CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74989

APPROVAL LETTER

ANDA 74-989

SEP 30 1998

Teva Pharmaceuticals USA
Attention: Deborah A. Jaskot
1510 Delp Drive
Kulpsville, PA 19443

Dear Madam:

This is in reference to your abbreviated new drug application dated October 15, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Labetalol Hydrochloride Tablets USP, 100 mg, 200 mg and 300 mg.

Reference is also made to your amendment dated April 24, 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 Labetalol Hydrochloride Tablets USP, 100 mg, 200 mg and 300 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Normodyne® Tablets, 100 mg, 200 mg and 300 mg, respectively, of Schering, Corp.). 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,

/S/

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

9-29-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74989

DRAFT FINAL PRINTED LABELING

R 1 3 567 1

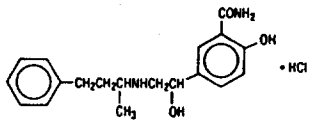
LABETALOL HYDROCHLORIDE TABLETS, USP

0100
0102
0106

Rev. A 8/97

single substance.

Labetalol Hydrochloride is a racemate, chemically designated as 5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl) amino] ethyl] salicylamide monohydrochloride. The structural formula is:



$C_{19}H_{24}N_2O_3 \cdot HCl$ M.W. 364.87

It has two asymmetric centers and therefore exists as a molecular complex of two diastereoisomeric pairs. Dilevalol, the R,R' stereoisomer, makes up 25% of racemic labetalol.

Labetalol Hydrochloride is a white or off-white crystalline powder, soluble in water.

Each tablet for oral administration contains 100 mg, 200 mg, or 300 mg of labetalol hydrochloride, USP. Each tablet also contains the following inactive ingredients: pregelatinized starch, lactose monohydrate, magnesium stearate, hydroxypropyl-methylcellulose, propylene glycol, and titanium dioxide. The 100 mg and 300 mg tablets also contain FD&C Blue No. 2 Aluminium Lake, FD&C Red No. 40 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, and talc (100 mg tablet only).

CLINICAL PHARMACOLOGY

Labetalol combines both selective, competitive alpha$_1$-adrenergic blocking and nonselective, competitive beta-adrenergic blocking activity in a single substance. In man, the ratios of alpha- to beta-blockade have been estimated to be approximately 1:3 and 1:7 following oral and intravenous administration, respectively. Beta$_2$-agonist activity has been demonstrated in animals with minimal beta$_1$-agonist (ISA) activity detected. In animals, at doses greater than those required for alpha- or beta-adrenergic blockade, a membrane-stabilizing effect has been demonstrated.

Pharmacodynamics The capacity of labetalol to block alpha receptors in man has been demonstrated by attenuation of the pressor effect of phenylephrine and by a significant reduction of the pressor response caused by immersing the hand in ice-cold water ("cold-pressor test"). Labetalol's beta$_1$-receptor blockade in man was demonstrated by a small decrease in the resting heart rate, attenuation of tachycardia produced by isoproterenol or exercise, and by attenuation of the reflex tachycardia to the hypotension produced by amyl nitrite. Beta$_2$-receptor blockade was demonstrated by inhibition of the isoproterenol-induced fall in diastolic blood pressure. Both the alpha-and beta-blocking actions of orally administered labetalol contribute to a decrease in blood pressure in hypertensive patients. Labetalol consistently, in dose-related fashion, blunted increases in exercise-induced blood pressure and heart rate, and in their double product. The pulmonary circulation during exercise was not affected by labetalol dosing.

Single oral doses of labetalol administered in patients with coronary artery disease had no significant effect on sinus rate, intraventricular conduction, or QRS duration. The AV conduction time was modestly prolonged in 2 of 7 patients. In another study, intravenous labetalol slightly prolonged AV nodal conduction time and atrial effective refractory period with only small changes in heart rate. The effects on AV nodal refractoriness were inconsistent.

Labetalol produces dose-related falls in blood pressure without reflex tachycardia and without significant reduction in heart rate, presumably through a mixture of its alpha-blocking and beta-blocking effects. Hemodynamic effects are variable with small nonsignificant changes in cardiac output seen in some studies but not others, and small decreases in total peripheral resistance. Elevated plasma renins are reduced.

Doses of labetalol that controlled hypertension did not affect renal function in mild to severe hypertensive patients with normal renal function.

Due to the alpha$_1$-receptor blocking activity of labetalol, blood pressure is lowered more in the standing than in the supine position, and symptoms of postural hypotension (2%), including rare instances of syncope, can occur. Following oral administration, when postural hypotension has occurred, it has been transient and is uncommon when the recommended starting dose and titration increments are closely followed. (See **DOSAGE AND ADMINISTRATION.**) Symptomatic postural hypotension is most likely to occur 2 to 4 hours after a dose, especially following the use of large initial doses or upon large changes in dose.

The peak effects of single oral doses of labetalol occur within 2 to 4 hours. The duration of effect depends upon dose, lasting at least 8 hours following single oral doses of 100 mg and more than 12 hours following single oral doses of 300 mg. The maximum, steady-state blood pressure response upon oral, twice-a-day dosing occurs within 24 to 72 hours.

The antihypertensive effect of labetalol has a linear correlation with the logarithm of labetalol plasma concentration, and there is also a linear correlation between the reduction in exercise-induced tachycardia occurring at 2 hours after oral administration of labetalol and the logarithm of the plasma concentration.

About 70% of the maximum beta-blocking effect is present for 5 hours after the administration of a single oral dose of 400 mg, with suggestion that about 40% remains at 8 hours.

The anti-anginal efficacy of labetalol has not been studied. In 37 patients with hypertension and coronary artery disease, labetalol did not increase the incidence or severity of angina attacks.

Exacerbation of angina and, in some cases, myocardial infarction and ventricular dysrhythmias have been reported after abrupt discontinuation of therapy with beta-adrenergic blocking agents in patients with coronary artery disease. Abrupt withdrawal of these agents in patients without coronary artery disease has resulted in transient symptoms, including tremulousness, sweating, palpitation, headache, and malaise. Several mechanisms have been proposed to explain these phenomena, among them increased sensitivity to catecholamines because of increased numbers of beta receptors.

Although beta-adrenergic receptor blockade is useful in the treatment of angina and hypertension, there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. Beta-adrenergic blockade may worsen AV block by preventing the necessary facilitating effects of sympathetic activity on conduction. Beta$_2$-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

Pharmacokinetics and Metabolism Labetalol is completely absorbed from the gastrointestinal tract with peak plasma levels occurring 1 to 2 hours after oral administration. The relative bioavailability of labetalol tablets compared to an oral solution is 100%. The absolute bioavailability (fraction of drug reaching systemic circulation) of labetalol when compared to an intravenous infusion is 25%; this is due to extensive "first-pass" metabolism. Despite "first-pass" metabolism there is a linear relationship between oral doses of 100 to 3000 mg and peak plasma levels. The absolute bioavailability of labetalol is increased when administered with food.

The plasma half-life of labetalol following oral administration is about 6 to 8 hours. Steady-state plasma levels of labetalol during repetitive dosing are reached by

[illegible] respectively. Impaired patients is increased due to decre "first-pass" metabolism.

The metabolism of labetalol is mainly through conjugation to glucuronide me lites. These metabolites are present in plasma and are excreted in the urine via the bile, into the feces. Approximately 55% to 60% of a dose appears i urine as conjugates or unchanged labetalol within the first 24 hours of dosin

Labetalol has been shown to cross the placental barrier in humans. Only ne ble amounts of the drug crossed the blood-brain barrier in animal stu Labetalol is approximately 50% protein bound. Neither hemodialysis nor toneal dialysis removes a significant amount of labetalol from the general ci tion (<1%).

INDICATIONS AND USAGE

Labetalol hydrochloride tablets are indicated in the management of hyperten Labetalol hydrochloride tablets may be used alone or in combination with antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS

Labetalol is contraindicated in bronchial asthma, overt cardiac failure, greater first degree heart block, cardiogenic shock, severe bradycardia, other condi associated with severe and prolonged hypotension, and in patients with a hi of hypersensitivity to any component of the product. (See **WARNINGS.**)

WARNINGS

Hepatic Injury Severe hepatocellular injury, confirmed by rechallenge in at one case, occurs rarely with labetalol therapy. The hepatic injury is us reversible, but hepatic necrosis and death have been reported. Injury has occ after both short- and long-term treatment and may be slowly progressive de minimal symptomatology. Similar hepatic events have been reported with a ed compound, dilevalol hydrochloride, including two deaths. Dilevalol hydro ride is one of the four isomers of labetalol. Thus, for patients taking labetalol, odic determination of suitable hepatic laboratory tests would be approp Laboratory testing should also be done at the very first symptom or sign of dysfunction (e.g., pruritis, dark urine, persistent anorexia, jaundice, right u quadrant tenderness, or unexplained "flu-like" symptoms). If the patient has dica or laboratory evidence of liver injury, labetalol should be stopped and restarted.

Cardiac Failure Sympathetic stimulation is a vital component supporting cir tory function in congestive heart failure. Beta blockade carries a potential ha of further depressing myocardial contractility and precipitating more severe fa Although beta-blockers should be avoided in overt congestive heart failure, if essary, labetalol can be used with caution in patients with a history of heart fa who are well-compensated. Congestive heart failure has been observed in pat receiving labetalol. Labetalol does not abolish the inotropic action of digitali heart muscle.

In Patients Without a History of Cardiac Failure In patients with latent ca insufficiency, continued depression of the myocardium with beta-blocking ag over a period of time can, in some cases, lead to cardiac failure. At the first or symptom of impending cardiac failure, patients should be fully digitalized ar be given a diuretic, and the response observed closely. If cardiac failure contin despite adequate digitalization and diuretic, labetalol therapy should be withd (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal Angina toris has not been reported upon labetalol discontinuation. However, hypersi tivity to catecholamines has been observed in patients withdrawn from beta-bl er therapy; exacerbation of angina and, in some cases, myocardial infarction occurred after *abrupt* discontinuation of such therapy. When discontinuing ch ically administered labetalol, particularly in patients with ischemic heart dise the dosage should be gradually reduced over a period of 1 to 2 weeks and patient should be carefully monitored. If angina markedly worsens or acute c nary insufficiency develops, labetalol administration should be reinstituted pro ly, at least temporarily, and other measures appropriate for the manageme unstable angina should be taken. Patients should be warned against interru or discontinuation of therapy without the physician's advice. Because coro artery disease is common and may be unrecognized, it may be prudent not to continue labetalol therapy abruptly even in patients treated only for hypertens

Nonallergic bronchospasm (e.g., chronic bronchitis and emphysema) pati with bronchospastic disease should, in general, not receive beta-blocl Labetalol may be used with caution, however, in patients who do not respon or cannot tolerate, other antihypertensive agents. It is prudent, if labetalol is u to use the smallest effective dose, so that inhibition of endogenous or exoge beta-agonists is minimized.

Pheochromocytoma Labetalol has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocyt However, paradoxical hypertensive responses have been reported in a few pat with this tumor; therefore, use caution when administering labetalol to pat with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia Beta-adrenergic blockade may preven appearance of premonitory signs and symptoms (e.g., tachycardia) of acute h glycemia. This is especially important with labile diabetics. Beta- blockade reduces the release of insulin in response to hyperglycemia; it may therefo necessary to adjust the dose of antidiabetic drugs.

Major Surgery The necessity or desirability of withdrawing beta-blocking the prior to major surgery is controversial. Protracted severe hypotension and culty in restarting or maintaining a heartbeat have been reported with beta-b ers. The effect of labetalol alpha-adrenergic activity has not been evaluated in setting.

