CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 74404

Trade Name Atenolol/Chlorthalidone Tablets 50mg/25mg and 100mg/25mg

Generic Name Atenolol/Chlorthalidone Tablets 50mg/25mg and 100mg/25mg

Sponsor Martec Pharmaceuticals, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74404

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74404

APPROVAL LETTER

ANDA 74-404

MAY 14 1998

Martec Pharmaceuticals, Inc.
Attention: Paul T. Sudhakar
1800 N. Topping Ave.
P.O. Box 33510
Kansas City, MO 64120-3510

Dear Sir:

This is in reference to your abbreviated new drug application dated September 3, 1993, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Atenolol and Chlorthalidone Tablets, 50 mg/25 mg and 100 mg/25 mg.

Reference is also made to your amendments dated April 3, September 14, November 1, and November 9, 1995; and March 24, 1997; and March 19, and April 6, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Atenolol and Chlorthalidone Tablets, 50 mg/25 mg and 100 mg/25 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Tenoretic® Tablets, 50 mg/25 mg and 100 mg/25 mg, respectively, of Zeneca Pharmaceuticals). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final

printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely, yours,

5/14/98

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74404

FINAL PRINTED LABELING

210028-04

ATENOLOL AND CHLORTHALIDONE TABLETS*

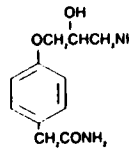
50 mg/25 mg and 100mg /25 mg

*Product does not meet U.S.P. requirements for dissolution

DESCRIPTION

Atenolol and chlorthalidone is for the treatment of hypertension. It combines the antihypertensive activity of two agents: a $beta_1$-selective (cardioselective) hydrophilic blocking agent (atenolol), and a monosulfonamyl diuretic (chlorthalidone).

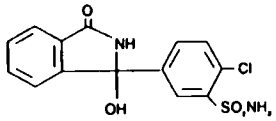
Atenolol is Benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl) amino] propoxy]-.



$C_{14}H_{22}N_2O_3$
266.34

Atenolol (free base) is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/mL at 37°C. It is freely soluble in 1 N HCl (300 mg/mL at 25°C) and less soluble in chloroform (3 mg/mL at 25°C).

Chlorthalidone is 2-Chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl) benzene sulfonamide.



$C_{14}H_{11}ClN_2O_4S$
338.76

Chlorthalidone has a water solubility of 12 mg/100 mL at 20°C

Each atenolol and chlorthalidone 50 mg/25 mg tablet for oral administration contains:

Atenolol	50 mg
Chlorthalidone	25 mg

Each atenolol and chlorthalidone 100 mg/25 mg tablet for oral administration contains:

Atenolol	100 mg
Chlorthalidone	25 mg

Inactive ingredients: corn starch, gelatin, glycerin, hydroxypropylmethyl cellulose, magnesium carbonate, magnesium stearate, sodium lauryl sulfate and titanium dioxide.

CLINICAL PHARMACOLOGY

Atenolol and chlorthalidone have been used singly and concomitantly for the treatment of hypertension. The antihypertensive effects of these agents are additive and studies have shown that there is no interference with bioavailability when these agents are given together in the single combination tablet. Therefore, this combination provides a convenient formulation for the concomitant administration of these two entities. In patients with more severe hypertension, atenolol and chlorthalidone may be administered with other antihypertensives such as vasodilators.

Atenolol: Atenolol is a $beta_1$-selective (cardioselective) beta-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 $beta_2$-adrenoreceptors chiefly located in the bronchial and vascular musculature.

Pharmacodynamics: In standard animal or human pharmacologial tests, beta-adrenoreceptor blocking activity of atenolol has been demonstrated by: 1) reduction in resting and exercise heart rate 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 1 hour following oral 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 $beta_1$-selectivity of atenolol has 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. In a placebo-controlled comparison of approximately equipotent oral doses of several beta blockers, atenolol produced a significantly smaller decrease of FEV_1 than nonselective beta blockers such as 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.

In controlled clinical trials, 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 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.

Pharmacokinetics and Metabolism: In man, 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. Unlike propranolol or metoprolol, but like nadolol, hydrophilic atenolol undergoes little or no metabolism by the liver and the absorbed portion is eliminated primarily by renal excretion. Atenolol also differs from propranolol in that 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. There is no information as to the pharmacokinetic effect of atenolol on chlorthalidone.

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/1.73 m^2. (See circular for atenolol).

Chlorthalidone: Chlorthalidone is a monosulfonamyl diuretic which differs chemically from thiazide diuretics in that a double ring system is incorporated in its structure. 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. At maximal therapeutic dosage, chlorthalidone is approximately equal in its diuretic effect to comparable maximal therapeutic doses of benzothiadiazine diuretics. The site of action appears to be the cortical diluting segment of the ascending limb of Henle's loop of the nephron.

INDICATIONS AND USAGE

Atenolol and Chlorthalidone Tablets are indicated for the treatment of hypertension. This fixed-dose combination drug is not indicated for initial therapy of hypertension. If the fixed-dose combination represents the dose appropriate to the individual patient's needs, it may be more convenient than the separate components.

CONTRAINDICATIONS

Atenolol and chlorthalidone is contraindicated in patients with: sinus bradycardia, heart block greater than first degree, cardiogenic shock, overt cardiac failure (see WARNINGS), anuria, hypersensitivity to this product or to sulfonamide-derived drugs.

WARNINGS

Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, 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 diuretics, atenolol 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 receiving atenolol and chlorthalidone should be digitalized and/or be given additional diuretic therapy. Observe the patient closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, atenolol and chlorthalidone therapy should be withdrawn.

Renal and Hepatic Disease and Electrolyte Disturbances: Since atenolol is excreted via the kidneys, atenolol and chlorthalidone should be used with caution in patients with impaired renal function.

In patients with renal disease, thiazides may precipitate azotemia. Since cumulative effects may develop in the presence of impaired renal function, if progressive renal impairment becomes evident, atenolol and chlorthalidone should be discontinued.

In patients with impaired hepatic function or progressive liver disease, minor alterations in fluid and electrolyte balance may precipitate hepatic coma. Atenolol and chlorthalidone should be used with caution in these patients.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of atenolol and chlorthalidone is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. Atenolol and chlorthalidone should be reinstated if withdrawal symptoms occur. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue atenolol and chlorthalidone therapy abruptly even in patients treated only for hypertension.

Concomitant Use of Calcium Channel Blockers: Bradycardia and heart block can occur and the left ventricular end diastolic pressure can rise when beta blockers are administered with verapamil or diltiazem. Patients with pre-existing conduction abnormalities or left ventricular dysfunction are particularly susceptible (See PRECAUTIONS).

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$-selectivity, however, atenolol and chlorthalidone may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$-selectivity is not absolute, the lowest possible dose of atenolol and chlorthalidone should be used and a $beta_2$-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: It is not advisable to withdraw beta-adrenoreceptor blocking drugs prior to surgery in majority of patients. However, care should be taken when using anesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV).

Beta blockers are competitive inhibitors of beta-receptor agonists and their effects on the heart can be reversed by administration of such agents; e.g., dobutamine or isoproterenol with caution (see section on OVERDOSAGE).

Metabolic and Endocrine Effects: Atenolol and chlorthalidone may be used with caution in diabetic patients. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses atenolol does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest during chlorthalidone administration.

Beta-adrenergic blockade may mask certain clinical signs (e.g.,tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis and from whom atenolol and chlorthalidone therapy is to be withdrawn should be monitored closely.

Because calcium excretion is decreased by thiazides, atenolol and chlorthalidone should be discontinued before carrying out tests for parathyroid function. Pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy; however, the common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen.

Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazide therapy.

Pregnancy and Fetal Injury Atenolol and chlorthalidone can cause fetal harm when administered to a pregnant woman. Atenolol crosses the placental barrier and appears in the 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.

Atenolol and chlorthalidone was studied for teratogenic potential in the rat and rabbit. Doses of atenolol/chlorthalidone of 8/2, 80/20, and 240/60 mg/kg/day were administered orally to pregnant rats with no evidance of embryofetotoxicity observed. Two studies were conducted in rabbits. In the first study, pregnant rabbits were dosed with 8/2, 80/20, and 160/40 mg/kg/day of atenolol/chlorthalidone. No teratogenic effects were noted, but embryogenic resorptions were observed at all dose levels (ranging from approximately 5 times to 100 times the maximum human dose*). In the second study, doses of atenolol/chlorthalidone were 4/1, 8/2, and 20/5 mg/kg/day. No teratogenic or embryotoxic effects were demonstrated.

Atenolol - Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human antihypertensive dose.* Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human antihypertensive dose.*

Chlorthalidone - Thiazides cross the placental barrier and appear in cord blood. The use of chlorthalidone and related drugs in pregnant women requires that the anticipated benefits of the drug be weighed against the possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult.

*Based on the maximum dose of 100 mg/day in 50 kg patient

1 4 1998

PRECAUTIONS

General: Atenolol and chlorthalidone tablets may aggravate peripheral arterial circulatory disorders.

Electrolyte and Fluid Balance Status: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Patients should be observed for clinical signs of fluid or electrolyte imbalance, i.e., hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Measurement of potassium levels is appropriate especially in elderly patients, those receiving digitalis preparations for cardiac failure, patients whose dietary intake of potassium is abnormally low, or those suffering from gastrointestinal complaints.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements or foods with a high potassium content.

Any chloride deficit during thiazide therapy is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Drug Interactions: Atenolol and chlorthalidone may potentiate the action of other antihypertensive agents used concomitantly. Patients treated with atenolol and chlorthalidone 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.

Calcium channel blockers may also have an additive effect when given with atenolol and chlorthalidone. (see WARNINGS).

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.

Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such preparations with atenolol and chlorthalidone.

Beta blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If two drugs are coadministered, the beta blocker should be withdrawn several days before gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta blockers 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 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.

Other Precautions: In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. The possible exacerbation or activation of systemic lupus erythematosus has been reported. The antihypertensive effects of thiazides may be enhanced in the postsympathectomy patient.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study with atenolol, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose*, did not indicate a carcinogenic potential of atenolol. A third (24 month) rat study, employing doses of 500 and 1500 mg/kg/day (250 and 750 times the maximum recommended antihypertensive dose*) resulted in increase incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. No evidence of mutagenic potential of atenolol was uncovered in the dominant lethal test(mouse), *in vivo* cytogenetics test(Chinese hamster) or Ames test (*S. typhimurium*).

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose*) was unaffected by atenolol administration.

Animal Toxicology: Six month oral administration studies were conducted in rats and dogs using atenolol and chlorthalidone dosages up to 12.5 mg/kg/day (atenolol and chlorthalidone 10/2.5 mg/kg/day - approximately 5 times the maximum recommended antihypertensive dose*). There were no functional or morphological abnormalities resulting from dosing either compound alone or together other than minor changes in heart rate, blood pressure, and urine chemistry, which were attributed to the known pharmacologic properties of atenolol and/or chlorthalidone.

Chronic studies of atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels (starting at 15 mg/kg/day or 7.5 times the maximum recommended antihypertensive dose*) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended antihypertensive dose*, respectively).

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

Pregnancy: Teratogenic Effects, *Pregnancy Category D:* See WARNINGS - Pregnancy and Fetal Injury.

Nursing Mothers: Atenolol is excreted in human breast milk at a ration 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.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS:

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

Atenolol: The frequency estimates in the following table were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited, e.g. by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both atenolol and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for atenolol and placebo is similar, causal relationship to atenolol is uncertain.

	Volunteered (U.S. Studies)		Total-Volunteered and Elicited (Foreign + US Studies)	
	Atenolol (n=164) %	Placebo (n=206) %	Atenolol (n=399) %	Placebo (n=407) %
CARDIOVASCULAR				
Bradycardia	3	0	3	0
Cold Extremities	0	0.5	12	5
Postural Hypotension	2	1	4	5
Leg Pain	0	0.5	3	1
CENTRAL NERVOUS SYSTEM/ NEUROMUSCULAR				
Dizziness	4	1	13	6
Vertigo	2	0.5	2	0.2
Light-headedness	1	0	3	0.7
Tiredness	0.6	0.5	26	13
Fatigue	3	1	6	5
Lethargy	1	0	3	0.7
Drowsiness	0.6	0	2	0.5
Depression	0.6	0.5	12	9
Dreaming	0	0	3	1
GASTROINTESTINAL				
Diarrhea	2	0	3	2
Nausea	4	1	3	1
RESPIRATORY (see WARNINGS)				
Wheeziness	0	0	3	3
Dyspnea	0.6	1	6	4

During postmarketing experience, the following have been reported in temporal relationship to the use of the drug: elevated liver enzymes and/or bilirubin, headache, impotence, Peyronie's disease, postural hypotension which may be associated with syncope, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia and thrombocytopenia and visual disturbances. Atenolol and chlorthalidone like other beta blockers, has been associated with the development of antinuclear antibodies (ANA) and lupus syndrome.

