Laboratories Limited
Sejavata District, Ratlam
Madhya Pradesh,
Pin, 457002, India

2.0 NAFDAC REGISTRATION NUMBER :

O4-7867