A synergism between labetalol and halothane anesthesia has been shown. **PRECAUTIONS-Drug Interactions.**)

PRECAUTIONS

General

Impaired Hepatic Function Labetalol should be used with caution in patients impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction. (See **WARNINGS.**)

Information for Patients

As with all drugs with beta-blocking activity, certain advice to patients t treated with labetalol is warranted. This information is intended to aid in safe and effective use of this medication. It is not a disclosure of all pos adverse or intended effects. While no incident of the abrupt withdrawal nomenon (exacerbation of angina pectoris) has been reported with labet dosing with labetalol should not be interrupted or discontinued without a ph cian's advice. Patients being treated with labetalol should consult a phys at any signs or symptoms of impending cardiac failure or hepatic dysfunc (See **WARNINGS.**) Also, transient scalp tingling may occur, usually when t ment with labetalol is initiated. (See **ADVERSE REACTIONS.**)

Laboratory Tests

As with any new drug given over prolonged periods, laboratory param should be observed over regular intervals. In patients with concomitan nesses, such as impaired renal function, appropriate tests should be don monitor these conditions.

Drug Interactions

In one survey, 2.3% of patients taking labetalol in combination with tric antidepressants experienced tremor as compared to 0.7% reported to c with labetalol alone. The contribution of each of the treatments to this adv

reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol. During controlled hypotensive anesthesia using labetalol in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol.

Labetalol blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Care should be taken if labetalol is used concomitantly with calcium channel antagonists of the verapamil type.

Risk of Anaphylactic Reaction While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Drug/Laboratory Test Interactions
The presence of labetalol metabolites in the urine may result in falsely elevated levels of urinary catecholamines, metanephrine, normetanephrine, and vanillylmandelic acid (VMA) when measured by fluorimetric or photometric methods. In screening patients suspected of having a pheochromocytoma and being treated with labetalol, a specific method, such as a high performance liquid chromatographic assay with solid phase extraction (e.g., *J Chromatogr* 385:241, 1987) should be employed in determining levels of catecholamines.

Labetalol has also been reported to produce a false-positive test for amphetamine when screening urine for the presence of drugs using the commercially available assay methods Toxi-Lab A® (thin-layer chromatographic assay) and Emit-d.a.u.® (radioenzymatic assay). When patients being treated with labetalol have a positive urine test for amphetamine using these techniques, confirmation should be made by using more specific methods, such as a gas chromatographic- mass spectrometer technique.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term oral dosing studies with labetalol for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

Pregnancy Category C
Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. A teratology study performed with labetalol in rabbits at intravenous doses up to 1.7 times the MRHD revealed no evidence of drug-related harm to the fetus. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects
Hypotension, bradycardia, hypoglycemia, and respiratory depression have been reported in infants of mothers who were treated with labetalol for hypertension during pregnancy. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

Labor and Delivery
Labetalol given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers
Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when labetalol is administered to a nursing woman.

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

ADVERSE REACTIONS

Most adverse effects are mild, transient and occur early in the course of treatment. In controlled clinical trials of 3 to 4 months duration, discontinuation of labetalol due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 5% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The incidence rates of adverse reactions listed in the following table were derived from multicenter controlled clinical trials comparing labetalol, placebo, metoprolol, and propranolol, over treatment periods of 3 and 4 months. Where the frequency of adverse effects for labetalol and placebo is similar, causal relationship is uncertain. The rates are based on adverse reactions considered probably drug related by the investigator. If all reports are considered, the rates are somewhat higher (e.g., dizziness 20%, nausea 14%, fatigue 11%), but the overall conclusions are unchanged.

	Labetalol (N = 227) %	Placebo (N=96) %	Propranolol (N=84) %	Metoprolol (N = 49) %
Body as a whole				
fatigue	5	0	12	12
asthenia	1	1	1	0
headache	2	1	1	2
Gastrointestinal				
nausea	6	1	1	2
vomiting	<1	0	0	0
dyspepsia	3	1	1	0
abdominal pain	0	0	1	2
diarrhea	<1	0	2	0
taste distortion	1	0	0	0
Central and Peripheral Nervous Systems				
dizziness	11	3	4	4
paresthesias	<1	0	0	0
drowsiness	<1	2	2	2
Autonomic Nervous System				
nasal stuffiness	3	0	0	0
ejaculation failure	2	0	0	0
impotence	1	0	1	3
increased sweating	<1	0	0	0

Cardiovascular				
edema	1	0	0	0
postural hypotension	1	0	0	0
bradycardia	0	0	5	12
Respiratory				
dyspnea	2	0	1	2
Skin				
rash	1	0	0	0
Special Senses				
vision abnormality	1	0	0	0
vertigo	2	1	0	0

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, i.e., a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2400 mg in more severely hypertensive patients. Certain of the side effects increased with increasing dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly drug related.

Labetalol Daily Dose (mg)	200	300	400	600	800
Number of Patients	522	181	606	608	503
Dizziness (%)	2	3	3	3	5
Fatigue	2	1	4	4	5
Nausea	<1	0	1	2	4
Vomiting	0	0	<1	<1	<1
Dyspepsia	1	0	2	1	1
Paresthesias	2	0	2	2	1
Nasal Stuffiness	1	1	2	2	2
Ejaculation Failure	0	2	1	2	3
Impotence	1	1	1	1	2
Edema	1	0	1	1	1
Daily Dose (mg)	900	1200	1600	2400	
Number of Patients	117	411	242	175	
Dizziness (%)	1	9	13	16	
Fatigue	3	7	6	10	
Nausea	0	7	11	19	
Vomiting	0	1	2	3	
Dyspepsia	0	2	2	4	
Paresthesias	1	2	5	5	
Nasal Stuffiness	2	4	5	6	
Ejaculation Failure	0	4	3	5	
Impotence	4	3	4	3	
Edema	0	1	2	2	

In addition, a number of other less common adverse events have been reported:

Body as a Whole
Fever.

Cardiovascular
Hypotension, and rarely, syncope, bradycardia, heart block.

Central and Peripheral Nervous Systems
Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient and usually occurred at the beginning of treatment.

Collagen Disorders
Systemic lupus erythematosus; positive antinuclear factor (ANF).

Eyes
Dry eyes.

Immunological System
Antimitochondrial antibodies.

Liver and Biliary System
Hepatic necrosis; hepatitis; cholestatic jaundice; elevated liver function tests.

Musculoskeletal System
Muscle cramps; toxic myopathy.

Respiratory System
Bronchospasm.

Skin and Appendages
Rashes of various types, such as generalized maculopapular; lichenoid; urticarial; bullous lichen planus; psoriaform; facial erythema; Peyronie's disease; reversible alopecia.

Urinary System
Difficulty in micturition, including acute urinary bladder retention.

Hypersensitivity
Rare reports of hypersensitivity (e.g., rash, urticaria, pruritus, angioedema, dyspnea) and anaphylactoid reactions.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects
In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central 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**).

Allergic
Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic
Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal
Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol.

Clinical Laboratory Tests
There have been reversible increases of serum transaminases in 4% of patients treated with labetalol and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE

Overdosage with labetalol causes excessive hypotension that is posture sensitive, and sometimes, excessive bradycardia. Patients should be placed supine and their legs raised if necessary to improve the blood supply to the brain. If overdosage with labetalol follows oral ingestion, gastric lavage or pharmacologically induced emesis (using syrup of ipecac) may be useful for removal of the drug shortly after ingestion. The following additional measures should be employed if necessary: *Excessive bradycardia* - administer atropine or epinephrine. *Cardiac Failure* - administer a digitalis glycoside and a diuretic. Dopamine or dobutamine may also be useful. *Hypotension* - administer vasopressors, e.g., norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. *Bronchospasm* - administer epinephrine and/or an aerosolized $beta_2$-agonist. *Seizures* - administer diazepam.

In severe beta-blocker overdosage resulting in hypotension and/or bradycardia, glucagon has been shown to be effective when administered in large doses (5 to 10 mg rapidly over 30 seconds, followed by continuous infusion of 5 mg/hr that can be reduced as the patient improves).

Neither hemodialysis nor peritoneal dialysis removes a significant amount of labetalol from the general circulation (<1%).

The oral LD_{50} value of labetalol in the mouse is approximately 600 mg/kg and in the rat is greater than 2 g/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The recommended initial dose is 100 mg twice daily whether used alone or added to a diuretic regimen. After 2 or 3 days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg b.i.d. every 2 or 3 days. The usual maintenance dosage of labetalol is between 200 and 400 mg twice daily.

Since the full antihypertensive effect of labetalol is usually seen within the first 1 to 3 hours of the initial dose or dose increment, the assurance of a lack of an exaggerated hypotensive response can be clinically established in the office setting. The antihypertensive effects of continued dosing can be measured at subsequent visits, approximately 12 hours after a dose, to determine whether further titration is necessary.

Patients with severe hypertension may require from 1200 mg to 2400 mg per day, with or without thiazide diuretics. Should side effects (principally nausea or dizziness) occur with these doses administered b.i.d., the same total daily dose administered t.i.d. may improve tolerability and facilitate further titration. Titration increments should not exceed 200 mg b.i.d..

When a diuretic is added, an additive antihypertensive effect can be expected. In some cases this may necessitate a labetalol dosage adjustment. As with most antihypertensive drugs, optimal dosages of labetalol are usually lower in patients also receiving a diuretic.

When transferring patients from other antihypertensive drugs, labetalol should be introduced as recommended and the dosage of the existing therapy progressively decreased.

HOW SUPPLIED

Labetalol Hydrochloride Tablets USP are available as:

100 mg tablets; film-coated, round, concave, light pink, scored, debossed "93" - "100", packaged in bottles of 100 and 1000.

200 mg tablets; film-coated, round, concave, white to off-white, scored, debossed "93" - "102", packaged in bottles of 100 and 1000.

300 mg tablets; film-coated, round, concave, light purple, unscored, debossed "93" - "106", packaged in bottles of 100 and 1000.

Store at controlled room temperature 15° - 30°C (59° - 86°F).

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, ISRAEL

For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Printed in USA
Rev. A 8/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74989

CHEMISTRY REVIEW(S)

DIVISION REVIEW SUMMARY

ANDA #: 74-989 **DRUG PRODUCT: Labetalol HCl Tablets, USP**

FIRM: Teva Pharmaceuticals USA

DOSAGE: Tablets

STRENGTH: 100, 200 and 300 mg

cGMP STATEMENT/EIR UPDATE STATUS:
cGMP: GMP Certification (pages # 2616 and 2619); adequate
EER: Acceptable as of 4/13/98

BIO STUDY(ies)/BIOEQUIVALENCE STATUS:
On 9/15/97 the Division of Bioequivalence issued a no comments letter to the firm.

METHODS VALIDATION(Including dosage form description):
Not required because it is a USP drug; Field picked up samples and analyzed them. The results are acceptable and filed in Volume 1.1.

STABILITY(Conditions, Containers, methods):
Bio batch

Specifications

TEST	SPECIFICATION
Appearance	**100 mg:** Light pink, round 7.9 mm diameter, concave, bevelled edges, film coated tablet, scored on one side and debossed on the other side with the numbers "93" and "100". **200 mg:** White to Off-white, round 10.3 mm diameter, concave, bevelled edges, film coated tablet, scored and debossed on one side with the numbers "93" and "102" and plain on the other. **300 mg:** Light purple, round 11.1 mm diameter, concave, bevelled edges, film coated tablet, debossed on one side with the numbers "93" and "106" and plain on the other
Assay	% for each active
Dissolution	Q= % in 45 min

Impurities Single Total Impurities	 NMT % NMT %

Stability studies were done on the bio batch. Containers are the same as those listed in the container section (packaged in 100 count and 1000 count). Stability studies are in conformance with the FDA Guidelines.

LABELING REVIEW STATUS: Satisfactory. See review dated 3/5/98.

STERILIZATION VALIDATION (If Applicable): N/A

BATCH SIZES:

BIO BATCH (identity #, DS source)

Batch #: K-20251 (300 mg)
Batch size: Tablets
NDS source:

STABILITY BATCHES (different from BIO BATCH, manuf. site, process)
Stability batch is the same as the bio batch

PROPOSED PRODUCTION BATCH
Tablets for 100 mg; tablets for 200 mg and cores for 300 mg.

Process is the same as the demonstration batch. Scale-up equipment is identified on page 2758 of the ANDA. Reprocessing statement is also provided on page 2756.