Chlorthalidone: Cardiovascular: orthostatic hypotension; Gastrointestinal: anorexia, gastric irritation, vomiting, cramping, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; CNS: vertigo, paresthesias, 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. Clinical trials of atenolol and chlorthalidone conducted in the United States (89 patients treated with atenolol and chlorthalidone) revealed no new or unexpected adverse effects.

Potential Adverse Effects: In addition, a variety of adverse effects not observed in clinical trials 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, and decreased performance on neuropsychometrics; Cardiovascular: intensification of AV block (see CONTRAINDICATIONS); Gastrointestinal: mesenteric arterial thrombosis, ischemic colitis; Hematologic: agranulocytosis; Allergic: erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; Other: Raynaud's phenomenon.

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic 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. (See DOSAGE AND ADMINISTRATION).

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 quescence of the reaction.

Clinical Laboratory Test Findings: Clinically important changes in standard laboratory parameters were rarely associated with the administration of atenolol and chlorthalidone. The changes in laboratory parameters were not progressive and usually were not associated with clinical manifestations. The most common changes were increases in uric acid and decreases in serum potassium.

OVERDOSAGE

No specific information is available with regard to overdosage to atenolol and chlorthalidone in humans. Treatment should be symptomatic and supportive and directed to the removal of any unabsorbed drug by induced emesis, or administration of activated charcoal. Atenolol can be removed from the general circulation by hemodialysis. Further consideration should be given to dehydration, electrolyte imbalance and hypotension by established procedures.

Atenolol: Overdosage of atenolol has been reported with patients surviving acute doses as high as 5 g. One death was reported in a man who may have taken as much as 10 g acutely.

The predominant symptoms reported following atenolol overdose are lethargy, disorder of respiratory drive, wheezing, sinus pause, and bradycardia. Additionally, common effects expected with overdosage of any beta-adrenergic blocking agent are congestive heart failure, hypotension, bronchospasm, and/or hypoglycemia. Other treatment modalities should be employed at the physicians discretion and may include.

BRADYCARDIA: Atropine 1-2 mg intravenously. If there is no response to vagal blockade, give isoproterenol cautiously. In refractory cases, a transvenous cardiac pacemaker may be indicated. Glucagon in a 10 mg intravenous bolus has been reported to be useful. If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10 mg/h depending on response.

HEART BLOCK (SECOND OR THIRD DEGREE): Isoproterenol or transvenous cardiac pacemaker.

CONGESTIVE HEART FAILURE: Digitalize the patient and administer a diuretic. Glucagon has been reported to be useful.

HYPOTENSION: Vasopressors such as dopamine or norepinephrine (levarterenol). Monitor blood pressure continuously.

BRONCHOSPASM: A beta$_2$-stimulant such as isoproternol or terbutaline and/or aminophylline.

HYPOGLYCEMIA: Intravenous glucose.

ELECTROLYTE DISTURBANCE: Monitor electrolyte levels and renal function. Institute measures to maintain hydration and electrolytes.

Based on the severity of symptoms, management may require intensive support care and facilities for applying cardiac and respiratory support.

Chlorthalidone: Symptoms of chlorthalidone overdose include nausea, weakness, dizziness, and disturbances of electrolyte balance.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED (SEE INDICATIONS AND USAGE). Chlorthalidone 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 atenolol and chlorthalidone 50mg/25 mg tablet given once a day. If an optimal response is not achieved, the dosage should be increased to one atenolol and chlorthalidone 100 mg/25 mg tablet given once a day.

When necessary, another antihypertensive agent may be added gradually beginning with 50% of the usual recommended starting dose to avoid an excessive fall in blood pressure.

Since atenolol is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of atenolol occurs until creatinine clearance falls below 35 mL/min/1.73 m^2 (normal range is 100-150 mL/min/1.73 m^2); therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance mL/min/1.73 m^2)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

HOW SUPPLIED

Atenolol and chlorthalidone tablets, USP are supplied as white film coated tablets. Each 50 mg/25 mg tablet is white, round, bisected, embossed with "M" and 450 and is available in bottles of 100 (NDC 52555-450-10) and bottles of 1000 (NDC 52555-450-10).

Each 100 mg/25 mg tablet is white, round, unscored, embossed with "M" and 451 and is available in bottles of 100 (NDC 52555-451-01) and bottles of 1000 (NDC 52555-451-10).

The tablets should be protected from heat, light, and moisture and stored at controlled room temperature, 15-30°C (59-86°F).

℞ Only.

Manufactured by:
Merckle GmbH
Blaubeuren, Germany
For:
Martec Pharmaceutical, Inc.
Kansas City, MO 64120

Revised March 1998

Printed in the U.S.A.

201378-02

USUAL DOSAGE: One tablet daily, or as directed by physician.
Professional information brochure attached.
Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a well closed, light-resistant container as defined in the USP.

WARNING: AS WITH ALL MEDICATIONS, KEEP OUT OF REACH OF CHILDREN.

EACH TABLET CONTAINS:
Atenolol, USP ..... 100 mg
Chlorthalidone, USP ..... 25 mg

MARTEC
PHARMACEUTICAL INC

NDC 52555-451-10

Atenolol and Chlorthalidone Tablets*

*Product does not meet U.S.P. requirements for dissolution.
R only

1000 Tablets

Manufactured by:
Merckle GmbH
Blaubeuren, Germany
For:
Martec Pharmaceutical, Inc.
Kansas City, MO 64120

Lot No:
Exp. Date:

N 3 54328-451-10 6

201375-02

USUAL DOSAGE: One tablet daily, or as directed by physician.
Professional information brochure attached.
Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a well closed, light-resistant container as defined in the USP.

WARNING: AS WITH ALL MEDICATIONS, KEEP OUT OF REACH OF CHILDREN.

EACH TABLET CONTAINS:
Atenolol, USP ..... 50 mg
Chlorthalidone, USP ..... 25 mg

MARTEC
PHARMACEUTICAL INC

NDC 52555-450-01

Atenolol and Chlorthalidone Tablets*
50 mg/25 mg

*Product does not meet U.S.P. requirements for dissolution.
R only

100 Tablets

APPROVED

Manufactured by:
Merckle GmbH
Blaubeuren, Germany
For:
Martec Pharmaceutical, Inc.
Kansas City, MO 64120

Lot No:
Exp. Date: MAY 14 1998

N 3 54328-450-01 7

201377-02

USUAL DOSAGE: One tablet daily, or as directed by physician.
Professional information brochure attached.
Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a well closed, light-resistant container as defined in the USP.

WARNING: AS WITH ALL MEDICATIONS, KEEP OUT OF REACH OF CHILDREN.

EACH TABLET CONTAINS:
Atenolol, USP ..... 100 mg
Chlorthalidone, USP ..... 25 mg

MARTEC
PHARMACEUTICAL INC

NDC 52555-451-01

Atenolol and Chlorthalidone Tablets*

*Product does not meet U.S.P. requirements for dissolution.
R only

100 Tablets

Manufactured by:
Merckle GmbH
Blaubeuren, Germany
For:
Martec Pharmaceutical, Inc.
Kansas City, MO 64120

Lot No:
Exp. Date: MAY 14 1998

N 3 54328-451-01 4

201376-02

USUAL DOSAGE: One tablet daily, or as directed by physician.
Professional information brochure attached.
Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a well closed, light-resistant container as defined in the USP.

WARNING: AS WITH ALL MEDICATIONS, KEEP OUT OF REACH OF CHILDREN.

EACH TABLET CONTAINS:
Atenolol, USP ..... 50 mg
Chlorthalidone, USP ..... 25 mg

MARTEC
PHARMACEUTICAL INC

NDC 52555-450-10

Atenolol and Chlorthalidone Tablets*
50 mg/25 mg

*Product does not meet U.S.P. requirements for dissolution.
R only

1000 Tablets

Manufactured by:
Merckle GmbH
Blaubeuren, Germany
For:
Martec Pharmaceutical, Inc.
Kansas City, MO 64120

Lot No:
Exp. Date:

N 3 54328-450-10 9

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74404

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 6

2. [redacted]74-404

3. NAME AND ADDRESS OF APPLICANT

Martec Pharmaceuticals, Inc.

1800 N. Topping Ave.
P.O. Box 33510
Kansas City, MO 64120-3510

4. LEGAL BASIS FOR ANDA SUBMISSION

Tenoretic Tablets- ICI Pharma

Tenoretic® Tablets, 50 mg/25 mg, 100 mg/25 mg
Zeneca Pharmaceuticals Group
A Business Unit of Zeneca, Inc.
P.O. Box 751
Wilmington, Delaware 19897

Patent #3934032 for Tenoretic® 100 and 50 expired 1/20/93, and no exclusivities are shown in the current Approved Drug Products (1992).

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Atenolol/Chlorthalidone

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

9-3-93: Original submission
11-9-93: Acceptable filing
4-3-95: Amendment
6-16-96: Amendment
7-18-97: Amendment
12-8-97: Fax amendment
4-6-98: Amendment (Subject of this review)

FDA:

10-20-93: Refuse filing

3-11-94: 1st NA letter
9-13-96: 2nd NA letter
2-18-97: 3rd NA letter
12-8-97: 4th telephone NA letter
3-2-98: 5th NA letter

10. PHARMACOLOGICAL CATEGORY

antihypertensive agent

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

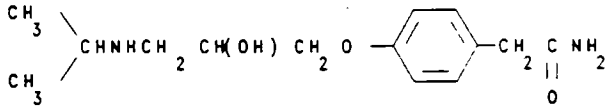
Tablet

14. POTENCY

50 mg/25 mg (scored) and 100 mg/25 mg (scored)

15. CHEMICAL NAME AND STRUCTURE

Atenolol:



Molecular Formula: $C_{14}H_{22}N_2O_3$

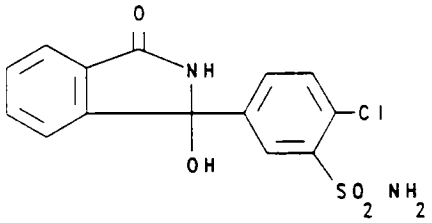
Molecular Weight: 266.34

1. Benzeneacetamide, 4-(2-hydroxy-3-[(1-methylethyl) amino]-propoxyl]-;

2. 2-[p-[2-Hydroxy-3-(isopropylamino)propoxy] phenyl] acetamide.

A white or almost white powder, odorless or almost odorless. Sparingly soluble in water, soluble in absolute ethanol, practically insoluble in ether. Melting point 152 - 155°C.

Chlorthalidone:



Molecular Formula: $C_{14}H_{11}ClN_2O_4S$

Molecular Weight: 338.76

1. Benzene-sulfonamide, 2-chloro-5-(2,3-dihydro-1-hydroxy-3-oxo-1H-isoindol-yl)-;

2. 2-Chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl) benzenesulfonamide.

A white or creamy-white, crystalline powder, odorless or almost odorless. Practically insoluble in water (12 mg/100 mL at 20°C, 27 mg/100 mL at 37°C), slightly soluble in ethanol (96%), soluble in 25 parts methanol. It dissolves in solutions of alkali hydroxides. Melting point about 220°C with decomposition.

16. RECORDS AND REPORTS: N/A

17. COMMENTS

The following comments address the issue of setting a dissolution specification, for your Atenolol/ Chlorthalidone Tablets U.S.P., different from that found in United States Pharmacopeia 23.

Q: 1. On evaluation of your abbreviated application and

review of formulation data, various dissolution profiles, and your discussion of the specific effects of your chosen formulation, we agree that the components of this formulation affect solubility to such an extent that current U.S.P. dissolution requirements cannot be met. We also note that your bioequivalence study demonstrates your product and the reference listed drug to be equivalent.