COMMENTS: Approvable

CHEMISTRY REVIEWER:
/S/
Radhika Rajagopalan

DATE:
8/28/98
August 17, 1998

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 74-989

3. NAME AND ADDRESS OF APPLICANT

Teva Pharmaceuticals USA
Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

4. LEGAL BASIS for ANDA SUBMISSION page 2-15

Reference Drug Product: Normodyne®Tablets; Schering; Patent #4012444 expired on August 2, 1998. No exclusivity remaining.

5. SUPPLEMENT(s) None

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Labetalol Hydrochloride Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: None

9. AMENDMENTS AND OTHER DATES:

Applicant:

10/15/1996: Original application
9/12/97: Major amendment
4/24/98: Major amendment

FDA:

12/10/1996:Acceptable for filing letter
5/20/97: Major deficiency by chemistry and labeling
9/15/97: Bio letter out with acceptance of study
3/5/98: Acceptable label review
4/13/98: Major deficiency by chemistry

10. PHARMACOLOGICAL CATEGORY

Hypertension; Labetolol HCl is an antihypertensive agent that is a specific competitive antagonist at both α- and β-adrenergic receptor sites.

11. Rx or OTC

Rx

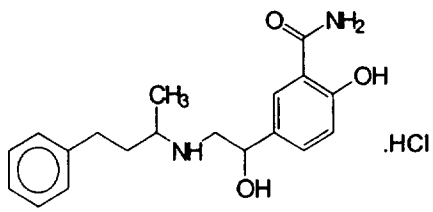
12. RELATED IND/NDA/DMF(s)

See review element #37 for list of DMFs

13. POTENCY

Tab
mg,

Labetalol Hydrochloride



.HCl

$C_{19}H_{24}N_2O_3.HCl$ MOL. WT. 364.87

5-[1-Hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]-salicyl monohydrochloride

DOSAGE FORM

lets
200 mg, 300 mg

14. 100

15. STRUCTUR

CHEMICAL NAME AND E

16. RECORDS AND REPORTS

None

17. COMMENTS

a. DMF for drug substance is satisfactory.
b. Labeling review - satisfactory, A. Vezza, 3.5.98.
c. Bio review - acceptable
d. MV not required - methods have been shown to be equivalent to compendial methods.
e. EER acceptable - 4/13/98

18. CONCLUSIONS AND RECOMMENDATIONS

Chemistry review is acceptable; approval recommended.

19. REVIEWER: DATE COMPLETED:

Radhika Rajagopalan, Ph.D. 8/17/98

/S/ 8/28/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74989

BIOEQUIVALENCY REVIEW(S)

AUG 26 1997

Labetalol Hydrochloride Tablets, USP
100 mg, 200 mg, and 300 mg
ANDA #74989
Reviewer: Kuldeep R. Dhariwal
File name: 74989SDW.096

Teva Pharmaceuticals USA
650 Cathill Road
Sellersville
PA 18960
Submission Date:
October 15, 1996

Review of Fasting and Fed Studies, Dissolution Data and Waiver Request

The firm has submitted fasting and fed single-dose *in vivo* bioequivalence studies and dissolution data comparing its labetalol hydrochloride tablets, 300 mg with Schering Corporation's Normodyne® tablets, 300 mg. The firm has also requested waivers of *in vivo* bioequivalence study requirements for its 100 mg and 200 mg tablets. To support the request, the firm has submitted comparative dissolution profiles on 100 mg and 200 mg strengths of its product and reference listed drug Normodyne® tablets 100 mg and 200 mg.

Introduction:

Labetalol hydrochloride is an adrenergic receptor blocking agent that has both selective alpha$_1$ and non-selective beta-adrenergic receptor blocking actions in a single substance. Labetalol hydrochloride is a racemate, chemically designated as 5-[1-hydroxy-2[(1-methyl-3-phenylpropyl) amino] ethyl] salicylamide monohydrochloride. It is indicated in the management of hypertension and may be used alone or in combination with other antihypertensive agents.

Labetalol hydrochloride is completely absorbed from the gastrointestinal tract with peak plasma levels occurring one to two hours after oral administration. The relative bioavailability of labetalol hydrochloride tablets compared to an oral solution is 100%. The absolute bioavailability of labetalol when compared to an intravenous infusion is 25%; this is due to extensive first-pass metabolism. Despite first-pass metabolism there is a linear relationship between oral doses of 100 to 3000 mg and peak plasma levels. The absolute bioavailability of labetalol is increased when administered with food. The plasma half-life of labetalol following oral administration is about six to eight hours.

The recommended initial dose is 100 mg twice daily. After 2 or 3 days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every 2 or 3 days. The usual maintenance dosage is between 200 and 400 mg twice daily. The orange book lists Normodyne® of Schering as reference listed drug. Glaxo Wellcome has labetalol hydrochloride (Trandate®, coded AB) in the market which was also filed as NDA. Both of these tablets are available in three strengths: 100, 200, and 300 mg. There are no approved generics of this product in the market.

Bioavailability of labetalol hydrochloride, 300 mg tablet under fasting conditions:

A. Objective: To compare the bioavailability of Teva's formulation of labetalol hydrochloride tablets, 300 mg to that of a marketed reference formulation, Normodyne®, 300 mg tablet manufactured by Schering Corporation, after oral administration under fasting conditions.

B. Study Sites and Investigators:

Clinical and Analytical Site:

Principal Investigator:
Protocol # 10997A: Bioavailability of labetalol hydrochloride tablets, 300 mg was approved by the National Institutional Review Board for
Consent Form: A copy of volunteer informed consent form used in the study is given on page 347, vol.1.2.
Study Dates: Period I January 19-21, 1996
Period II January 26-28, 1996
Analysis dates: February 1 to August 10, 1996

C. Study Design:

The study was designed as randomized, single-dose, two-treatment, two-period, two-sequence crossover study with a one week wash-out period between drug administrations. Subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration until at least 24 hours after drug administration. The subjects were assigned to two sequences at random as follows:

Sequence	Subject number	Period I	Period II
1	1,3,5,8,9,12,14,15,17,20,21,23,26,27,29	A	B
2,	2,4,6,7,10,11,13,16,18,19,22,24,25,28,30	B	A

Subject number 4 did not complete the study
A: Labetalol Hydrochloride tablets 1x300 mg, Teva Pharmaceuticals; Lot #K-20251; Lot size: tablets; Manufacture date: August 27, 1995; Assay: %; Uniformity of Dosage Units: %

B: Normodyne® tablets 1x300 mg; Schering Corporation; Lot #94199; Expiry Date: September 1997; Assay: %; Uniformity of Dosage Units: %

Formulation of the test product is given in Table 1.

The subjects fasted for ten hours before dosing and for five hours after dosing. Water was freely available except within one hour of drug administration. One 300 mg labetalol tablet was given with 240 mL of water and the subjects were required to remain seated for 4 hours postdose. Vital signs were measured at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, and 24 hours postdose. Diagnostic blood and urine specimens were obtained from the subjects prior to discharge from the study at the end of period II.

D. Subject Selection:

Thirty male subjects were enrolled in the study using following inclusion criteria:

- 18-50 years of age weighing no more than ±15% from ideal weight for his height as defined by Metropolitan Life Insurance Company Statistical Bulletin 1983
- good health as determined by medical histories and physical examination. Blood chemistry, hematology, and urinalysis values within clinically acceptable limits

Subjects were excluded from this study based on the following criteria:

- history of asthma, diabetes, serious cardiovascular, neurological, hepatic, renal, hematopoietic, gastrointestinal diseases or ongoing infectious diseases
- history of alcohol or drug abuse
- known allergy to labetalol or other alpha or beta blockers
- blood pressure lower than 100/60 before dosing
- participation in another clinical study within 30 days of study start
- donation of blood/plasma within 30 days of study start
- positive HIV-1, hepatitis B surface antigen
- positive urine screen for drugs
- smoking within 3 months of study start

Subjects were imposed with following restrictions:

- no prescription drugs within 14 days or OTC medications within 7 days of the first dose
- no aspirin within 24 hours before dosing
- no alcohol consumption for at least 24 hours prior to drug administration
- no caffeine for at least 48 hours prior to dosing, each period
- no strenuous physical activity during the in-house portion of the study

E. Sample Collection:

Blood samples (10 mL) were collected in EDTA Vacutainers at predose (0 hour) and at 0.25, 0.50, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 14, 18 and 24 hours postdose. The samples were centrifuged at 10°C for 20 minutes. The plasma was separated, transferred, and stored at -20°C. The samples were transferred to the analytical laboratory on January 30, 1996.

F. Analytical Methods:

G. Pharmacokinetics/Statistical Analysis:

Area under the concentration-time curve (AUC) was calculated by linear interpolation between consecutive drug levels. AUC_{0-t} was calculated from zero to the last non-zero concentration (C(T)). AUC_{0-inf} was calculated by extrapolation of AUC_{0-t} by C(T)/KE. The elimination rate constant (KE) was estimated by linear squares

fitting of the logarithms of the last three to five concentrations versus time. Half-life, C_{max}, T_{max} were also calculated. The statistical analysis was performed using SAS version 6.08 and PROC GLM for the Analysis of Variance. All parameters were analyzed by analysis of variance and the F-test to determine statistically significant ($\alpha = 0.05$) differences between the drug formulations. The 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means and the standard error of the formulation difference from the ANOVA.

H. Results:

1. Clinical:

Thirty subjects entered the study. Subject #4 was withdrawn prior to period II dosing because of his low blood pressure measurement during period I (1.5 hour time point). Plasma samples from all twenty-nine subjects who completed the study were analyzed.

Adverse events:

Twenty-one subjects reported 71 adverse events. The most frequently reported events were decreased blood pressure (29 events: 14 test drug and 15 reference drug) and headache (17 events: 6 test and 11 reference drug). All events were possibly related to drug products. One subject was withdrawn prior to period II dosing because of a decreased blood pressure measurement.

Deviations in blood sampling:

A significant deviation was defined as greater than 5% of time since dosing for samples up to 10 hours and greater than 30 minutes for samples obtained thereafter. There was one deviation meeting this definition. The 15 minute sample for subject #3 in period I was drawn 2 minutes late. The difference in AUC_{0-t} calculated using actual time and scheduled time was less than 0.3%, therefore scheduled times were used for AUC calculations.

Reassays:

Of the 986 samples assayed in the study, 26 samples (2.64%) were reassayed for following reasons:

# of samples	Reason for reassay
4	pharmacokinetic anomaly
1	processing error

12	chromatographic interference
5	assay conc. > highest validated standard
1	inadvertently reassayed
3	to reexamine the presence of peak at the retention time of the drug

2. Analytical:

Standard labetalol and internal standard propranolol were obtained from USP.

SPECIFICITY: Plasma used to prepare standards and quality control samples was

LINEARITY: Actual standard curve range: 5.00 to 450 ng/mL. For analytical runs in which the QC criteria for acceptance were met, the coefficients of determination of the calibration lines were greater than 0.984 for labetalol. The lower limit of quantitation of the assay was 5 ng/mL for labetalol. The sample values calculated to be less than 5 ng/mL were reported as zero.

ACCURACY: Inter-day
Standards: 96.0% to 103%
QC samples: 99.1% to 101%

PRECISION: Inter-day
Standards: 2.74% to 6.52%
QC samples: 4.96% to 8.95%

STABILITY: Plasma samples spiked with 10 and 100 ng/mL concentrations of labetalol were stored at -20°C for several months. Analysis of these samples revealed that labetalol is stable in plasma at these concentrations for 14 months.

Comment: Samples in the present study were stored for not more than 205 days.

In addition, stability samples at 0, 12, and 150 ng/mL concentrations were prepared and stored with the study samples. These stability samples were assayed during the course of study sample analysis. The data demonstrates the stability of labetalol in plasma for 205 days.

The firm has provided following pre-study method validation results:

The initial method validation was performed with a range appropriate for a single 200 mg dose. The assay range was between ng/mL. The analytical method was used for labetalol biostudy submitted by
acceptable in August 1996 - File name:74787SDW.N95). A one-day validation was then performed to extend the range of the assay so that the range would be appropriate for this study (300 mg dose). The extended range is between 5.00 and 450 ng/mL.

LINEARITY: The calibration standard lines were linear from 5.00 to 450 ng/mL for labetalol in human plasma. The limit of quantification was 5 ng/mL for labetalol. The coefficient of variation for labetalol at 5 ng/mL was 1.21%.