A: OK (See response as follows: Firm intend to meet the compendial monograph by submitting a petition to the USP immediately after the FDA approval is granted requesting revision of the current USP monograph to include their dissolution method).

Q: 2. The U.S.P. proposal and implementation of these requirements were after submission of your application. However, the Office position is that products described in a U.S.P. monograph are in fact official articles under the law, and should comply fully with the provisions of that monograph. In general, this could be accomplished through reformulation of your product, or through petition by you to the U.S.P. to change the current monograph dissolution specifications. Reformulation, depending on its extent, might require additional bioequivalence determination.

A: OK (Firm states in container Labeling "Product does not meet USP requirements for dissolution").

Status:

a. EER status: Acceptable 4/20/98

EER was requested by L. Tang and T. Ames 8-28-95 and found not satisfactory on 9-11-95. Updated and proapproval EER was requested on 1-3-97 and found acceptable on 1-23-97, and requested by T Ames again on April 14, 1998. Acceptable 4/20/98

b. Method Validation status: Satisfactory

Methods validation is not required since active ingredients and drug product are monographs in USP 23 Supplement 4 now.

c. Bio-review status: Satisfactory, **however, does not meet USP requirements.**

Satisfactory reviewed per Sikta Pradhan on 10-20-97.

d. Labeling review status: **Satisfactory**

Satisfactory per A. Vezza on 4-8-98.

e. Satisfactory

The was found acceptable by L. Tang on January 3, 1997 and was found satisfactory by Lucia Tang on 1/3/97.

18. CONCLUSIONS AND RECOMMENDATIONS

These application is considered as approval.

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 4-14-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74404

BIOEQUIVALENCE REVIEW(S)

4.1

ANDA 74-404

OCT 21 1997

Martec Pharmaceuticals, Inc.
Attention: Paul Sudhaker
1800 N. Topping Ave.
P.O. Box 33510
Kansas City, MO 64120-3510

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Atenolol and Chlorthalidone Tablets, 50 mg/25 mg and 100 mg/25 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing should be incorporated into your manufacturing controls and stability program. The dissolution testing should be conducted in **900 mL of 0.1 N HCl at 37 °C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following Specifications:**

   NLT (Q) of the labeled amount of atenolol and of chlorthalidone in the tablet is dissolved in 45 minutes.

3. As the test product does not meet the current USP dissolution specification, you should submit a petition to the USP for modification of the current monograph for this product.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OCT 17 1997

Atenolol/Chlorthalidone
50 mg/25 mg, 100 mg/25 mg Tablets
ANDA #74-404
Reviewer: Sikta Pradhan, Ph.D.
WP #74404AD.397

Martec Pharmaceutical, Inc.
Kansas City, MO
Submission Date:
March 24, 1997

Review of an Amendment to a Bioequivalence Study, Dissolution testing and Waiver Request

INTRODUCTION:

Atenolol/chlorthalidone is an orally administered antihypertensive combination drug product. Martec Pharmacal, Inc. previously conducted an in vivo bioequivalence study and in vitro dissolution testing on its test product, Atenolol/ Chlorthalidone 100mg/25mg tablets (lot #0599A1) versus the listed reference product, Tenoretic 100[R] (Atenolol/Chlorthalidone 100mg/25mg) of Zeneca Pharmaceuticals. The bioequivalence study was found to be incomplete by the Division of Bioequivalence due to the fact that the in vitro dissolution testing conducted on the test and reference products was not aeceptable.

Since the test product failed to satisfy the in vitro specifications for dissolution as specified in USP 23, the firm wanted to submit a petition to the USP to modify the monograph for this product, and as a part of this process, the firm has submitted the following information to the Agency in order to obtain the Agency's endorsement on the proposed method:

1. The firm's proposed dissolution testing for Atenolol/Chlorthalidone 50mg/25mg and 100mg/25mg tablets in **900 mL of 0.1N HCl at 37 °C using USP XXIII apparatus II (paddle) at 50 rpm.**

   Specifications: Not less tha[illegible] Q) of the labeled amount of **atenolol** and of **chlorthalidone** in the tablet is dissolved in 45 minutes.

2. The results (see Attachment #1) of "Class-C" dissolution (multiple media) at multiple time points 10 minute intervals for 60 minute duration to generate dissolution profile for **each** medium, as specified in the SUPAC-IR guidance.

3. An explanation as to why the test product is not able to satisfy the USP dissolution specifications.
   (i) The firm has stated that the test product is an immediate-release **film coated** tablet whereas the reference listed product (Tenoretic 50 and 100 mg tablets) is an immediate-release **uncoated** tablet.

(ii) Test product, in addition to other inactive ingredients, contains Magnesium carbonate as the major filling agent. However, the reference listed drug product contains microcrystalline cellulose as the major filling agent.

The firm has further stated that at neutral and higher pH conditions magnesium carbonate exhibits poor solubility in aqueous media, but it exhibits rapid and higher solubility in acidic media. Due to the bulkiness of magnesium carbonate, this difference in solution characteristics appears to be exaggerated at lower paddle speed (50 rpm) in the dissolution test. Hence the solubility characteristics and bulkiness of the magnesium carbonate is responsible for the difference in dissolution profile at various pH conditions (see attached CASE-C dissolution testing data).

Formulations:

The compositions of Atenolol/Chlorthalidone 50mg/25mg and 100mg/25mg tablets are presented in Table 1 (attached). The formulation of the Atenolol/Chlorthalidone 50mg/25mg tablet is proportionally similar to the 100mg/25mg strength of the test product which underwent bioequivalence testing.

Dissolution Testing:

Table 2. In Vitro Dissolution Testing

Drug: Atenolol/Chlorthalidone Tablets
Dose Strengths: 100 mg/25 mg and 50 mg/25 mg
ANDA No.: 74-404
Firm: Martec Pharmaceutical. Inc.

I. Conditions for Dissolution Testing:

USP XXIII Paddle; RPM: 50
No. Units Tested: 12
Medium: 0.1N HCl at 37°C; Volume: 900 mL
Specifications: NLT [illegible]) of the labeled amount of atenolol and [illegible]f chlorthalidone in the tablet is dissolved in 45 minutes.
Reference Drug: Tenoretic 100/25 mg and 50/25 Tablets
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hour)	Test Product: Atenolol /Chlorthalidone QC92070 Lot #0599A1 (Bio batch) Strength 100 /25 mg Tablet ATENOLOL / Tablet Submission Date: March 24, 1997			Reference Product: Tenoretic QC91758 Lot DA181 Strength 100 /25 mg Tablet ATENOLOL / Tablet Submission Date: November 1, 1995 and November 9, 1995		
	Mean %	Range	%CV	Mean %	Range	%CV
15	94.30		2.2			
30	97.03		1.3	99.3		2.0
45	96.98		1.3			
60	96.81		1.2	103.5		3.62
120	96.94		1.1			
Sampling Times (Hour)	CHLORTHALIDONE / Tablet			CHLORTHALIDONE / Tablet		
15	58.14		4.7			
30	88.53		1.9	94.0		9.2
45	96.33		1.5			
60	98.34		1.4	100.2		3.58
120	101.1		1.2			

III. Results of In Vitro Dissolution Testing:

Sampling Times (Hour)	Test Product: Atenolol /Chlorthalidone QC920689 Lot #0596B1 Strength 50 /25 mg Tablet ATENOLOL / Tablet Submission Date: March 24, 1997			Reference Product: Tenoretic Strength 50 /25 mg Tablet ATENOLOL / Tablet		
	Mean %	Range	%CV	Mean %	Range	%CV
15	88.5		5.8			
30	100.2		1.5			
45	100.9		1.5			
60	100.5		1.5			
120	100.7		1.4			
Sampling Times (Hour)	CHLORTHALIDONE / Tablet			CHLORTHALIDONE / Tablet		
15	43.4		8.4			
30	84.5		3.5			
45	98.6		2.2			
60	103.2		1.8			
120	105.8		1.7			

The firm has currently conducted dissolution testing only on its test product (two different strengths). However, as an Agency requirement, the comparative dissolution testing should always be conducted on the test and reference products. Since the dissolution data previously submitted (dated September 3, 1993; November 1, 1995 and November 9, 1995) by the firm, indicate that the dissolution of the reference product in both water and 0.1N HCl is faster than

that of the test product, the dissolution data currently submitted for the test product are found to be acceptable.

"CASE-C" -per SUPAC-IR guidance:

Multi-point dissolution profiles performed in water, 0.1N HCl, and buffer media at 4.5, 6.5, and 7.5 are attached herewith. There are five separate profiles for each strength of the test product. It is evident from these profiles that at neutral and higher pH conditions the test product exhibits poor solubility in aqueous media, but it exhibits rapid and higher solubility in acidic media.

COMMENTS:

1. The explanations (solubility characteristics and bulkiness of magnesium carbonate) provided by the firm for the in vitro dissolution deficiency (not able to satisfy the USP specifications) of its test product is acceptable. The presence of magnesium carbonate brings about immediate dissolution of the test product in the acidic environment of the stomach producing no significant difference in the in vivo bioequivalence study.

2. The firm's proposed dissolution testing method for Atenolol/Chlorthalidone 50mg/25mg and 100mg/25mg tablets in **900 mL of 0.1N HCl at 37 °C using USP XXIII apparatus II (paddle) at 50 rpm** (Specifications: NLT (Q) of the labeled amount of **atenolol** an[illegible] of **chlorthalidone** in the tablet is dissolved in 45 minutes) is justifiable.

3. Hence, the firm should be encouraged to submit a petition to the USP to modify the monograph for this product.

RECOMMENDATIONS:

1. The in vivo bioequivalence study conducted by Martec Pharmaceutical, Inc. on its test product, Atenolol/Chlorthalidone 100mg/25mg tablets (lot #0599A1) versus the listed reference product, Tenoretic 100[R] (Atenolol/Chlorthalidone 100mg/25mg) of Zeneca Pharmaceuticals has been found acceptable by the Division of Bioequivalence.

2. The in vitro dissolution testing conducted by Martec Pharmaceutical, Inc. on its test product, Atenolol/Chlorthalidone 100mg/25mg tablets (lot #0599A1) versus the listed reference product, Tenoretic 100[R] (Atenolol/Chlorthalidone 100mg/25mg) of Zeneca Pharmaceuticals has been found acceptable by the Division of Bioequivalence.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in **900 mL of 0.1N HCl at**

37 °C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following Specifications:

> **NLT (Q) of the labeled amount of atenolol and of chlorthalidone in the tablet is dissolved in 45 minutes).**

4. As the test product does not meet the current USP dissolution specification, the firm should be encouraged to submit a petition to the USP for modification of the current monograph for this product.

5. The comparative compositions of the test product, Atenolol/Chlorthalidone 100mg/25mg and Atenolol/Chlorthalidone 50mg/25mg tablets are proportional. The in vitro dissolution testing conducted by Martec Pharmaceutical, Inc. on its test product, Atenolol / Chlorthalidone 50mg/25mg tablets is also acceptable. Therefore, the waiver of in vivo bioequivalence study on Atenolol/Chlorthalidone 50mg/25mg tablets has been granted.

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG 7/14/97

Concur: Date: 10/17/97
Nicholas Fleischer, Ph. D.
Director, Division of Bioequivalence

cc: ANDA # 74-404 (original, duplicate), HFD-650 (Director), HFD-652 (Huang, Pradhan), Drug File, Division File.