SPECIFICITY: Three lots of plasma were tested for interfering peaks near the retention times of labetalol and internal standard. In addition, six lots of plasma were tested during original validation. Compounds like nicotine, acetaminophen, caffeine, and ibuprofen did not interfere with chromatography. Salicylic acid interfered with the assay.

The precision of the method was 0.85% to 1.21%. The accuracy of the method ranged from 102% to 111%.

RECOVERY: Labetalol

5 ng/mL	85.7%
50 ng/mL	84.5%
300 ng/mL	78.3%
Propranolol (INT STD)	
500 ng/mL	90.5%

STABILITY:
a) Freeze-thaw: stable after three freeze-thaw cycles at concentrations of 10 ng/mL and 100 ng/mL.
b) Room temperature: Triplicate samples at concentrations of 10 ng/mL and 100 ng/mL were kept at room temperature for 24 hours and then extracted. The mean concentrations of the stability samples were compared to the calculated concentrations of these samples at zero hour:

0 hour	24 hours
94.7 ng/mL	93.2 ng/mL
10.2 ng/mL	9.93 ng/mL

c) Autosampler stability: This was measured by comparing the mean concentration of the reinjected samples at each concentration to the mean from the original injection of those samples at that concentration:

Theoretical Conc. ng/mL	Original Conc. ng/mL	Reinjected after 45 hours Conc. ng/mL
200	183.6	185
50	45.6	45.16
10	9.54	9.34
5	4.65	4.54

3. Pharmacokinetics/Statistics:

The mean plasma concentrations of labetalol at each time point after test and reference products are shown in Table 2. There were no significant differences in mean concentrations between the formulations at any time after dosing. The time courses of labetalol concentration after the two products are plotted in Figure 1. The pharmacokinetic parameters are shown in Table 3. There was no statistically significant difference between the formulations for any parameter. The AUC_{0-t} of the test formulation was 1% higher than that of reference formulation. The AUC_{0-inf} of the test formulation was about 3% lower than that of the reference formulation. The test C_{max} occurred about 4 minutes earlier and was 1% higher than that of the reference formulation.

The reviewer performed some calculations to determine the accuracy of the values given in the application:

Subject #	Reviewer		Firm	
	AUC_{0-t}	AUC_{0-inf}	AUC_{0-t}	AUC_{0-inf}
1	948	1108	948	1108
10	670	772	670	772
20	345	406	346	407

The results of these calculations indicate good agreement between reviewer's calculations and the data reported by the firm.

The test/reference ratios for AUC_{0-t} ranged from 0.716 to 1.290 (mean 1.006), AUC_{0-inf} ranged from 0.745 to 1.268 (mean 1.007) and for C_{max} ranged from 0.372 to 2.121 with a mean of 1.127 (Table 4).

Table 5 shows the AUC_{0-t}/AUC_{0-inf} ratios for individual subjects. The ratios ranged from 0.81 to 0.93 for test and 0.82 to 0.93 for reference product.

The following are the 90% confidence intervals provided by the firm along with those calculated by the reviewer:

Parameter	90% Confidence Interval	
	Firm's values	Reviewer's values
$LNAUC_{0-t}$	96.29-103.74%	96.29-103.74%
$LNAUC_{0-inf}$	96.57-103.88%	96.57-103.87%
LNC_{max}	90.15-118.89%	90.15-118.88%

The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within the acceptable limits of 80-125%.

There were no statistically significant treatment, sequence or period effect for AUC_{0-t}, AUC_{0-inf}, and C_{max}.

Bioavailability of Labetalol Hydrochloride Tablets, 300 mg Under Fed Conditions:

A. Objective: a) To compare the relative bioavailability of labetalol test formulation with that of reference product, after a standard meal and b) to compare the relative bioavailability of labetalol test formulation under fasting and fed conditions

B. Study Sites and Investigators: same as for fasting study

Protocol # 10998A: Bioavailability of Labetalol Hydrochloride Tablets, 300 mg, Effect of Food Study was approved by the National Institutional Review Board for

Consent Form: A copy of volunteer informed consent form used in the study is given on page 1749, vol. 1.6

Study Dates: Phase I January 25-27, 1996
Phase II February 1-3, 1996
Phase III February 8-10, 1996

Analysis Dates: March 13 to August 15, 1996

C. Study Design:

This study was designed as a randomized, three treatment, single dose study. The study was executed in three phases with a one week wash-out period. Eighteen subjects were enrolled in the study. Subjects (who completed the study) were assigned as follows:

Subject #	Period I	Period II	Period III
4,10,13	A	B	C
1,16	C	A	B
2,12	B	C	A
3,9,17	B	A	C
5,18	A	C	B
6,11,14	C	B	A

A = Labetalol Hydrochloride tablets, 1x300 mg; Teva Pharmaceuticals; Lot # K20251; Manufacture Date: August 27, 1995; administered after a standard meal

B = Normodyne® tablets, 1x300 mg; Schering Corporation; Lot #94199; Expiration Date: September, 1997; administered after a standard meal

C = Labetalol Hydrochloride tablets, 1x300 mg; Teva Pharmaceuticals; administered after an overnight fast

Lot numbers of drug products administered in this study are the same as those used for the fasting study

D. Subject Selection:

Eighteen subjects were enrolled in the study with essentially same inclusion and exclusion criteria as in the fasting study. They were subjected to same screening procedure and restrictions.

E. Study Procedure:

Treatments A and B: Subjects were given a standardized breakfast after a fast lasting at least 10 hours. The breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, 180 mL of orange juice, and 240 mL of whole milk. All subjects completed their entire meal within 30 minutes. Five minutes after finishing the breakfast they were given a single oral dose of the assigned formulation with 240 mL of water.

Treatment C: Subjects were given a single oral dose of the assigned formulation with 240 mL of water after a fast of at least 10 hours.

F. Sample collection, Analytical Methods, and Pharmacokinetics/ Statistical Analysis:

Ten mL of venous blood were collected in Vacutainers with EDTA at 0 (predose), 0.25, 0.5, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 18, and 24 hours. Analytical methods and statistical analysis used in the study were same as for fasting study.

G. Results:

1. Clinical:

Eighteen subjects entered the study. Fifteen subjects completed the study. Three subjects were withdrawn due to non-compliance. Subject #7 tested positive for cocaine at entry of period I; however he was mistakenly dosed, but withdrawn during period I. Subject #15 tested positive for alcohol at entry of period II and therefore was not dosed. Subject #8 did not return for period II.

Fourteen subjects reported a total of 71 adverse events. Headache (16), decreased diastolic blood pressure (15), and fatigue (14) were the most frequently reported events. These events were possibly thought to be related to study drugs. None of the events required any medications.

One subject had high poststudy WBC/HPF counts in urine. The firm plans to follow-up this subject.

Deviation in the study:

No sampling or other deviations are reported.

Repeat assays:

Of the 765 samples assayed for this study, 8 samples were reassayed for following reasons: 2 due to chromatographic interference, 6 due to their concentration outside the range of the calibration line.

The first analysis of subject #17 samples indicated only one measurable concentration in Period I. Reassay of few samples did not confirm this observation. Therefore, all samples from subject #17 were reassayed.

2. Analytical:

Accuracy: Inter-run
- Standards: 93.6% to 103%
- QC Samples: 98.7% to 103%

Precision: Inter-run
- Standards: 2.28% to 7.23%
- QC Samples: 4.44% to 10.4%

Specificity: None of the predose samples showed interferences near the retention times of labetalol or internal standard.

3. Pharmacokinetics/Statistics:

The mean plasma concentrations of labetalol measured at each time point is given in Table 6. The time courses of labetalol concentration after the three treatments are given in Figure 2.

When the test and reference formulations were administered after a meal, the arithmetic means for AUC_{0-t} and AUC_{0-inf} of the test product were 15% higher than the respective means of the reference product. The mean C_{max} of the test product was 19% higher than that of the reference product and occurred about 5 minutes earlier.

The arithmetic means for AUC_{0-t} and AUC_{0-inf} were 9% higher in test fed compared to test-fasted subjects. The C_{max} in test-fed was 6% lower compared to test-fasted and occurred about 50 minutes later.

The least squares means and geometric means are given in Table 7.

Following are the ratios of the means of the pharmacokinetic parameters:

Test-fed/Ref-fed

Parameter	Ratio of Arithmetic Means	Ratio of Geometric Means
AUC_{0-t}	1.15	1.06
AUC_{0-inf}	1.15	1.05
C_{max}	1.19	1.12

Test-fed/Test-fast

AUC_{0-t}	1.09	1.16
AUC_{0-inf}	1.09	1.18
C_{max}	0.94	0.94

In Vitro Dissolution Testing:

The firm has submitted comparative dissolution data for test and reference products. The dissolution testing was done using USP method: 900 mL water as medium using apparatus 2 at 50 rpm. The test and reference products used in the dissolution testing were from the same lots used in the *in vivo* bioequivalence studies. The test and reference products dissolve more than % in 45 minutes (Table 8).

Waiver Request:

The firm is requesting for a waiver of *in vivo* bioequivalence study for its 100 and 200 mg labetalol hydrochloride tablets. The comparative quantitative composition of all strengths are shown in Table 1. The 100 and 200 mg tablets are proportionally similar in their active and inactive ingredients to 300 mg tablets. The dissolution profiles of all strengths are acceptable.

Comments:

Fasting Study:

1. Thirty subjects entered the study. One subject was withdrawn prior to period II dosing because of his low blood pressure measurement during period I (1.5 hour time point). Twenty-one subjects reported 71 adverse events. All events were possibly related to drug products. None of the events required any medications.

2. The AUC_{0-t} of the test formulation was 1% higher than that of reference formulation. The AUC_{0-inf} of the test formulation was about 3% lower than that of the reference formulation. The test C_{max} occurred about 4 minutes earlier and was 1% higher than that of the reference formulation.

3. There were three instances when first measurable plasma concentration of the drug was the maximum concentration: subject #17 (test drug) and 20 (test and reference drug) 0.5 h sampling time. The reviewer repeated statistical analysis after omitting subject numbers 17 and 20. The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} remained within 80-125% limit.

4. The 90% confidence intervals are within the acceptable range of 80-125%. The fasting study is acceptable. There were no statistically significant treatment, sequence or period effect for AUC_{0-t}, AUC_{0-inf}, and C_{max}.

Food Study:

1. Eighteen subjects entered the study. Fifteen subjects completed the study. Three subjects were withdrawn due to non-compliance. Fourteen subjects reported a total of 71 adverse events. These events were possibly thought to be related to study drugs. None of the events required any medications.

2. When the test and reference formulations were administered after a meal, the arithmetic means for AUC_{0-t} and AUC_{0-inf} of the test product were 15% higher than the respective means of the

reference product. The mean C_{max} of the test product was 19% higher than that of the reference product and occurred about 5 minutes earlier. The test/reference ratios for mean AUC_{0-t}, AUC_{0-inf}, and C_{max} are within the 0.8-1.2 limit. The food study is acceptable.

3. Labetalol was not detected in the plasma samples obtained from two subjects (#1, period III and #17, period I) after administration of the reference drug under fed conditions. Subject #17 experienced diarrhea prior to dosing, but did not report for fear of being excluded from participation. The firm does not have any explanation for subject #1. The means of AUC_{0-t}, AUC_{0-inf}, and C_{max} for the three treatments were calculated using the values for these subjects as zero. The ratios of means are within 0.8-1.2 limit. The arithmetic ratio of means for AUC_{0-t}, AUC_{0-inf}, and C_{max} were 1.08, 1.08, and 1.11 respectively after omitting subject #17. The geometric mean ratios (omitting subject #17) were as follows: AUC_{0-t} 1.05, AUC_{0-inf} 1.05, and C_{max} 1.11. The arithmetic and geometric mean ratios after omitting both subjects (#1 and 17) also remained within acceptable limits.

4. First measurable concentration of the drug (at 1.0 h) was the maximum concentration in subject #4 (test-fed). The arithmetic as well as geometric mean ratios of pharmacokinetic parameters remained within acceptable limits after omitting (a) subject #4 (b) subject #4 and 17, and (c) subject #1,4, and 17.