SP/7-1-97/7-8-97/7-14-97//X:\wpfile\Biofinal\74404AD.397

Table 1

ATENOLOL AND CHLORTHALIDONE TABLETS 50MG/25MG AND 100MG/25MG
FORMULATION SUMMARY

COMPONENTS AND UNIT DOSAGE COMPOSITION		QUANTITY PER TABLET	
Ingredient	Quality Standard	100 mg/25 mg	50 mg/25 mg
Atenolol	BP 88	100.00 mg	50.00 mg
Chlorthalidone	BP 88	25.00 mg	25.00 mg
Magnesium Carbonate	USP XXII		
Corn Starch	NF XVII		
Sodium Lauryl Sulfate	NF XVII		
Gelatin	NF XVII		
Magnesium Stearate	NF XVII		
Purified Water	DAB 9		
Total Weight(Core)			
Percent Active			
Coating:			
Pharmacoat 606 (HPMC)	USP XXII		
Titanium Dioxide	USP XXII		
Glycerin	USP XXII		
Purified Water	DAB 9		
Acetone	NF XVII		
Total Weight(Coating)			
Total Weight(Film Coated Tablet)		451.25 mg	228.25 mg

	50/25 mg	100/25 mg
Biobatch size :		
Final production market batch size:		

Attachment

"CASE-C" Dissolution

Atenolol/Chlorthalidone 100/25 mg Tablets

900 ml Media @ 50 rpm

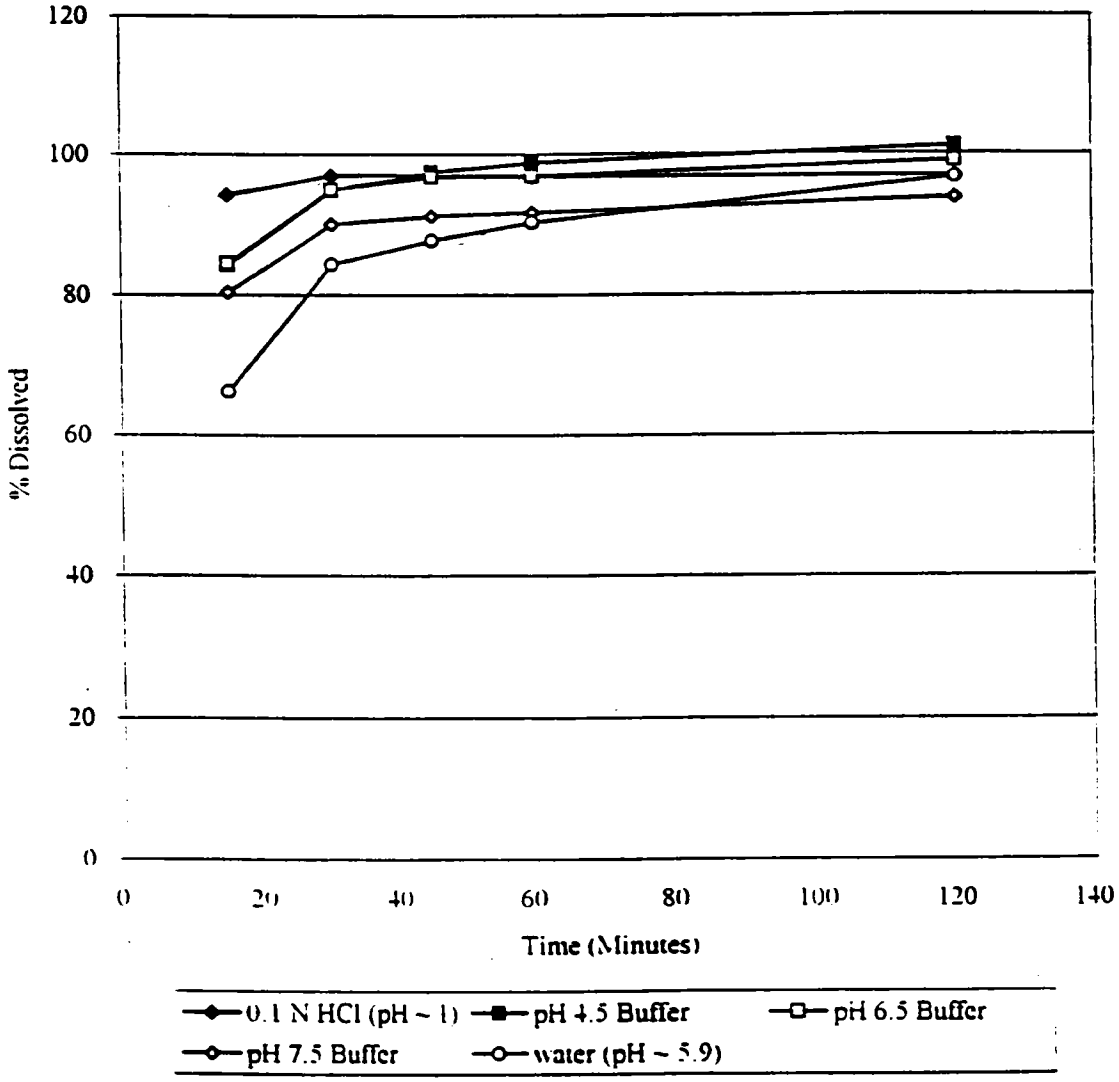
Summary of Diss. Profile for FDA letter on Sep. 6, 1996

Atenolol portion of Samples

QC#: 92070; Lot#: 0599A1; 100/25mg Tablets; 1000 count Bottles; ANDA/BIO batch 1

Average % Dissolved of Atenolol

Media	Sampling Time in Minutes				
	15	30	45	60	120
0.1 N HCl (pH ~ 1)	94.3	97.03	96.98	96.81	96.94
pH 4.5 Buffer	84.2	94.88	97.5	98.82	101.07
pH 6.5 Buffer	84.5	94.93	96.74	96.92	98.95
pH 7.5 Buffer	80.35	89.97	91.19	91.66	93.72
water (pH ~ 5.9)	66.17	84.35	87.65	90.24	96.64



File: Summary - Tab: 100-25 mg Tabs (Atenolol) - Printed: 3/18/97

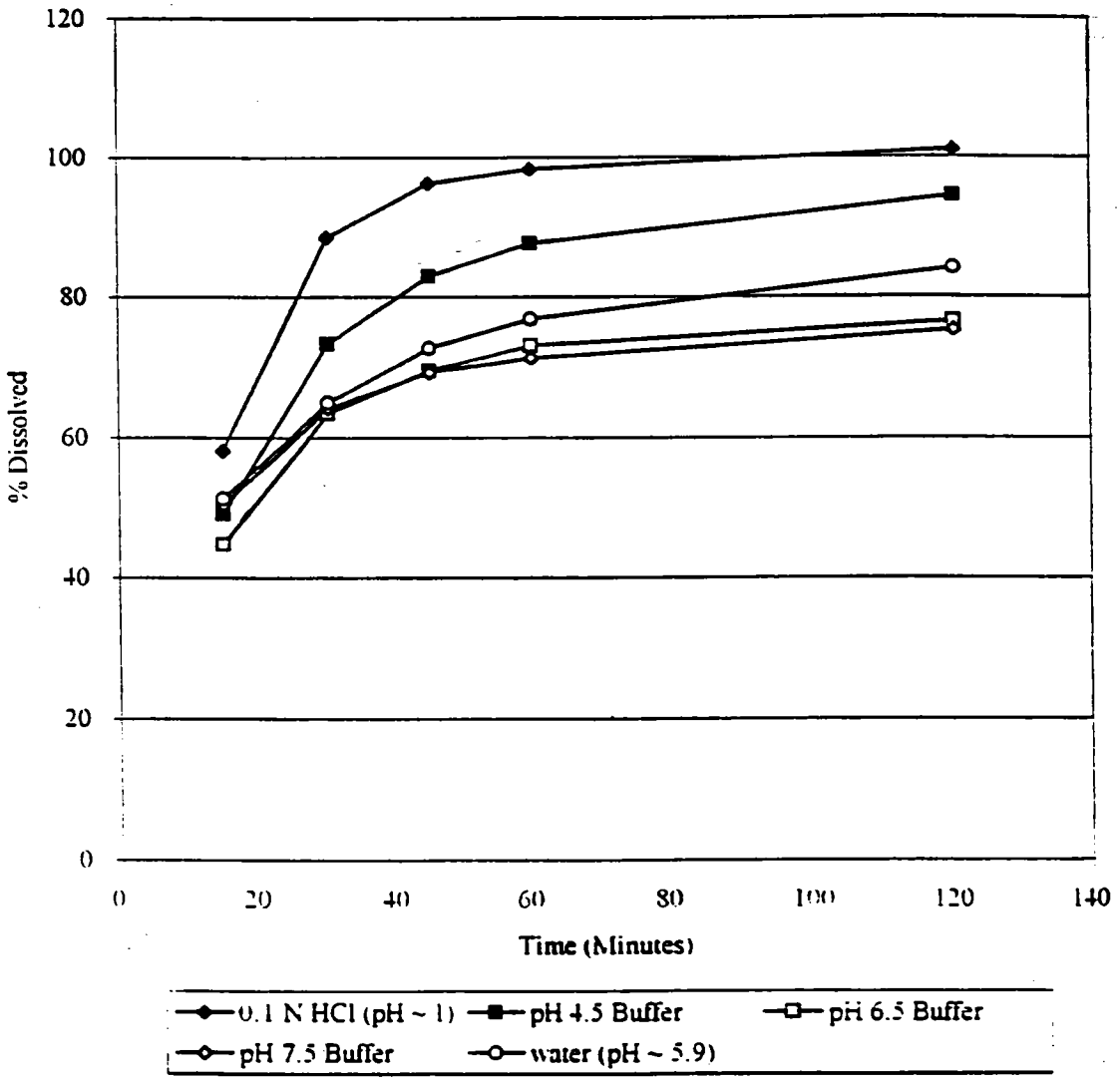
WH 3-18-97

Atenolol/Chlorthalidone100/25 mg Tablets
900 ml Media @ 50 rpm
Summary of Diss. Profile for FDA letter on Sep. 6. 1996
Chlorthalidone portion of Samples

QC#: 92070; Lot#: 0599A1; 100/25mg Tablets; 1000 count Bottles: ANDA/BIO batch 1

Average % Dissolved of Chlorthalidone

Media	Sampling Time in Minutes				
	15	30	45	60	120
0.1 N HCl (pH ~ 1)	58.14	88.53	96.33	98.34	101.06
pH 4.5 Buffer	49.12	73.32	82.86	87.6	94.45
pH 6.5 Buffer	44.73	63.49	69.49	73.05	76.42
pH 7.5 Buffer	50.41	64.2	69.19	71.26	75.22
water (pH ~ 5.9)	51.31	64.98	72.68	76.78	84.05

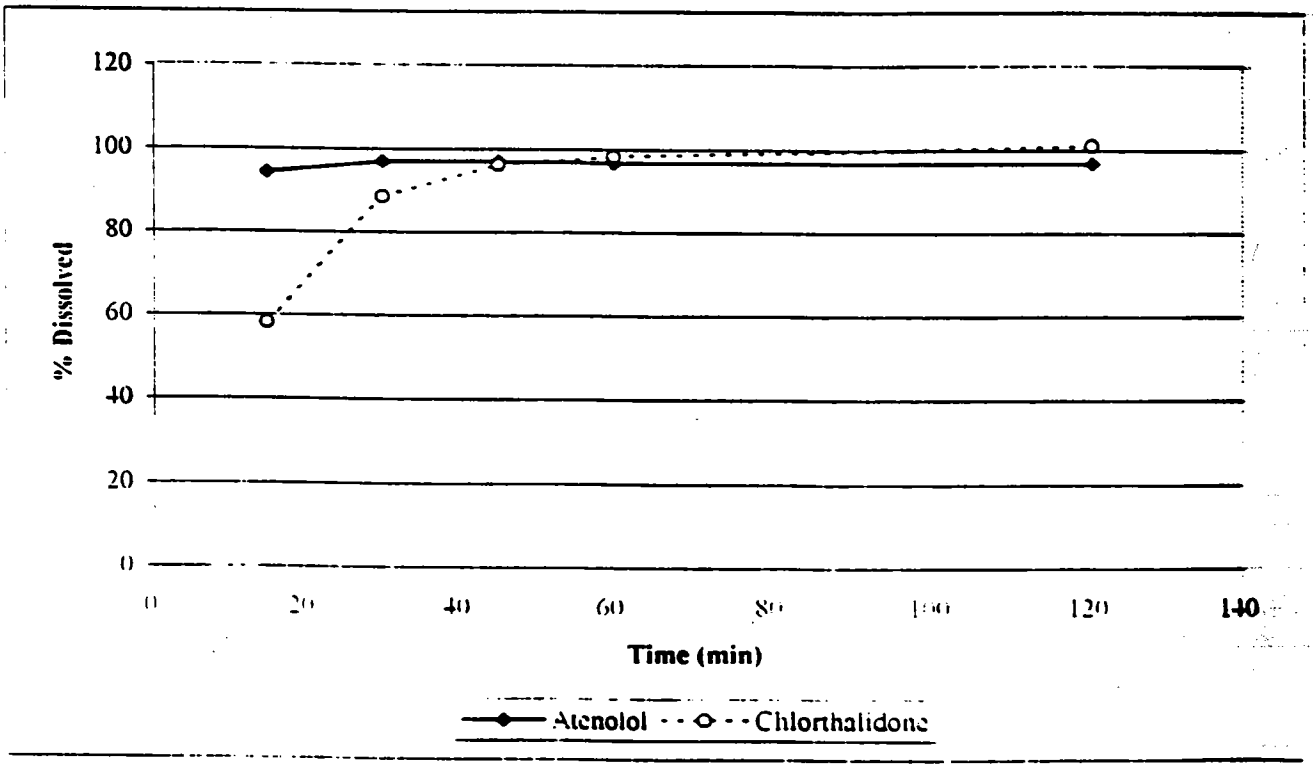


File: Summary - Tab: 100-25 mg Tabs (Chlorthalidone) - Printed: 3/18/97

JM 3-13-97

Atenolol/Chlorthalidone 100 mg/25 mg Tablets
900 ml 0.1 N HCl (pH~1.2) @ 50 rpm. USP Apparatus II
Summary of Diss. Profile for FDA letter on Sep. 6. 1996
QC#: 92070; Lot#: 0599A1; 1000 count Bottles; ANDA/BIO batch 1

Sample #	Average % Dissolved of Atenolol					Average % Dissolved of Chlorthalidone				
	15	30	45	60	120	15	30	45	60	120
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Average	94.30	97.03	96.98	96.81	96.94	58.14	88.53	96.33	98.34	101.06
SD	2.11	1.25	1.27	1.15	1.06	2.74	1.65	1.49	1.41	1.23
%RSD	2.24	1.29	1.31	1.19	1.09	4.71	1.86	1.55	1.43	1.21
Range-High	97.03	99.22	98.95	99.29	98.43	61.40	90.23	98.00	100.73	103.04
Range-Low	89.85	94.61	94.92	94.84	94.80	52.53	84.46	93.18	95.96	99.02

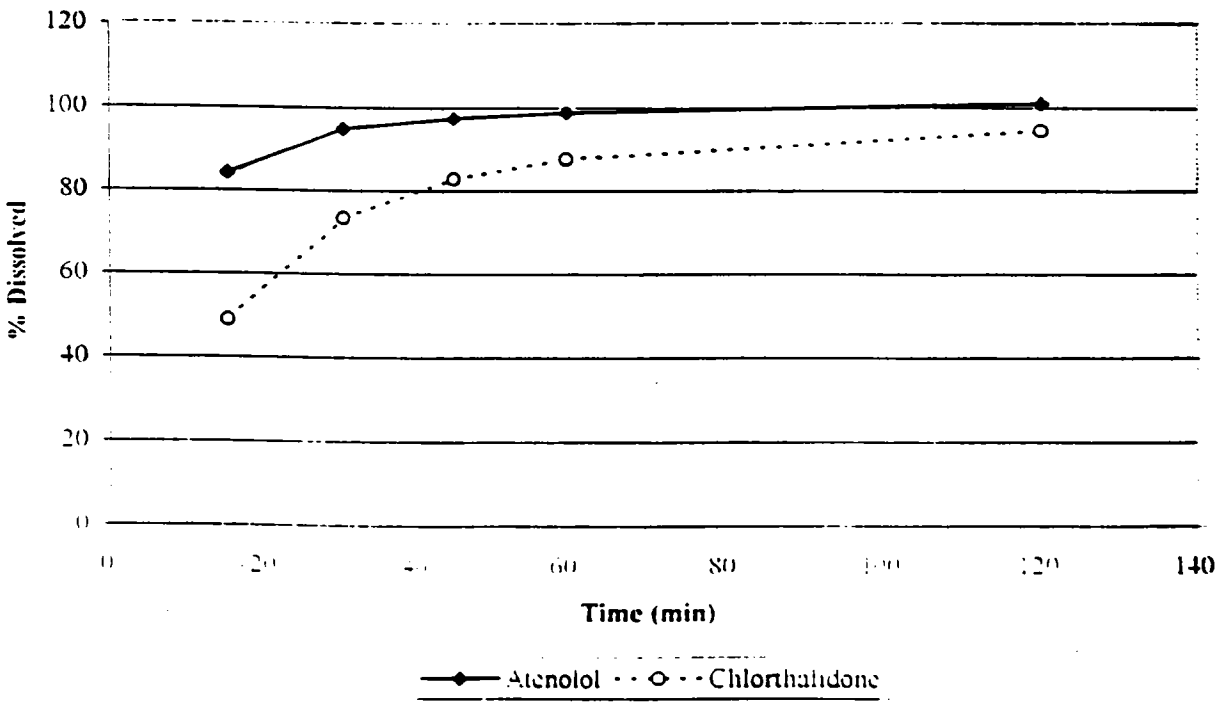


File: Detailed Summary - Tab: 100-25 mg Tabs in 0.1N HCl - Printed: 3/18/97

DJH 3-18-97

Atenolol/Chlorthalidone 100 mg/25 mg Tablets
900 mL pH 4.5 Buffer @ 50 rpm, USP Apparatus
Summary of Diss. Profile for FDA letter of Sep. 6. 1996
QC#: 92070; Lot#: 0599A1; 1000 count Bottles; ANDA/BIO batch 1

	Average % Dissolved of Atenolol					Average % Dissolved of Chlorthalidone				
Sample #	15	30	45	60	120	15	30	45	60	120
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Average	84.20	94.88	97.50	98.82	101.07	49.12	73.32	82.86	87.60	94.45
SD	8.88	4.79	3.12	2.51	1.74	6.34	5.13	4.25	3.71	2.39
%RSD	10.54	5.05	3.20	2.54	1.72	12.90	7.00	5.13	4.24	2.53
Range-High	92.29	99.73	101.58	102.15	103.38	59.81	80.50	88.45	92.58	98.30
Range-Low	65.32	81.62	89.49	92.92	98.07	37.61	61.53	73.72	79.33	88.91

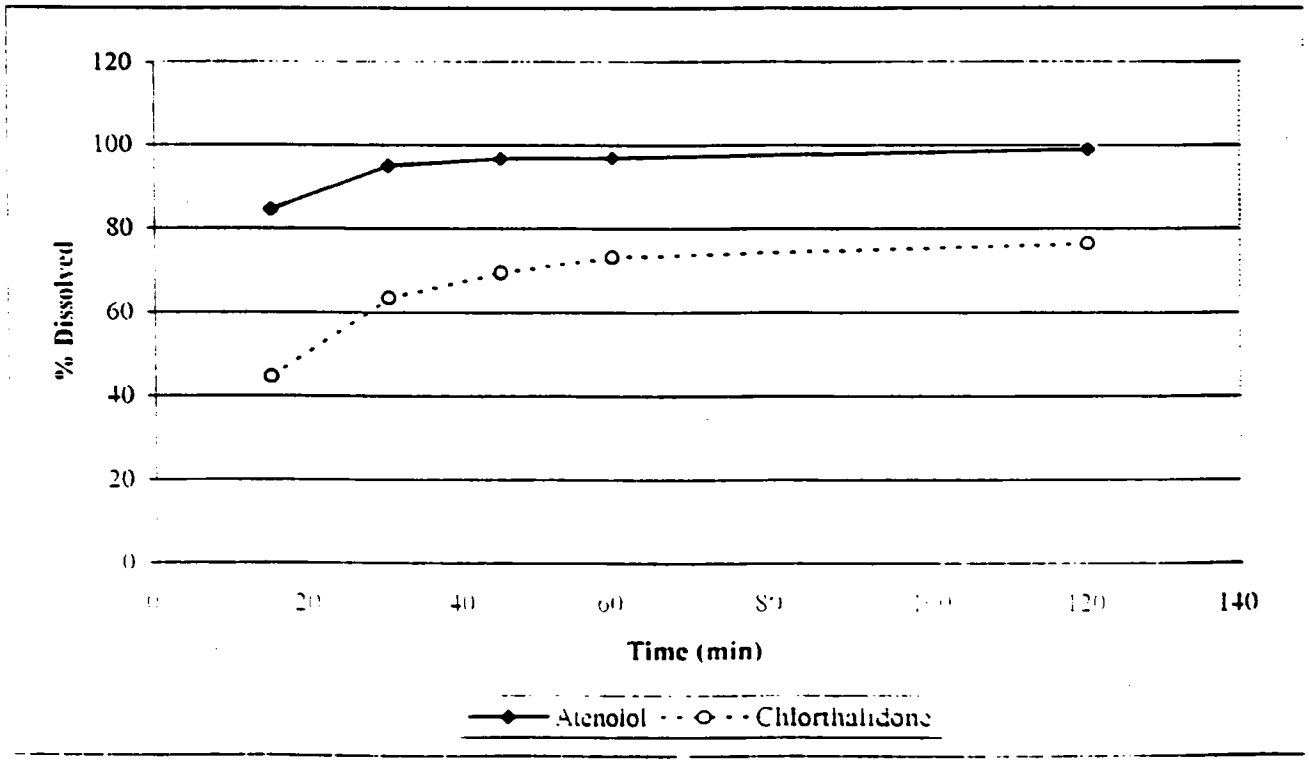


File: Detailed Summary - Tab 100-25 mg Tabs in pH 4.5 Buffer - Printed 3/18/97

3-10-97

Atenolol/Chlorthalidone 100 mg/25 mg Tablets
900 mL pH 6.5 Buffer @ 50 rpm, USP Apparatus II
Summary of Diss. Profile for FDA letter of Sep. 6, 1996
QC#: 92070; Lot#: 0599A1; 1000 count Bottles; ANDA/BIO batch 1

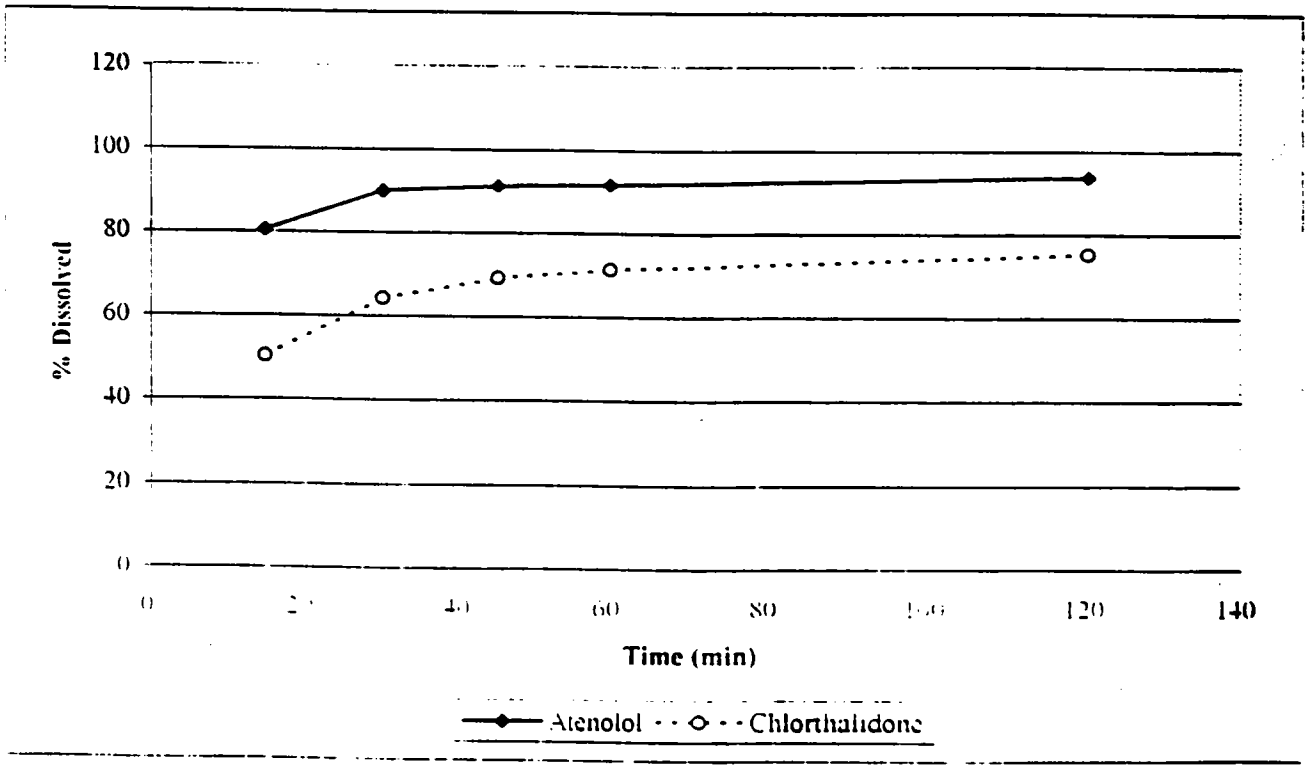
	Average % Dissolved of Atenolol					Average % Dissolved of Chlorthalidone				
Sample #	15	30	45	60	120	15	30	45	60	120
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Average	**84.50**	**94.93**	**96.74**	**96.92**	**98.95**	**44.73**	**63.49**	**69.49**	**73.05**	**76.42**
SD	9.71	8.22	7.76	7.10	5.74	6.42	6.11	6.09	5.78	**5.87**
%RSD	11.49	8.66	8.02	7.33	5.80	14.34	9.63	8.77	7.91	**7.68**
Range-High	92.50	98.43	100.36	100.68	102.18	50.40	68.36	74.60	77.95	**82.59**
Range-Low	56.43	68.91	72.32	74.63	81.08	27.71	46.64	52.71	57.14	**60.99**