5. The arithmetic means for AUC_{0-t} and AUC_{0-inf} were 9% higher and C_{max} was 6% lower when the test drug was given with food compared to without food.

Dissolution:

The dissolution testing was done according to USP specifications. The firm has demonstrated that greater than % of the test product is dissolved in 45 minutes. The *in vitro* dissolution data are acceptable.

Waiver:

1. The 100 and 200 mg tablets are proportionally similar in their active and inactive ingredients to 300 mg tablets.

2. The dissolution data are acceptable. The test products meet the specifications. The waivers can be granted.

Recommendations:

1. The bioequivalence study conducted under fasting conditions by Teva Pharmaceuticals, on its labetalol hydrochloride tablets, 300 mg, lot #K20251 comparing it to Normodyne® 300 mg tablets, lot #94199 manufactured by Schering Corporation has been found acceptable to the Division of Bioequivalence. The study demonstrates that Teva's labetalol hydrochloride 300 mg tablet is bioequivalent to the reference product, Normodyne® 300 mg tablet manufactured by Schering.

2. The bioequivalence study conducted under fed conditions by Teva Pharmaceuticals on its labetalol hydrochloride tablets, 300 mg lot #K20251, comparing it to the reference product Normodyne® tablets 300 mg, lot #94199 manufactured by Schering has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fed conditions, the bioavailability of Teva's labetalol hydrochloride 300 mg tablet is similar to that of the reference product Normodyne® 300 mg tablet manufactured by Schering.

3. The dissolution testing conducted by the firm on its labetalol hydrochloride tablets 100 mg (lot #K20555), 200 mg (lot #K20554), and 300 mg (lot #K20251) is acceptable. The firm has conducted an acceptable *in vivo* bioequivalence study comparing 300 mg tablets of the test product with 300 mg tablets of the reference product Normodyne® manufactured by Schering. The formulations for 100 mg and 200 mg strengths of the test product are proportionally similar to the 300 mg strength of the test product which underwent bioequivalency testing. The waiver of *in vivo* bioequivalence study requirements for the 100 and 200 mg tablets of the test product is granted. The 100 and 200 mg tablets of the test product are therefore deemed bioequivalent to the 100 and 200 mg tablets of Normodyne® manufactured by Schering.

4. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of water at 37^0C using apparatus II (paddles) at 50 rpm. The test products should meet the following specifications:

> Not less than % of the labeled amount of labetalol hydrochloride in the dosage form is dissolved in 45 minutes.

5. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing, and the application is acceptable.

/S/ 3/17/97

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR /S/ Date 3/18/1997

Concur: /S/ Date 8/26/97
for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #74989 (original, duplicate), Dhariwal, HFD-655 (Nerurkar), Drug File, Division File

Draft: 021497, Final: 031797

Table 1

Comparative Quantitative Composition of Labetalol Hydrochloride Tablets

Ingredients	100 mg mg/tab	%	200mg mg/tab	%	300mg mg/tab	%
Core						
Labetalol HCl USP						
Pregelatinized Starch NF						
Lactose Monohydrate 200 mesh NF						
Magnesium Stearate NF						
CORE TOTAL						
Aqueous Film Coating						
Composition of Film Coating						
Hydroxypropyl Methylcellulose USP						
Propylene Glycol USP						
Titanium Dioxide USP						
Talc USP						
Indigo Carmine Alu. Lake FD&C Blue #2						
Allura Red AC Alu. Lake FD&C Red #40						
Sunset Yellow FCF Alu. Lake FD&C Yellow #6						
Total						

Table 2

Labetalol Plasma Concentrations in Fasting Study (ng/mL)
Arithmetic Means ± Standard Deviation (n=29)

Time h	Test	Reference	Test/Ref	Significance
0	0	0	-	-
0.25	13.66±16.44	24.70±49.90	0.55	NS
0.50	192.5±128.5	162.4±109.3	1.19	NS
0.75	197.2±98.76	192.7±107.5	1.02	NS
1.00	162.9±75.95	160.5±92.40	1.01	NS
1.33	123.8±66.40	118.8±58.35	1.04	NS
1.67	105.7±45.07	101.3±43.97	1.04	NS
2.00	91.24±35.80	88.16±35.16	1.03	NS
2.50	72.05±29.92	70.76±28.57	1.02	NS
3.00	60.63±24.13	61.93±28.29	0.98	NS
4.00	49.30±19.61	50.54±21.00	0.98	NS
6.00	37.39±15.30	36.53±14.81	1.02	NS
8.00	29.11±12.30	29.10±11.06	1.00	NS
10.0	21.47±9.273	21.47±8.846	1.00	NS
14.0	12.58±5.966	12.52±6.109	1.00	NS
18.0	8.219±5.721	8.395±5.374	0.98	NS
24.0	5.822±4.483	6.180±4.271	0.94	NS
Parameters				
AUC_{0-t} (ng/mLxh)	720.0±307.5	712.3±282.1	1.01	
AUC_{0-inf} (ng/mLxh)	813.8±346.5	835.3±309.4*	0.97	
C_{max} (ng/mL)	241.6±104.4	239.0±105.9	1.01	
T_{max} (h)	0.750±0.362	0.813±0.464	0.92	
Half-life (h)	7.968±2.530	8.042±2.083*	0.99	
Elim. Constant	0.097±0.035 (h^{-1})	0.094±0.034*	1.03	

* n=27

Table 3

Labetalol Plasma Concentrations in Fasting Study (n=29)
Pharmacokinetic Parameters: Least Squares Means±Standard Error

Parameter	Test	Reference	Test/Ref	90% Confidence Interval
AUC_{0-t} (ng/mLxh)	719.5±12.35	711.7±12.35	1.01	97-105%
AUC_{0-inf} (ng/mLxh)	813.5±13.13	802.8±14.07*	1.01	97-105%
C_{max} (ng/mL)	241.0±13.24	238.5±13.24	1.01	88-114%
T_{max} (h)	0.7536±0.079	0.8098±0.079	0.93	69-117%
$LNAUC_{0-t}$	6.4845±0.015	6.4850±0.015	1.00	96-104%
$LNAUC_{0-inf}$	6.6084±0.014	6.6068±0.015	1.00	97-104%
LNC_{max}	5.4032±0.057	5.3685±0.057	1.04	90-119%

* n=27

Table 4

Test/Reference Ratios for Labetalol Pharmacokinetic Parameters in Individual Subjects: Fasting Study

Subject	Sequence	Ratio		
		AUC_{0-t}	AUC_{0-inf}	C_{max}
1				
2				
3				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				
29				
30				
Mean		1.006	1.007	1.127
Range				

Table 5

Labetalol AUC_{0-t}/AUC_{0-inf} Ratio for Individual Subjects In Fasting Study

Subject	AUC_{0-t}/AUC_{0-inf} Ratio	
	Test	Reference
1		
2		
3		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		
27		
28		
29		
30		

Table 6

Labetalol Plasma Concentrations and Pharmacokinetic Parameters (arithmetic means ± SD) in Food Study (ng/mL) (n=15)

Time h	Test-fed A	Ref-fed B	Test-fasted C	A/B	A/C	B/C
0	0	0	0	-	-	-
0.25	0.0	0.353±1.36	17.85±33	0.0	0.0	0.02
0.50	7.82±23	2.966±4.96	124.8±120	2.64	0.06	0.02
1.00	91.86±149	61.91±93.7	182.8±154	1.48	0.50	0.34
1.33	141.6±119	138.0±127	135.4±107	1.03	1.05	1.02
1.67	142.6±87	139.7±116	114.7±82	1.02	1.24	1.22
2.0	119.6±61	120.3±99	94.35±65	0.99	1.27	1.28
2.5	103.4±43	93.57±65	73.04±48	1.11	1.42	1.28
3.0	92.97±50	80.29±60	61.14±39	1.16	1.52	1.31
4.0	70.88±37	54.90±41	48.09±31	1.29	1.47	1.14
6.0	40.55±19	34.48±26	34.01±23	1.18	1.19	1.01
8.0	27.35±11	25.07±18	25.07±17	1.09	1.09	1.00
10	22.67±11	20.28±15	20.36±14	1.12	1.11	1.00
12	17.24±8	14.91±11	15.31±10	1.16	1.13	0.97
14	14.36±6	12.87±9	12.47±9	1.12	1.15	1.03
18	9.566±5	7.931±6	8.140±6	1.21	1.18	0.97
24	6.393±4	5.577±5	3.850±6	1.15	1.66	1.45
Parameters:						
AUC_{0-t} (ng/mLxh)	736.8±337	640.9±460	673.7±455	1.15	1.09	0.95
AUC_{0-inf} (ng/mLxh)	829.9±358	723.9±510	758.9±517+	1.15	1.09	0.95
C_{max} (ng/mL)	210.5±110	176.3±136	224.2±153	1.19	0.94	0.79
T_{max} (h)	1.833±0.73	1.909±0.82*	1.011±0.4	0.96	1.81	1.89
Half-life (h)	8.807±1.7	8.427±2.01*	7.108±1.9+	1.05	1.24	1.19
Elim. constant (h^{-1})	0.0812±0.01	0.0886±0.03*	0.105±0.03+	0.92	0.77	0.84

* n=13
\+ n=14

Table 7

Labetalol Pharmacokinetic Parameters in Food Study (n=15)
Least Squares Means and Geometric Means

Parameter	Test-fed A	Ref-fed B	Test-fasted C	A/B	A/C	B/C
Least Squares Means						
AUC_{0-t} (ng/mLxh)	702.74	606.20*	640.34	1.16	1.10	0.95
AUC_{0-inf} (ng/mLxh)	792.20	685.66*	716.07**	1.16	1.10	0.96
C_{max} (ng/mL)	204.99	172.57*	217.01	1.19	0.94	0.80
Geometric Means						
AUC_{0-t}	677.42	641.32*	583.64	1.06	1.16	1.10
AUC_{0-inf}	770.21	731.46*	653.75**	1.05	1.18	1.12
C_{max}	179.38	159.97*	190.80	1.12	0.94	0.84

* n=13, ** n=14

Table 8. In Vitro Dissolution Testing

Drug (Generic Name): Labetalol Hydrochloride Tablets
Dose Strength: 100 mg, 200 mg, and 300 mg
ANDA No.: 74989
Firm: Teva Pharmaceuticals, USA
Submission Date: October 15, 1996
File Name: 74989SDW.096

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications: NLT % (Q) in 45 minutes
Reference Drug: Normodyne (Schering) USP method
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # K-20555 Strength(mg) 100			Reference Product Lot # 95211 Strength(mg) 100		
	Mean %	Range	%CV	Mean %	Range	%CV
10	97.9		3.9	72.1		9.9
15	99.9		2.9	96.1		0.8
30	100.4		2.4	99.6		0.6
45	101.1		2.9	99.9		0.6

Sampling Times (Minutes)	Test Product Lot # K20554 Strength(mg) 200			Reference Product Lot # 94184 Strength(mg) 200		
	Mean %	Range	%CV	Mean %	Range	%CV
10	102.7		1.5	90.9		6.8
15	103.3		1.2	97.9		1.1
30	103.5		1.2	98.1		1.0
45	103.9		0.9	98.6		1.0

Sampling Times (Minutes)	Test Product Lot # K-20251 Strength(mg) 300			Reference Product Lot # 94199 Strength(mg) 300		
	Mean %	Range	%CV	Mean %	Range	%CV
10	88.9		6.9	92.4		5.3
15	100.5		1.0	100.0		0.6
30	100.8		0.9	100.7		0.5
45	101.0		0.8	100.8		0.5
Sampling Times (Minutes)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