File: Detailed Summary - Tab: 100-25 mg Tabs in pH 6.5 Buffer - Printed: 3/18/97

Atenolol/Chlorthalidone 100 mg/25 mg Tablets
900 mL pH 7.5 Buffer @ 50 rpm, USP Apparatus II
Summary of Diss. Profile for FDA letter of Sep. 6. 1996
QC#: 92070; Lot#: 0599A1; 1000 count Bottles; ANDA/BIO batch 1

Sample #	Average % Dissolved of Atenolol					Average % Dissolved of Chlorthalidone				
	15	30	45	60	120	15	30	45	60	120
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Average	80.35	89.97	91.19	91.66	93.72	50.41	64.20	69.19	71.26	75.22
SD	14.26	13.49	11.47	10.86	8.53	9.02	8.69	8.28	8.04	7.07
%RSD	17.75	14.99	12.58	11.85	9.10	17.89	13.53	11.97	11.28	9.40
Range-High	89.55	104.00	97.78	98.07	99.25	59.41	72.87	78.19	79.91	83.86
Range-Low	37.57	48.90	55.25	57.61	67.14	24.69	38.81	45.35	48.15	55.69

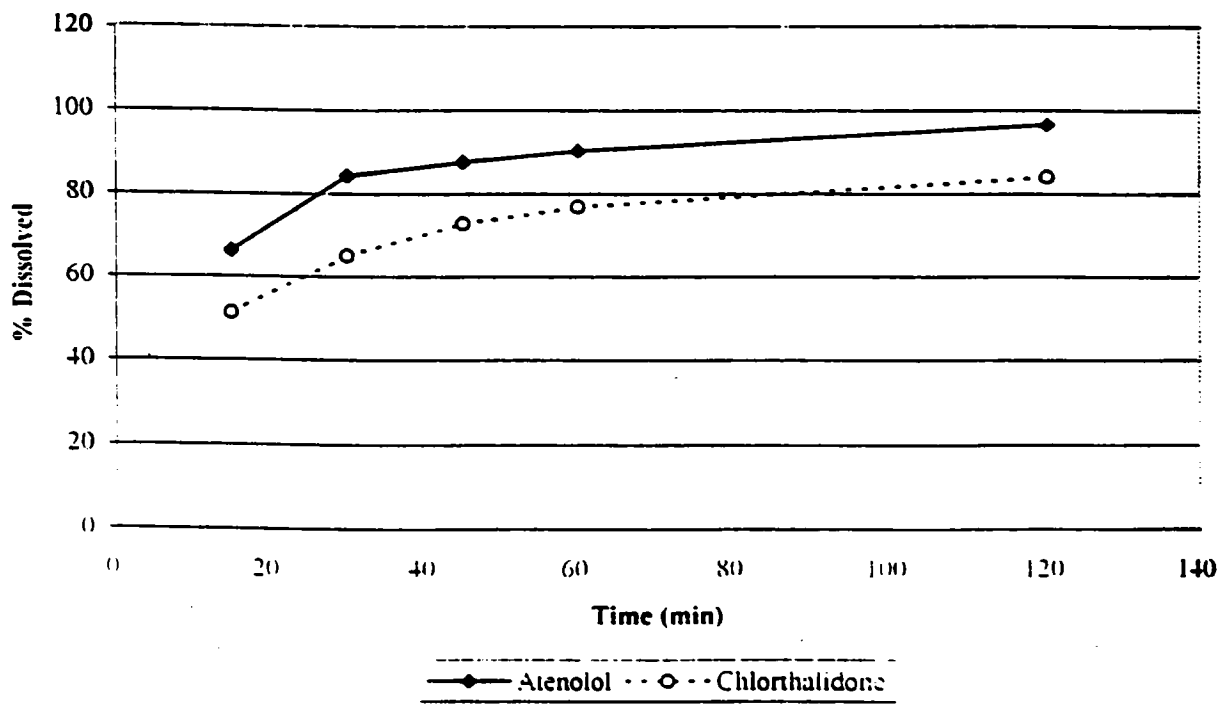


File: Detailed Summary - Tab 100-25 mg Tabs in pH 7.5 Buffer - Printed 3/18/97

DH 3-18-97

Atenolol/Chlorthalidone 100/25 mg Tablets
900 ml water (pH ~5.9) @ 50 rpm
Summary of Diss. Profile for FDA letter on Sep. 6. 1996
QC#: 92070; Lot#: 0599A1; 1000 count Bottles: ANDA/BIO batch 1

Sample #	Average % Dissolved of Atenolol					Average % Dissolved of Chlorthalidone				
	15	30	45	60	120	15	30	45	60	120
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Average	66.17	84.35	87.65	90.24	96.64	51.31	64.98	72.68	76.78	84.05
SD	20.96	19.15	15.44	14.77	10.73	15.12	14.97	13.33	12.30	10.40
%RSD	31.67	22.71	17.62	16.36	11.11	29.46	23.04	18.34	16.03	12.37
Range-High	92.85	103.98	104.02	106.86	108.99	69.84	82.43	88.51	92.95	98.10
Range-Low	34.98	52.82	59.72	62.54	74.86	28.83	44.94	51.36	55.77	65.96



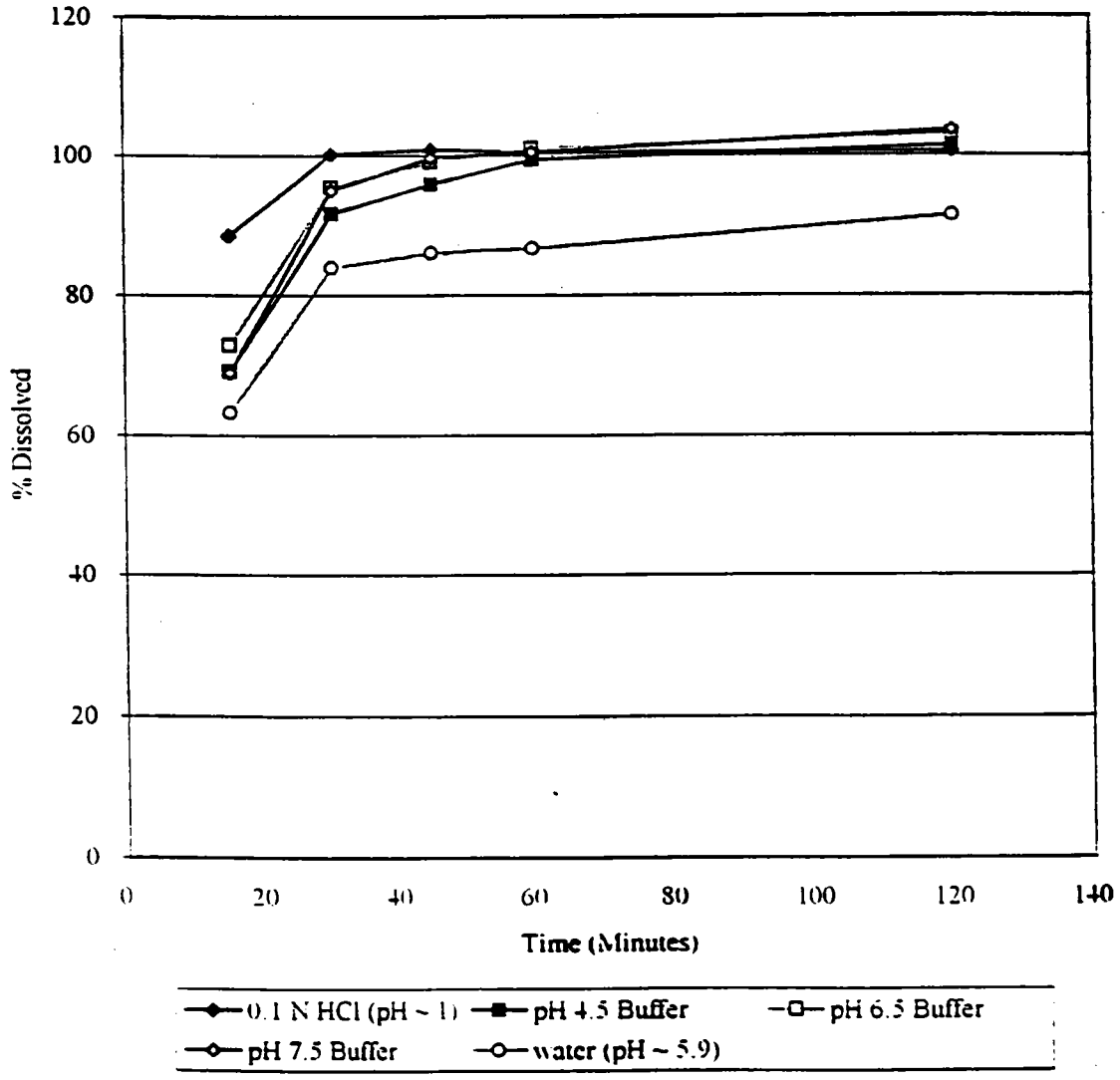
File: Detailed Summary - Tab: 100-25 mg Tabs in water pH ~5.9 - Printed: 3/18/97

DN 3-18-97

Atenolol/Chlorthalidone 50/25 mg Tablets
900 ml Media @ 50 rpm
Summary of Diss. Profile for FDA letter on Sep. 6. 1996
Atenolol portion of Samples
QC#: 92068; Lot#: 0596B1; 1000 count Bottles: ANDA/BIO batch 1

Average % Dissolved of Atenolol

Media	Sampling Time in Minutes				
	15	30	45	60	120
0.1 N HCl (pH ~ 1)	88.53	100.19	100.91	100.47	100.66
pH 4.5 Buffer	69.06	91.57	95.87	99.42	101.45
pH 6.5 Buffer	72.78	95.38	99.03	101.08	103.18
pH 7.5 Buffer	68.92	94.99	99.71	100.57	103.68
water (pH ~ 5.9)	63.21	83.92	86.04	86.6	91.33



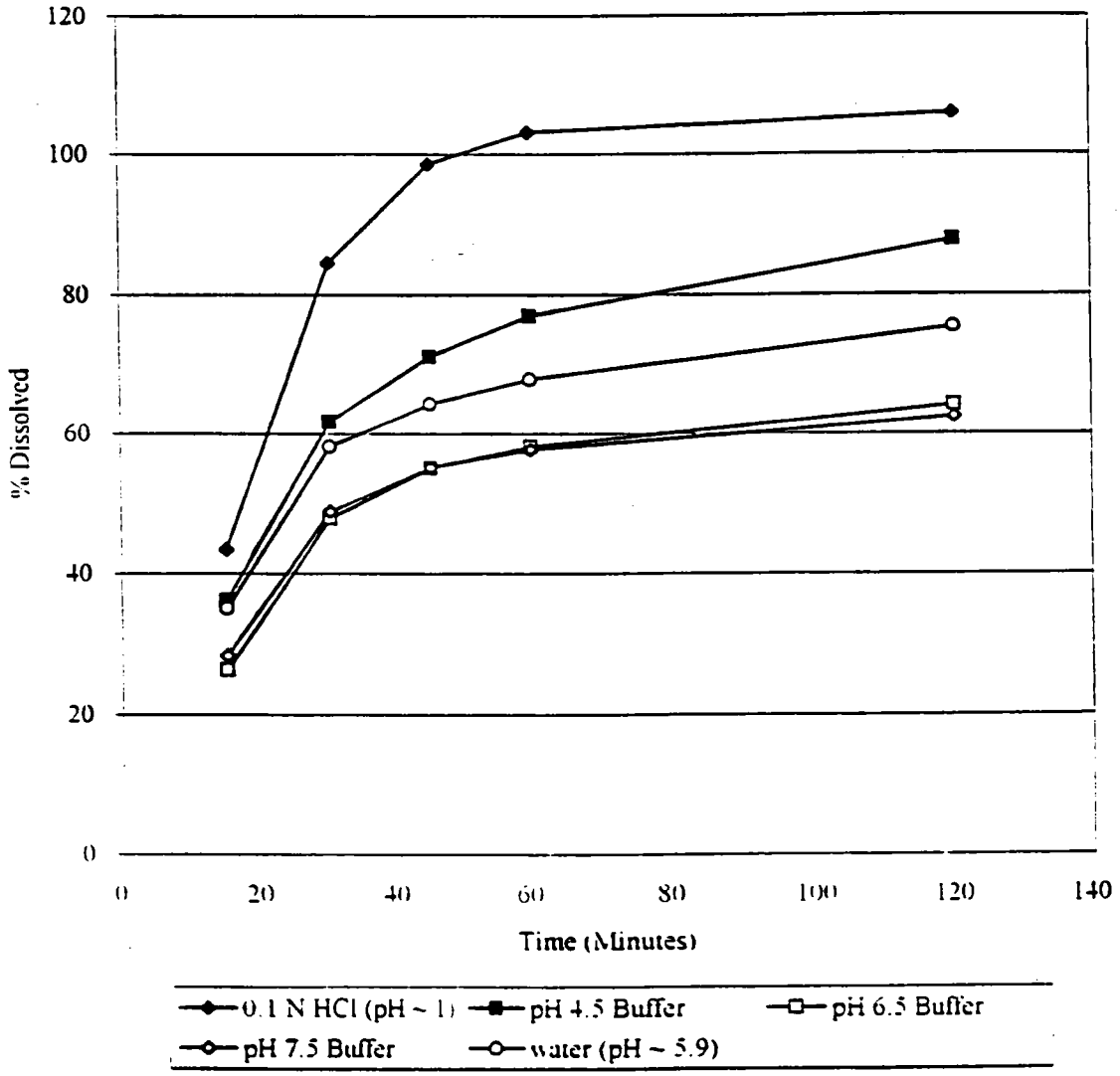
File: Summary - Tab: 50-25 mg Tabs (Atenolol) - Printed: 3/18/97

WN 3-10 97

Atenolol/Chlorthalidone 50/25 mg Tablets
900 ml Media @ 50 rpm
Summary of Diss. Profile for FDA letter on Sep. 6. 1996
Chlorthalidone portion of Samples
QC#: 92068; Lot#: 0596B1; 50/25mg Tablets: 1000 count Bottles: ANDA/BIO batch 1

Average % Dissolved of Chlorthalidone

Media	Sampling Time in Minutes				
	15	30	45	60	120
0.1 N HCl (pH ~ 1)	43.39	84.52	98.59	103.16	105.8
pH 4.5 Buffer	36.22	61.69	71.13	76.94	87.79
pH 6.5 Buffer	26.35	47.85	55.03	58.11	64.04
pH 7.5 Buffer	28.36	48.81	55.11	57.72	62.37
water (pH ~ 5.9)	35.1	58.14	64.28	67.8	75.32

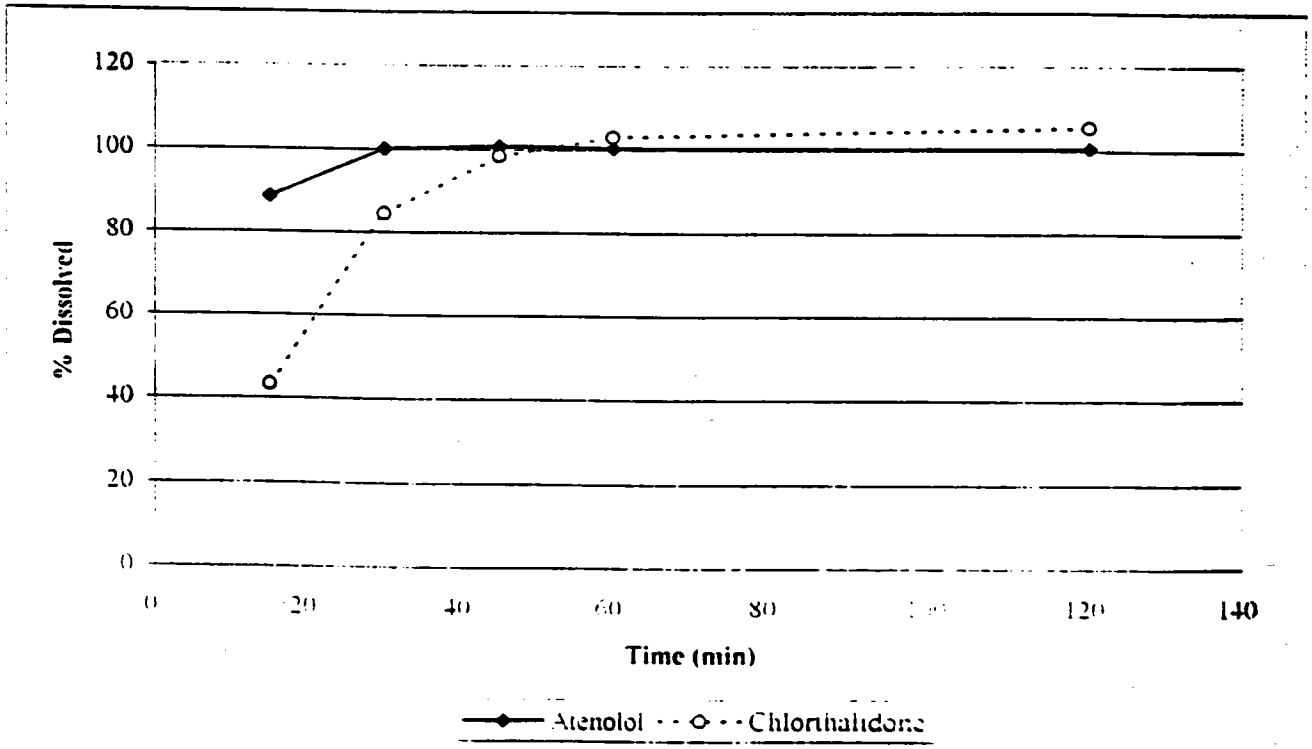


File: Summary - Tab: 50-25 mg Tabs (Chlorthalidone) - Printed: 3/18/97

NH 3-18-97

Atenolol/Chlorthalidone 50 mg/25 mg Tablets
900 mL 0.1 N HCl (pH~1.2) @ 50 rpm, USP Apparatus II
Summary of Diss. Profile for FDA letter of Sep. 6, 1996
QC#: 92068; Lot#: 0596B1; 1000 count Bottles; ANDABIO batch 1

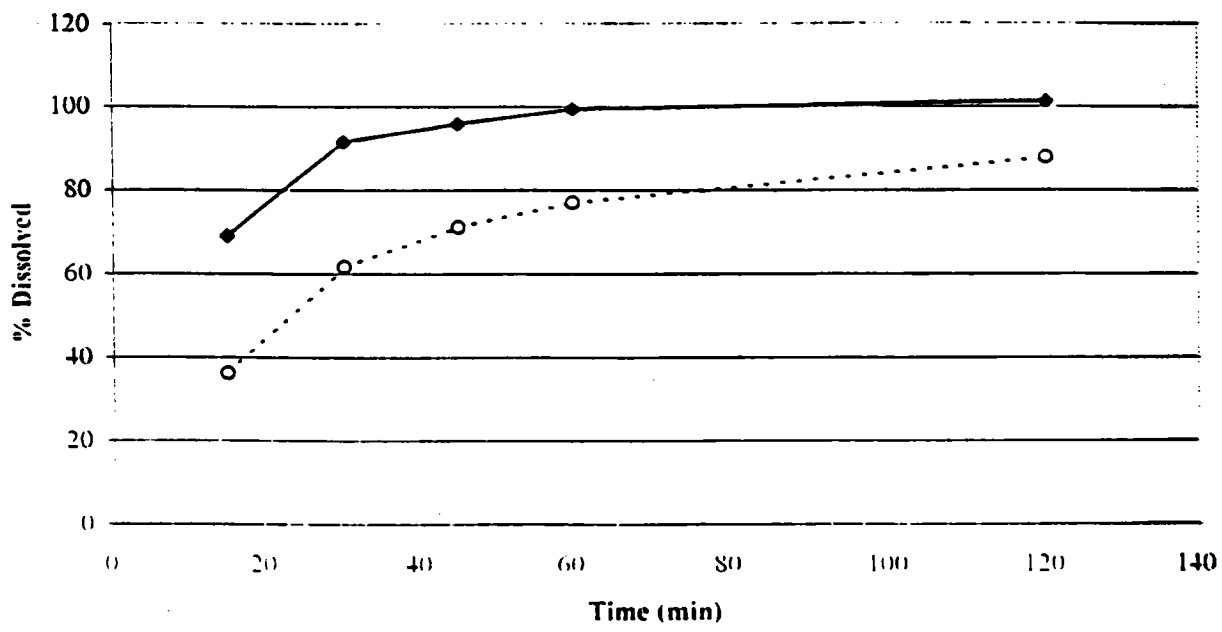
Sample #	Average % Dissolved of Atenolol					Average % Dissolved of Chlorthalidone				
	15	30	45	60	120	15	30	45	60	120
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Average	88.53	100.19	100.91	100.47	100.66	43.39	84.52	98.59	103.16	105.80
SD	5.11	1.47	1.57	1.49	1.38	3.66	3.00	2.22	1.86	1.84
%RSD	5.77	1.47	1.55	1.49	1.37	8.43	3.55	2.25	1.81	1.74
Range-High	97.06	102.99	104.15	102.66	102.63	47.76	88.85	101.01	104.93	108.55
Range-Low	80.06	97.91	98.46	98.35	98.25	36.98	79.98	94.64	99.33	101.92



File: Detailed Summary - Tab: 50-25 mg Tabs in 0.1N HCl - Printed 3/18/97

Atenolol/Chlorthalidone 50 mg/25 mg Tablets
900 mL pH 4.5 Buffer @ 50 rpm, USP Apparatus II
Summary of Diss. Profile for FDA letter on Sep. 6. 1996
QC#: 92068; Lot#: 0596B1; 1000 count Bottles; ANDA/BIO batch 1