Figure 1: Mean Labetalol Plasma Levels

#095-26-10997

N = 29

Fasting Study

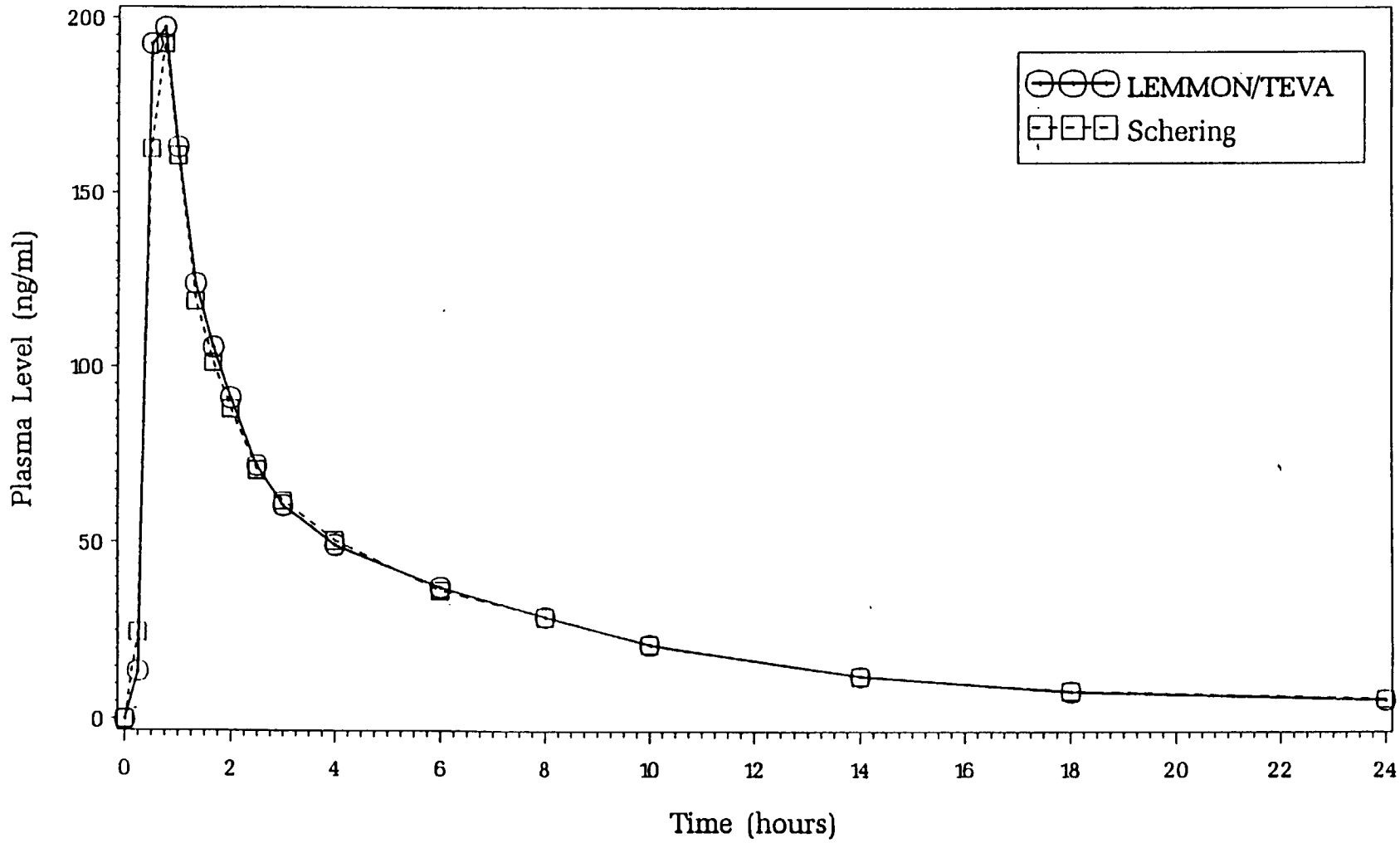
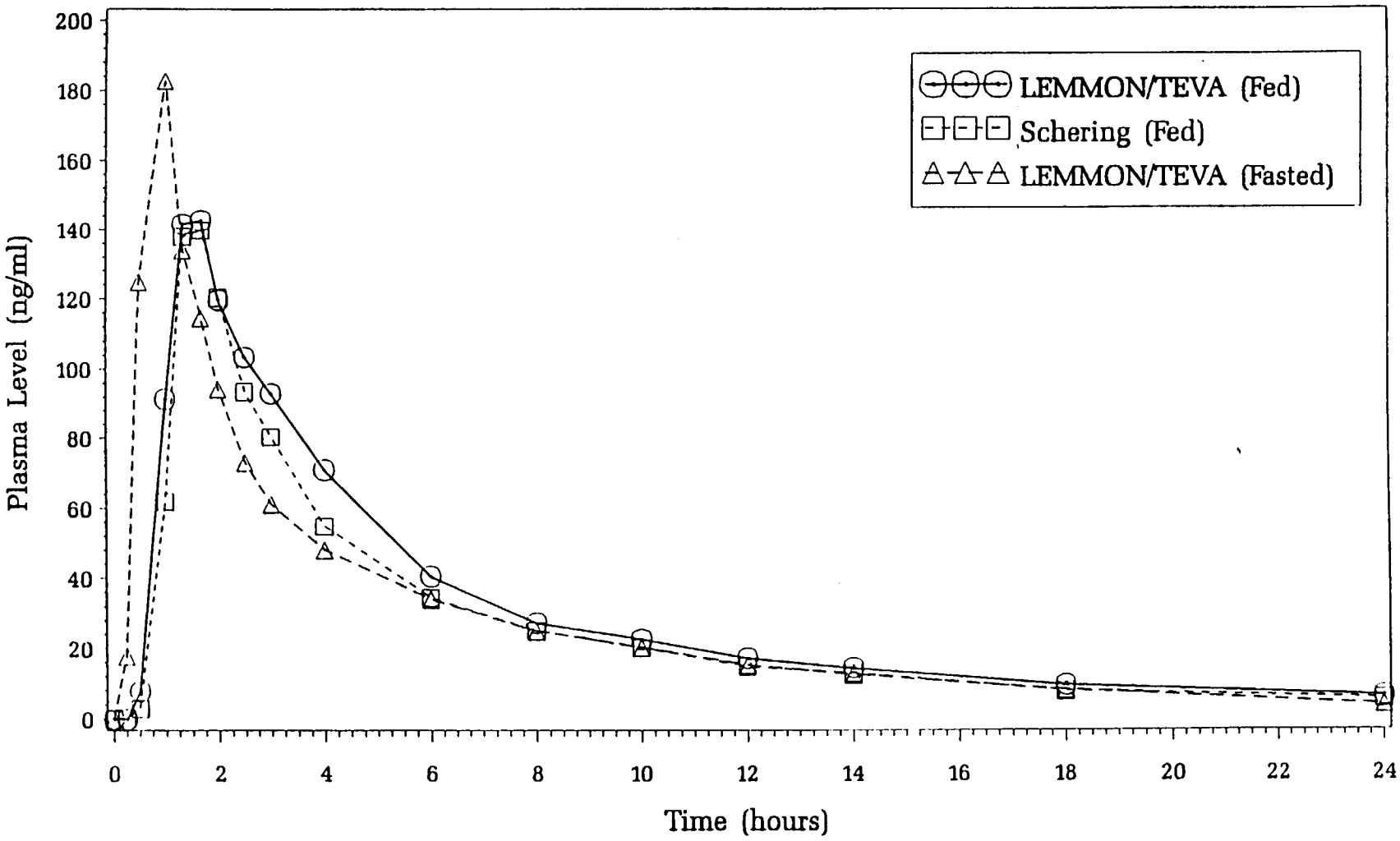


Figure 1

Figure 1: Mean Labetalol Plasma Levels

#095 – 27 – 10998

N = 15

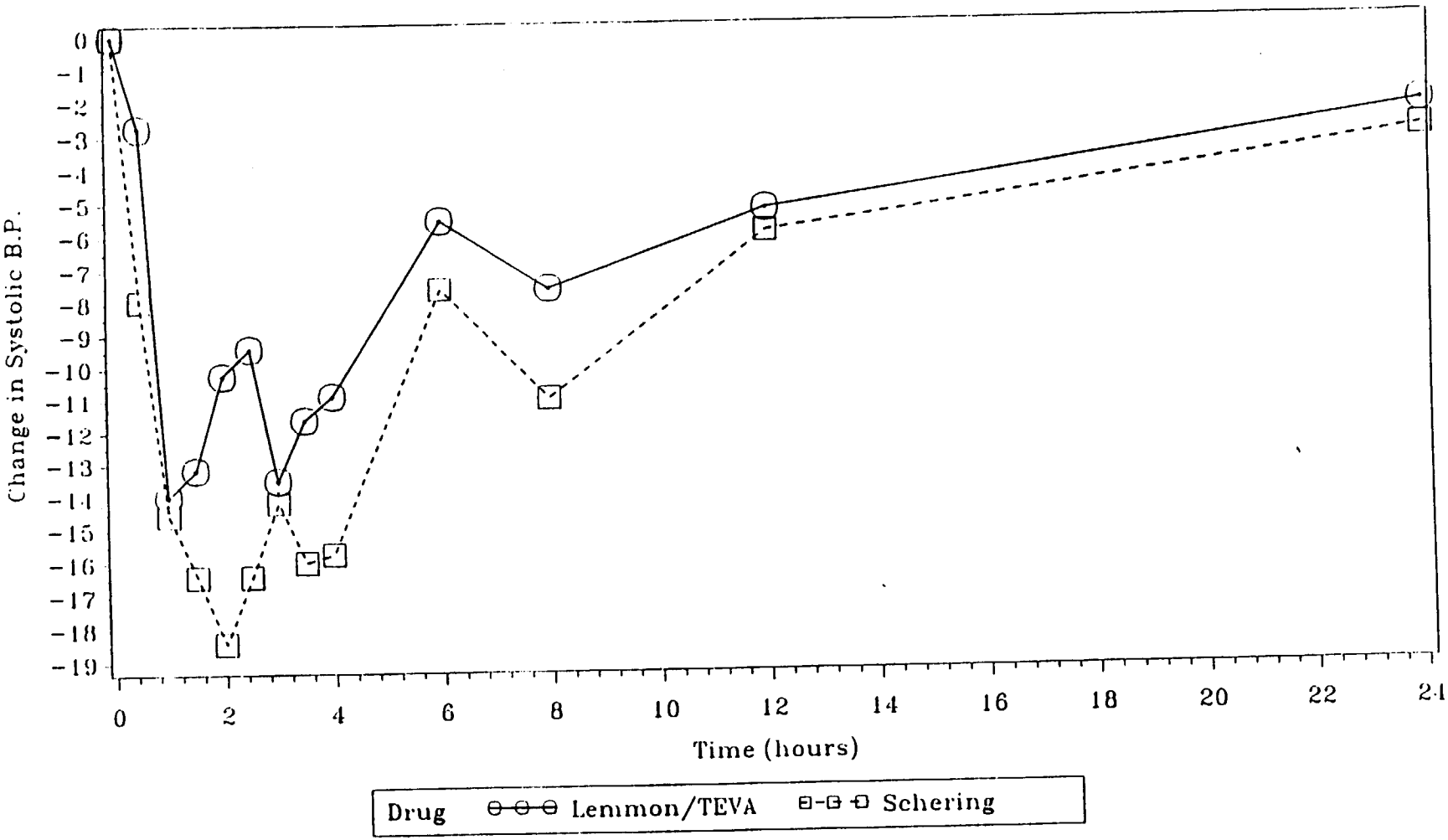


1521

Figure 2

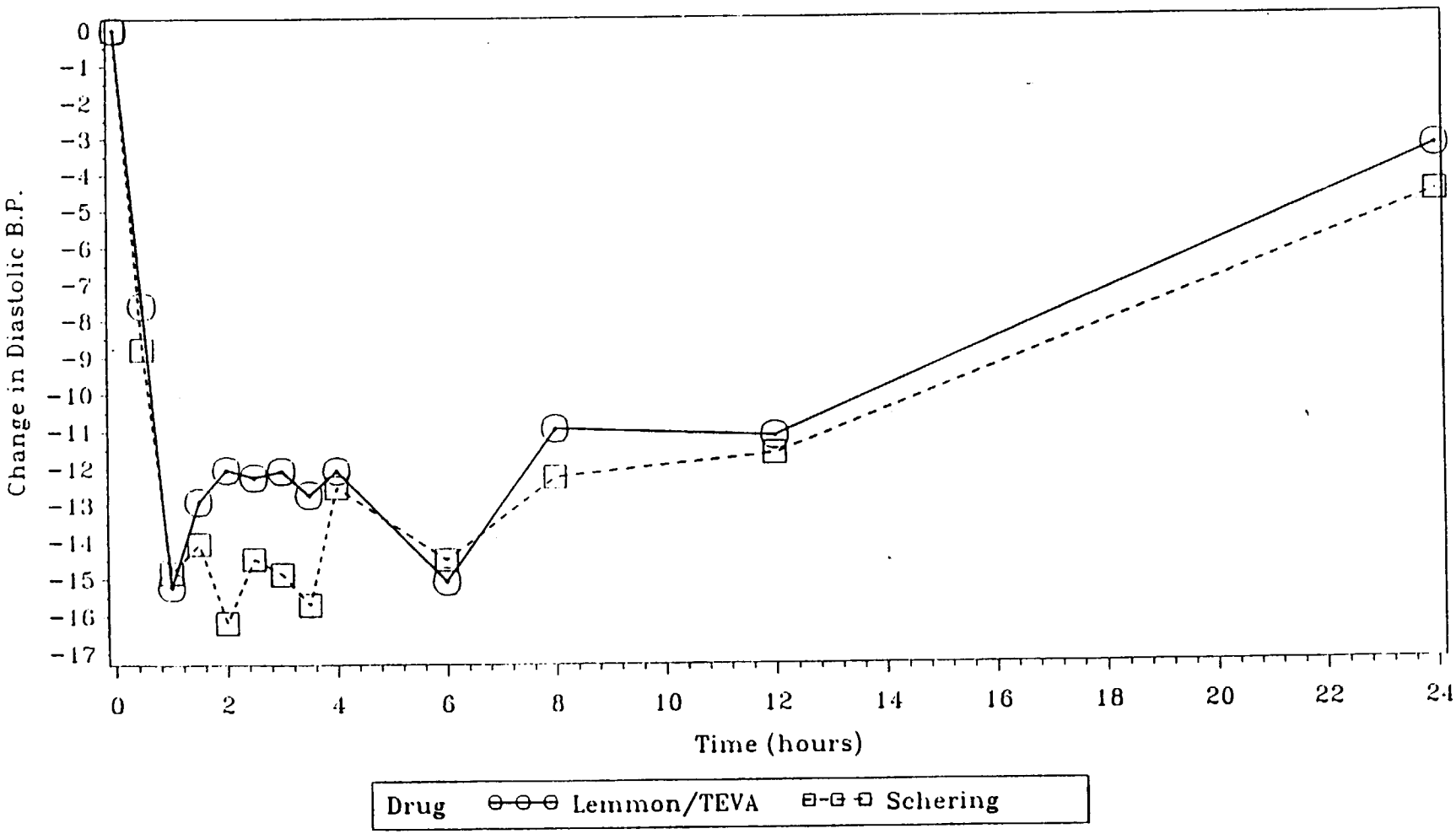
PharmaKinetics Laboratories, Inc.
Labetalol HCL 300 mg Tablets, Study #095-26-10997
Mean Change in Systolic Blood Pressure (mm Hg)
After 300 mg Dose
N = 29

Fasting Study



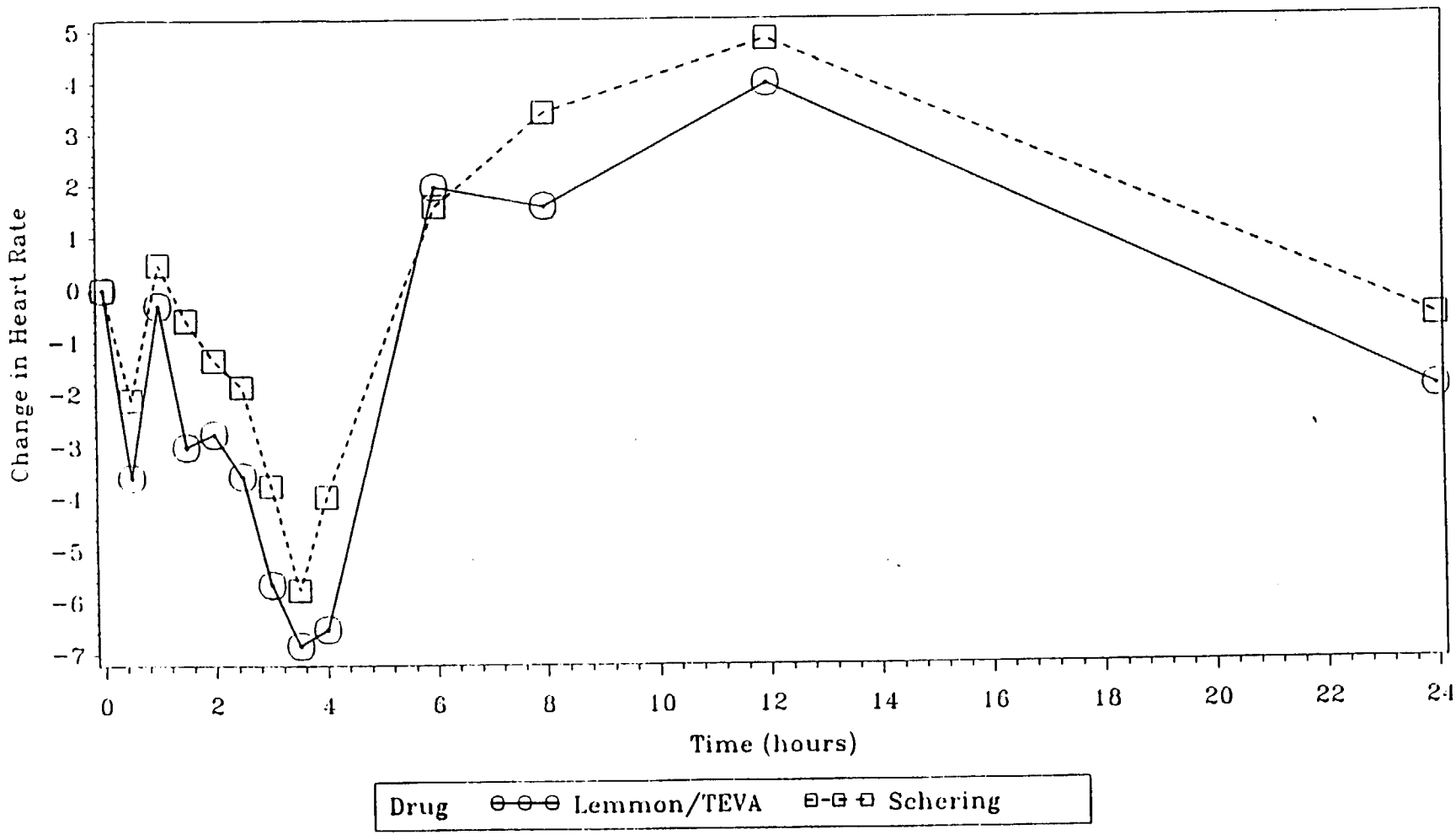
PharmaKinetics Laboratories, Inc.
Labetalol HCL 300 mg Tablets, Study #095-26-10997
Mean Change in Diastolic Blood Pressure (mm Hg)
After 300 mg Dose
N = 29

Fasting Study



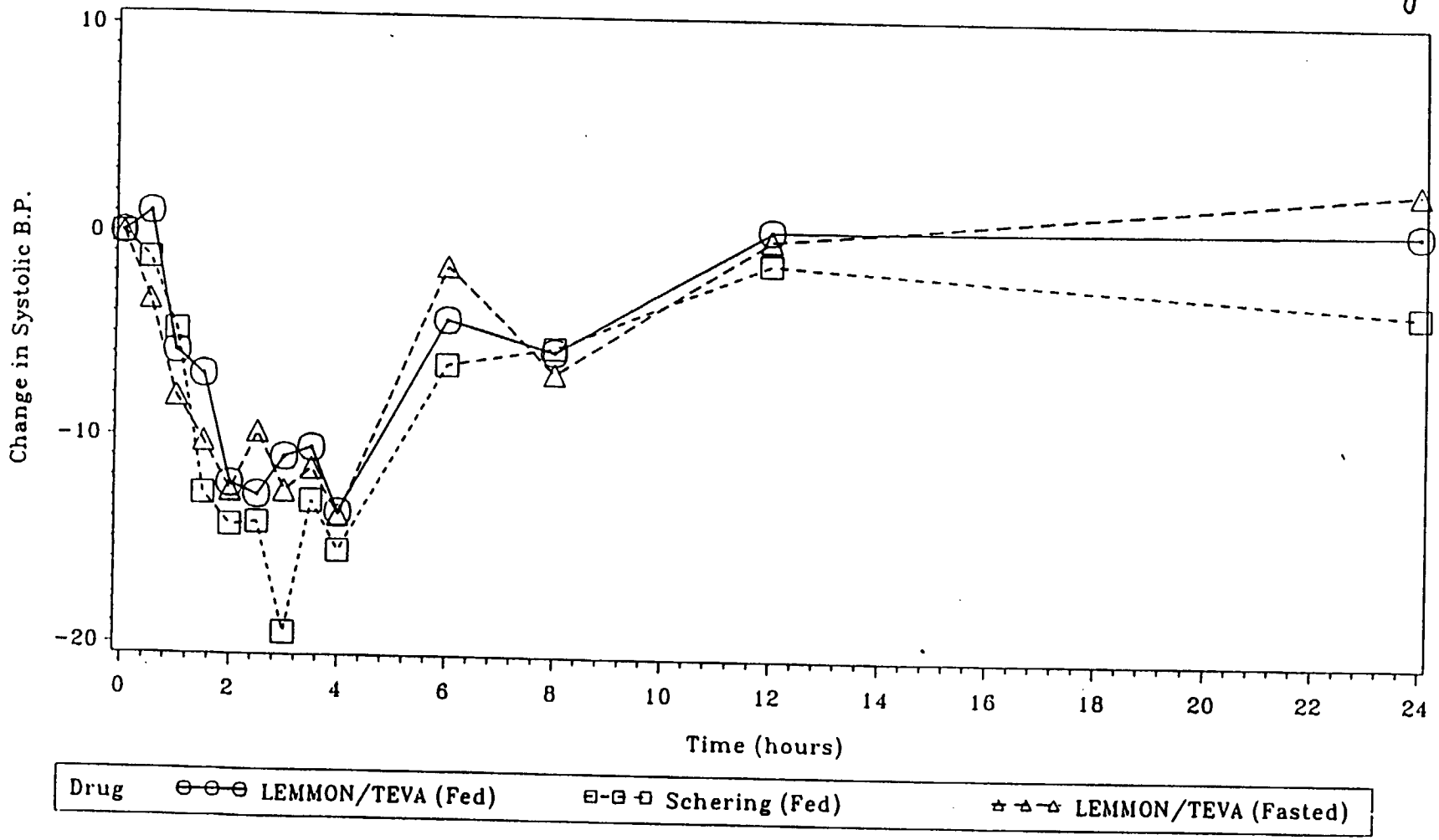
PharmaKinetics Laboratories, Inc.
Labetalol HCl 300 mg Tablets, Study #095-26-10997
Mean Change in Heart Rate (beats/minute)
After 300 mg Dose
N = 29

Fasting Study



PharmaKinetics Laboratories, Inc., Study #095-27-10998
Labetalol HCL 300 mg Tablets, Effect of Food Study
Mean Change in Systolic Blood Pressure (mm Hg)
After 300 mg Dose
N = 15