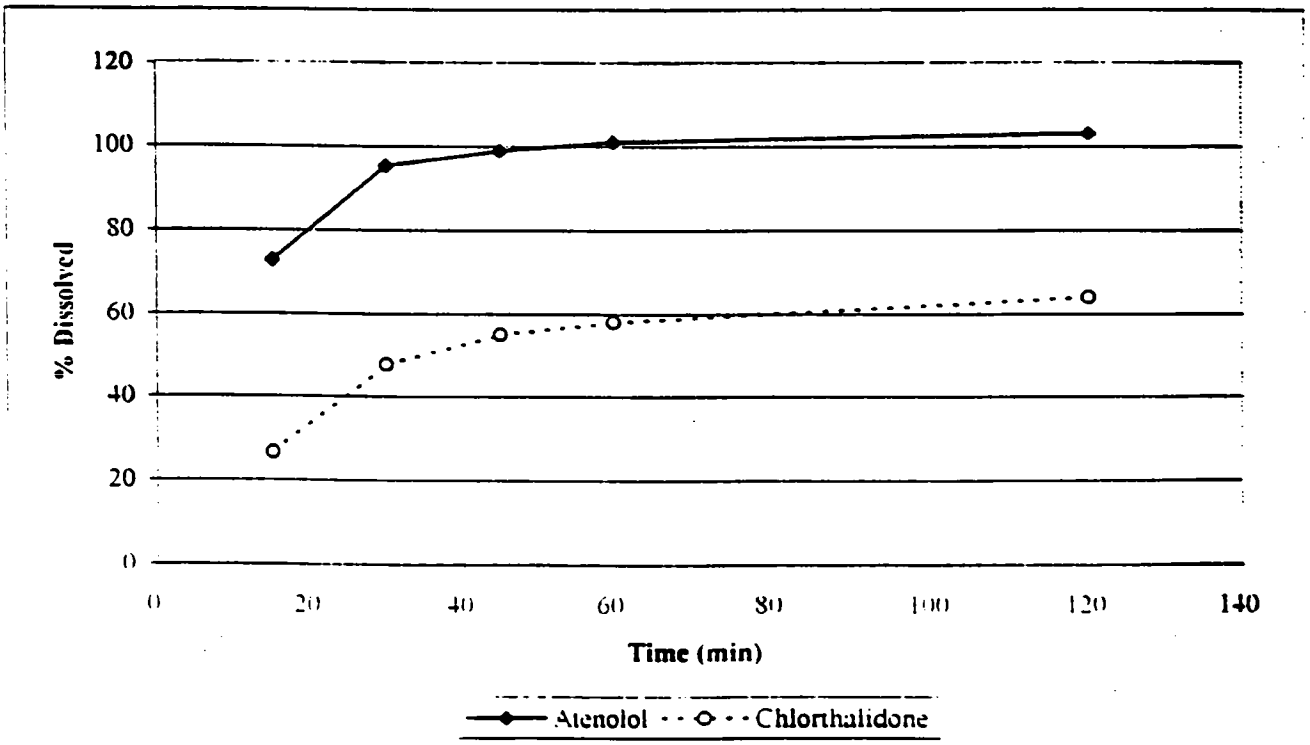
	Average % Dissolved of Atenolol					Average % Dissolved of Chlorthalidone				
Sample #	**15**	**30**	**45**	**60**	**120**	**15**	**30**	**45**	**60**	**120**
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Average	**69.06**	**91.57**	**95.87**	**99.42**	**101.45**	**36.22**	**61.69**	**71.13**	**76.94**	**87.79**
SD	5.71	4.18	4.13	2.54	1.20	5.45	6.47	6.31	5.92	**4.64**
%RSD	8.27	4.57	4.31	2.55	1.19	15.04	10.48	8.87	7.70	**5.29**
Range-High	75.87	95.47	99.54	102.46	103.51	48.38	73.95	81.04	85.22	**92.95**
Range-Low	58.83	82.76	87.98	94.62	99.92	29.20	49.40	58.26	64.72	**78.41**



File: Detailed Summary - Tab: 50-25 mg Tabs in pH 4.5 Buffer - Printed: 3/18/97

Atenolol/Chlorthalidone 50 mg/25 mg Tablets
900 ml pH 6.5 Buffer @ 50 rpm, USP Apparatus II
Summary of Diss. Profile for FDA letter on Sep. 6. 1996
QC#: 92068: Lot#: 0596B1: 1000 count Bottles: ANDA/BIO batch 1

	Average % Dissolved of Atenolol					Average % Dissolved of Chlorthalidone				
Sample #	15	30	45	60	120	15	30	45	60	120
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Average	72.78	95.38	99.03	101.08	103.18	26.35	47.85	55.03	58.11	64.04
SD	5.02	2.40	2.17	2.07	2.11	2.12	3.42	3.66	4.00	4.05
%RSD	6.89	2.52	2.19	2.05	2.04	8.06	7.16	6.66	6.88	6.33
Range-High	78.31	98.69	102.03	103.19	106.25	29.02	52.90	62.31	65.13	71.46
Range-Low	60.53	91.48	95.19	96.72	98.09	22.28	41.91	47.64	50.67	56.87

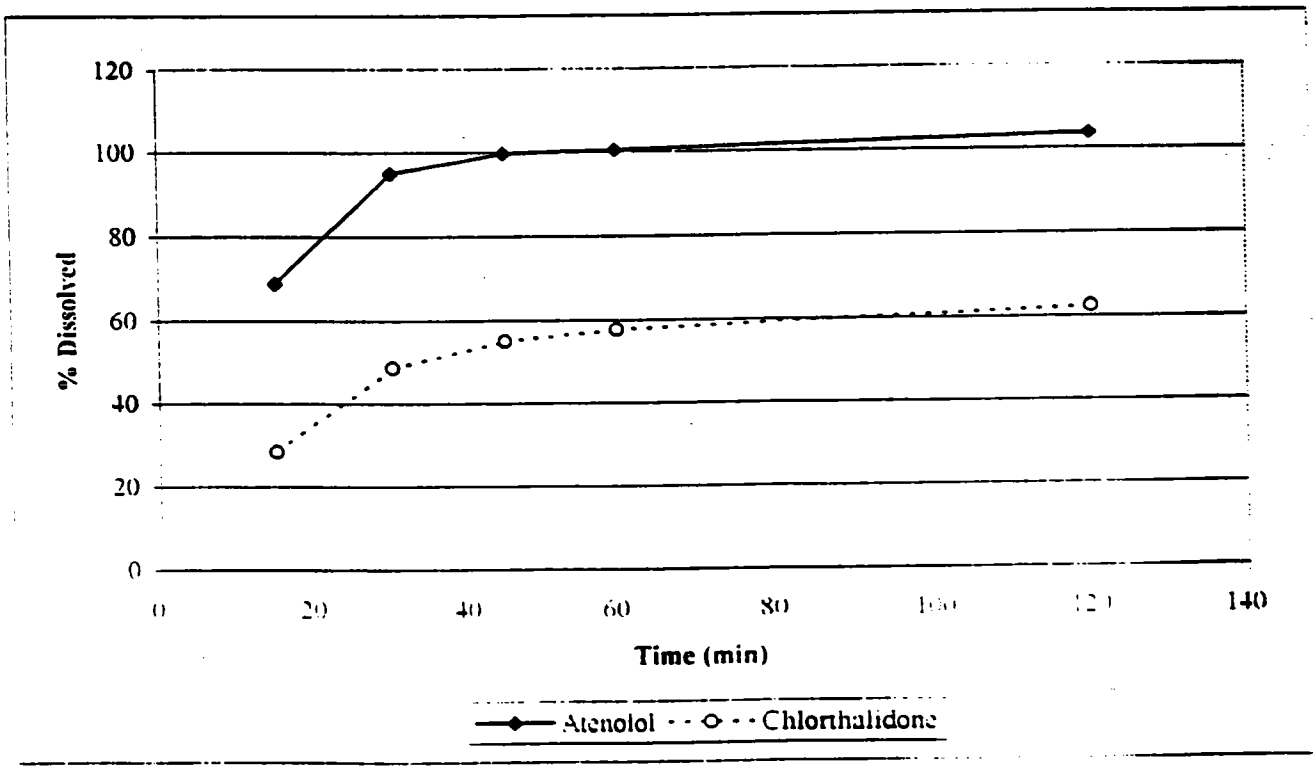


File: Detailed Summary - Tab: 50-25 mg Tabs in pH 6.5 Buffer - Printed. 3/18/97

N 3-18-97

Atenolol/Chlorthalidone 50 mg/25 mg Tablets
900 mL pH 7.5 Buffer @ 50 rpm, USP Apparatus II
Summary of Diss. Profile for FDA letter of Sep. 6. 1996
QC#: 92068; Lot#: 0596B1; 1000 count Bottles; ANDA/BIO batch 1

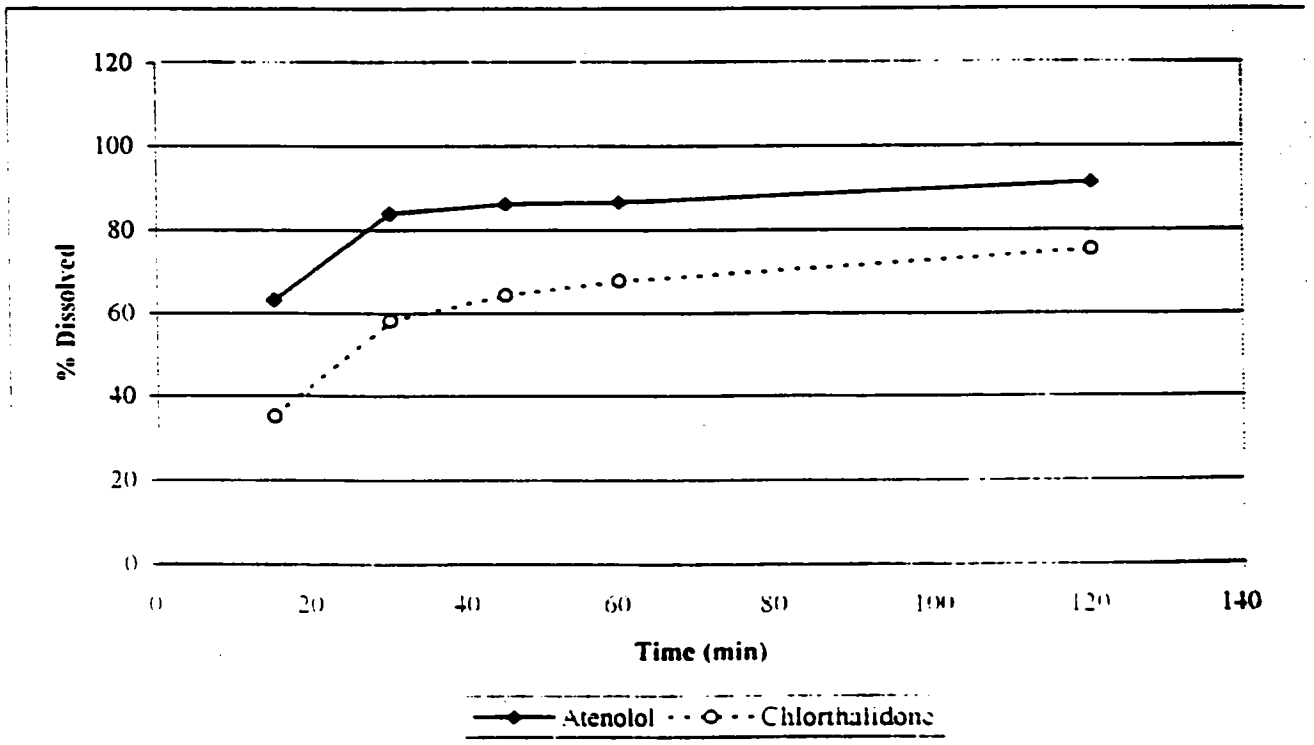
Sample #	Average % Dissolved of Atenolol					Average % Dissolved of Chlorthalidone				
	15	30	45	60	120	15	30	45	60	120
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Average	68.92	94.99	99.71	100.57	103.68	28.36	48.81	55.11	57.72	62.37
SD	8.21	3.09	1.91	1.28	1.28	3.84	3.79	4.03	3.66	3.68
%RSD	11.91	3.25	1.92	1.28	1.23	13.55	7.77	7.32	6.34	5.90
Range-High	77.59	99.03	102.50	102.65	104.91	35.08	56.89	62.83	64.80	68.90
Range-Low	52.68	88.55	97.83	98.99	101.28	22.72	43.17	47.90	50.33	54.24



File: Detailed Summary - Tab: 50-25 mg Tabs in pH 7.5 Buffer - Printed 3 18 97

Atenolol/Chlorthalidone 50 mg/25 mg Tablets
900 mL water (pH ~5.9) @ 50 rpm. USP Apparatus II
Summary of Diss. Profile for FDA letter of Sep. 6, 1996
QC#: 92068; Lot#: 0596B1; 1000 count Bottles; ANDA/BIO batch 1

Sample #	Average % Dissolved of Atenolol					Average % Dissolved of Chlorthalidone				
	15	30	45	60	120	15	30	45	60	120
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Average	63.21	83.92	86.04	86.60	91.33	35.10	58.14	64.28	67.80	75.32
SD	18.33	11.01	9.31	7.35	5.96	7.20	9.11	8.75	8.15	7.44
%RSD	29.00	13.12	10.82	8.48	6.53	20.51	15.68	13.62	12.02	9.88
Range-High	85.60	94.59	96.25	93.37	97.87	42.57	68.15	75.18	78.46	84.72
Range-Low	29.35	54.47	62.18	66.96	75.95	17.82	36.07	44.16	48.46	57.55



File: Detailed Summary - Tab: 50-25 mg Tabs in water pH ~5.9 - Printed: 3/18/97