Food study



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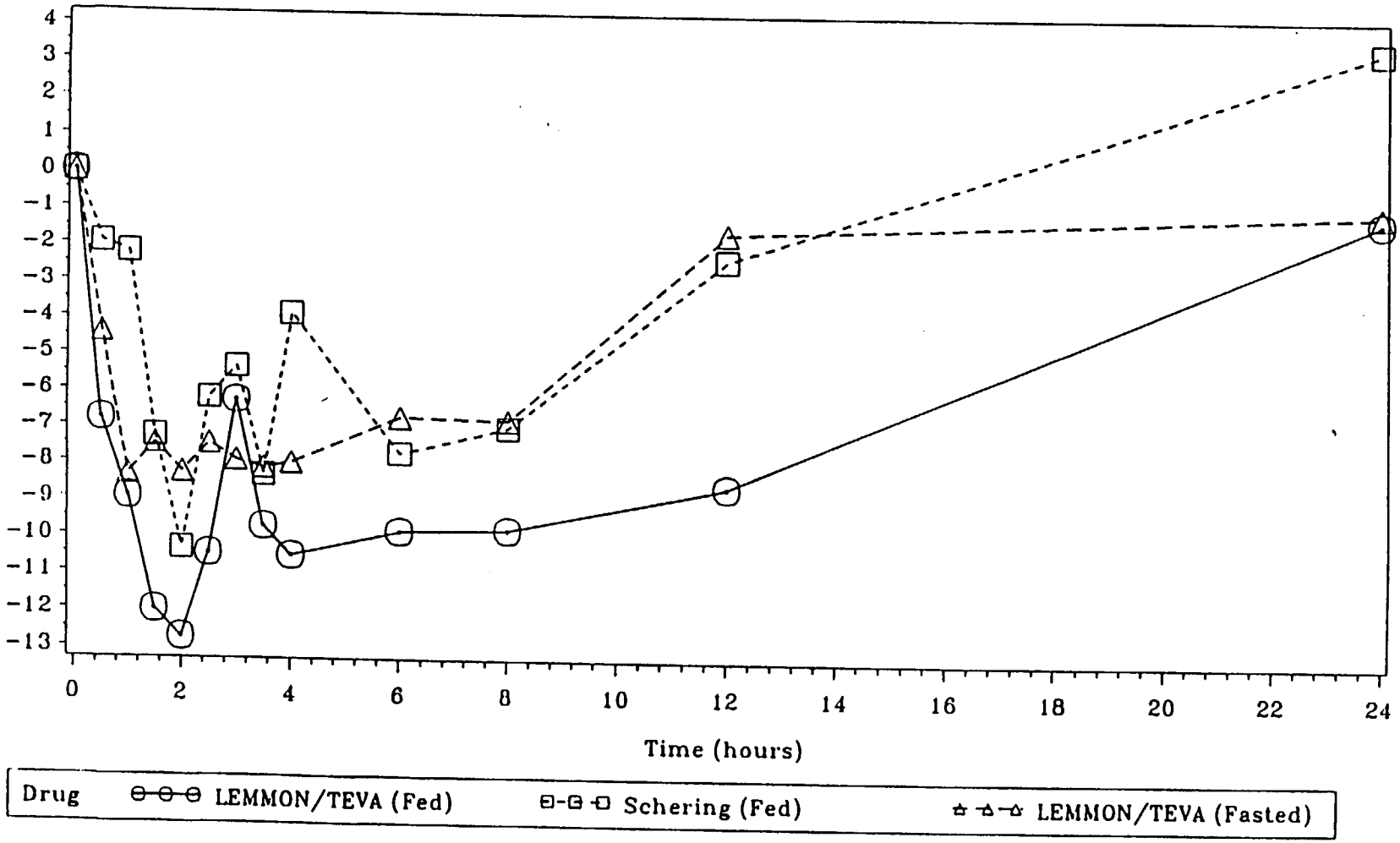
17179

APPENDIX I

PharmaKinetics Laboratories, Inc., Study #095-27-10998
Labetalol HCL 300 mg Tablets, Effect of Food Study
Mean Change in Diastolic Blood Pressure (mm Hg)
After 300 mg Dose
N = 15

Food study

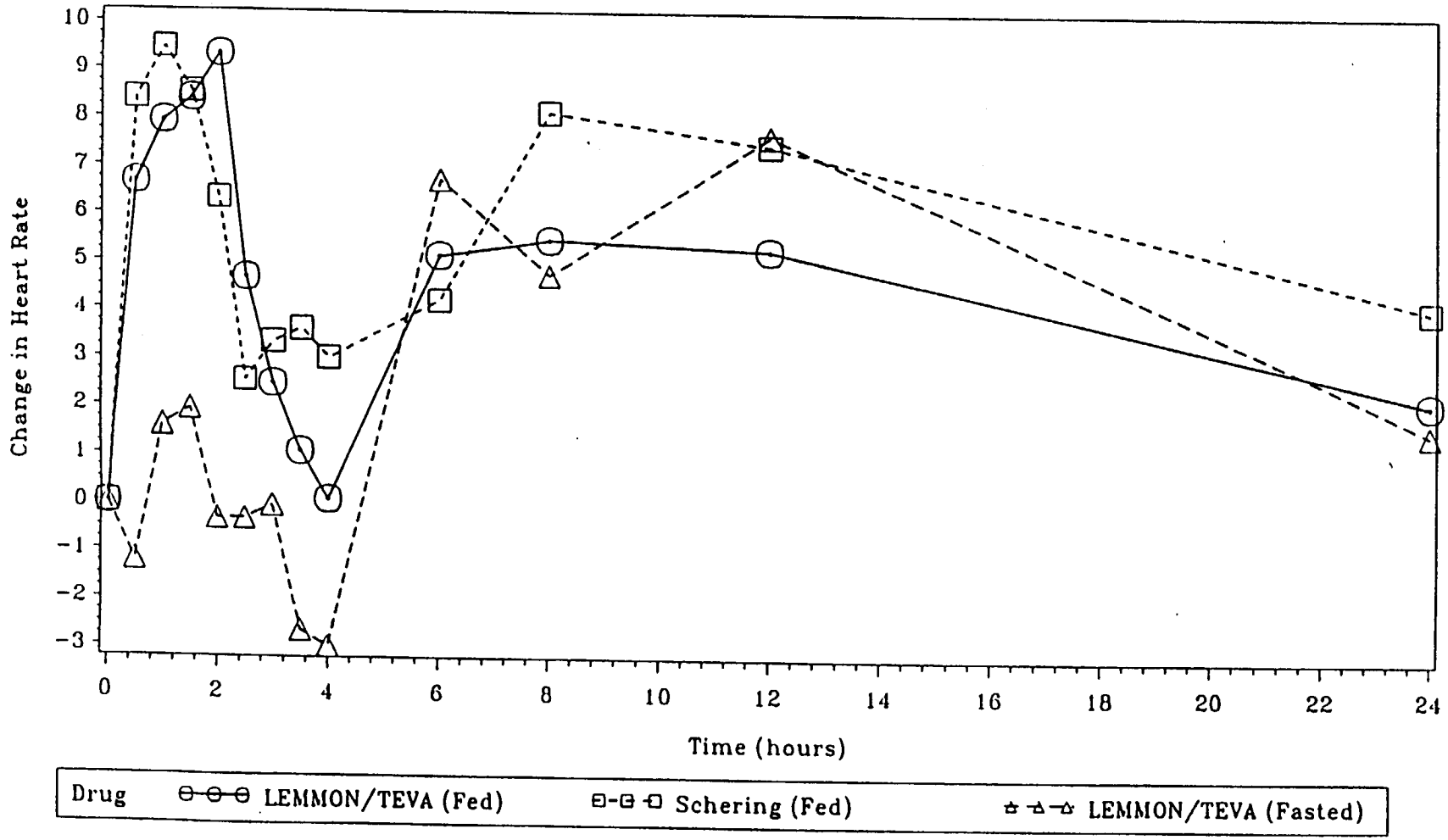


17219

181

PharmaKinetics Laboratories, Inc., Study #095-27-10998
Labetalol HCL 300 mg Tablets, Effect of Food Study
Mean Change in Heart Rate (beats/minute)
After 300 mg Dose
N = 15

Food study



1721

7 83

APPENDIX I
CLINICAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74989

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-989 Date of Submission: October 15, 1996

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Labetalol Hydrochloride Tablets USP, 100 mg, 200 mg and 300 mg

Labeling Deficiencies:

1. CONTAINER - 100 mg, 200 mg and 300 mg (100s and 1000s)

   We encourage you to differentiate your three product strengths by the use of boxing, contrasting colors, or some other means.

2. INSERT

   A. DESCRIPTION

      i. FD&C Blue No.2...,..No.40...No.6... (Add "No." to the coloring agents)

      ii. The molecular weight should read 364.87 rather than

   B. WARNINGS

      Delete from the fifth paragraph (two instances).

   C. PRECAUTIONS (Pediatric Use)

      Use "pediatric patients" rather than

   D. ADVERSE REACTIONS (Cardiovascular)

      Delete and replace it with "hypotension".

   E. DOSAGE AND ADMINISTRATION

      Penultimate paragraph, second sentence.

      ... some ... (spelling).

Please revise your labels and labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74989

CORRESPONDENCE

ANDA 74-989

SEP 15 1997

Teva Pharmaceuticals USA
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

Dear Sir/Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Labetalol Hydrochloride Tablets, USP 100 mg, 200 mg and 300 mg.

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

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

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,

/S/

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

ANDA 74-989

Teva Pharmaceuticals USA
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

DEC 10 1996

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Labetalol Hydrochloride Tablets USP, 100 mg, 200 mg and 300 mg

DATE OF APPLICATION: October 15, 1996

DATE OF RECEIPT: October 23, 1996

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 594-0305

Sincerely yours,

/S/ for 12/10/96

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

SALES OFFICE:

TEVA PHARMACEUTICALS USA
1510 Delp Drive
Kulpsville, PA 19443

TEL: 800 999 8382
FAX: (215) 513 0473

CORPORATE HEADQUARTERS:

TEVA PHARMACEUTICALS USA
650 Cathill Road
Sellersville, PA 18960

TEL: 888 TEVA USA
FAX: (215) 721 9669

October 15, 1996

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
LABETALOL HYDROCHLORIDE TABLETS USP, 100 mg, 200 mg, and 300 mg

Dear Mr. Sporn:

We submit herewith an abbreviated new drug application for the drug product Labetalol Hydrochloride Tablets USP, 100 mg, 200 mg, and 300 mg.

Enclosed are archival and review copies assembled in accord with Office of Generic Drugs Policy and Procedure Guide #30-91. These copies are presented in a total of 21 volumes; 10 for the archival copy and 11 for the review copy. The application contains a full report of two *in vivo* bioequivalence studies. These studies compared Labetalol Hydrochloride Tablets USP, 300 mg manufactured by TEVA Pharmaceutical Industries Ltd. (Israel) to the reference listed drug, Normodyne® Tablets, 300 mg under both fasting and post prandial conditions. The application also contains a request for waiver of *in vivo* bioequivalence studies for Labetalol Hydrochloride Tablets USP, 100 mg and 200 mg.

Since both the bulk and finished product assay and impurities/degradant methods are non-compendial methods, two separately bound copies of this methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

Please be advised that LEMMON Company, a wholly owned subsidiary of TEVA Pharmaceuticals, Inc. (Israel), has recently undergone a change in name to TEVA Pharmaceuticals USA. There has been no change in operations as a result of this name change, and the information presented in this application is accurate in its representation of the duties and responsibilities of the Sellersville and Kulpsville, Pennsylvania locations. However, due to this recent name change, some documentation, including DMF letters of authorization, still reference LEMMON Company.

We look forward to your review and comment.

Sincerely,

DAJ/rgk
Enclosures

SALES OFFICE:

TEVA PHARMACEUTICALS USA
1510 Delp Drive
Kulpsville, PA 19443

TEL: 800 999 8382
FAX: (215) 513 0473

CORPORATE HEADQUARTERS:

TEVA PHARMACEUTICALS USA
650 Cathill Road
Sellersville, PA 18960

TEL: 888 TEVA USA
FAX: (215) 721 9669

LABETALOL HYDROCHLORIDE TABLETS USP, 100 mg, 200 mg, and 300 mg

ORIGINAL ABBREVIATED NEW DRUG APPLICATION

In accord with the final rule published in the Federal Register of September 8, 1993, TEVA Pharmaceuticals USA hereby certifies that the field copy is a true copy of the technical section of this submission and has been provided to the Philadelphia District Office.

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

10/15/96
Date