CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75133

APPROVAL LETTER

ANDA 75-133

AUG 3 1998

Watson Laboratories, Inc.
Attention: Ron Lapre
311 Bonnie Circle
Corona, CA 91720

Dear Sir:

This is in reference to your abbreviated new drug application dated May 7, 1997, 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 amendments dated December 15, 1997; and March 24, May 13, June 12, and July 23, 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/ 7/3/96

Roger L. Williams, M.D.
Deputy Center Director for
Pharmaceutical Science
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75133

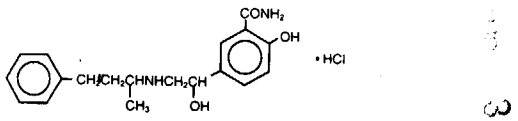
DRAFT FINAL PRINTED LABELING

LABETALOL HYDROCHLORIDE TABLETS, USP

DESCRIPTION

Labetalol HCl is an adrenergic receptor blocking agent that has both selective alpha$_1$- and nonselective beta-adrenergic receptor blocking actions in a single substance.

Labetalol HCl is a racemate, chemically designated as 5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl) amino] ethyl] salicylamide monohydrochloride, and has the following structural formula:



Labetalol HCl has the molecular formula $C_{19}H_{24}N_2O_3$•HCl and a molecular weight of 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 HCl is a white or off-white crystalline powder, soluble in water.

Labetalol Hydrochloride Tablets, USP for oral administration contain 100 mg, 200 mg, or 300 mg labetalol HCl. Each tablet also contains the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, purified water and titanium dioxide. Labetalol HCl Tablets 100 mg also contain synthetic red iron oxide and synthetic yellow iron oxide. Labetalol HCl Tablets 300 mg also contain FD & C blue No. 2 aluminum lake.

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 HCl 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 HCl dosing.

Single oral doses of labetalol HCl 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 HCl 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 HCl 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 HCl 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 about the third day of dosing. In patients with decreased hepatic or renal function, the elimination half-life of labetalol is not altered; however, the relative bioavailability in hepatically impaired patients is increased due to decreased "first-pass" metabolism.

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

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

INDICATIONS AND USAGE

Labetalol Hydrochloride Tablets, USP are indicated in the management of hypertension. Labetalol Hydrochloride Tablets, may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS

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

WARNINGS

Hepatic Injury: Severe hepatocellular injury, confirmed by rechallenge in at least one case, occurs rarely with labetalol therapy. The hepatic injury is usually reversible, but hepatic necrosis and death have been reported. Injury has occurred after both short- and long-term treatment and may be slowly progressive despite minimal symptomatology. Similar hepatic events have been reported with a related compound, dilevalol HCl, including two deaths. Dilevalol HCl is one of the four isomers of labetalol HCl. Thus, for patients taking labetalol, periodic determination of suitable hepatic laboratory tests would be appropriate. Laboratory testing should also be done at the very first symptom or sign of liver dysfunction (e.g., pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms). If the patient has jaundice or laboratory evidence of liver injury, labetalol should be stopped and not restarted.

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

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

Exacerbation Of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered labetalol, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1 to 2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, labetalol administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue labetalol therapy abruptly even in patients treated only for hypertension.

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

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

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

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol's alpha-adrenergic activity has not been evaluated in this setting.

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

PRECAUTIONS

General

Impaired Hepatic Function: Labetalol should be used with caution in patients with 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 being treated with labetalol is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol, dosing with labetalol HCl tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with labetalol HCl tablets should consult a physician at any signs or symptoms of impending cardiac failure or hepatic dysfunction (see **WARNINGS**). Also, transient scalp tingling may occur, usually when treatment with labetalol HCl tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests

As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions

In one survey, 2.3% of patients taking labetalol in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol alone. The contribution of each of the treatments to this adverse 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 HCl 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 approximately 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 HCl tablets are 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 HCl tablets 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 8% 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=98) %	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 HCl					
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 HCl tablets 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 overdose 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 HCl 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 HCl 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 HCl dosage adjustment. As with most antihypertensive drugs, optimal dosages of labetalol HCl tablets are usually lower in patients also receiving a diuretic.

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

HOW SUPPLIED

Labetalol HCl Tablets USP, 100 mg are available as round, beige, film-coated tablets debossed with Watson **605** on one side and scored on the other side. They are supplied as follow:

Bottles of 100	NDC-52544-605-01
Bottles of 500	NDC-52544-605-05
Bottles of 1000	NDC-52544-605-10

Labetalol HCl Tablets USP, 200 mg are available as round, white, film-coated tablets debossed with Watson **606** on one side and scored on the other side. They are supplied as follow:

Bottles of 100	NDC-52544-606-01
Bottles of 500	NDC-52544-606-05
Bottles of 1000	NDC-52544-606-10

Labetalol HCl Tablets USP, 300 mg are available as round, blue, film-coated tablets debossed with Watson **607** on one side and plain on the other side. They are supplied as follow:

Bottles of 100	NDC-52544-607-01
Bottles of 500	NDC-52544-607-05
Bottles of 1000	NDC-52544-607-10

Labetalol HCl Tablets, USP should be stored between 2° and 30°C (36° and 86° F).

Dispense in a tight, light resistant container as defined in USP/NF.

CAUTION: Federal law prohibits dispensing without prescription.

Watson Laboratories, Inc.
Corona, CA 91720

Revised: November 1997

NDC 52544-605-01

LABETALOL HYDROCHLORIDE TABLETS, USP

100 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

Each Tablet Contains:
Labetalol Hydrochloride, USP ..... 100 mg

Usual Dosage: See package insert for full prescribing information.

Dispense in tight, light resistant container as defined in USP/NF.

Store between 2°C and 30°C (36°F and 86°F).

Watson Laboratories, Inc.
Corona, CA 91720

N 3 52544-605-01 3

Lot No.:

Exp:

NDC 52544-605-05

LABETALOL HYDROCHLORIDE TABLETS, USP

100 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

Each Tablet Contains:
Labetalol Hydrochloride, USP ..... 100 mg

Usual Dosage: See package insert for full prescribing information.

Dispense in tight, light resistant container as defined in USP/NF.

Store between 2°C and 30°C (36°F and 86°F).

Watson Laboratories, Inc.
Corona, CA 91720

N 3 52544-605-05 1

Lot No.:

Exp:

NDC 52544-605-10

LABETALOL HYDROCHLORIDE TABLETS, USP

100 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

Each Tablet Contains:
Labetalol Hydrochloride, USP ..... 100 mg

Usual Dosage: See package insert for full prescribing information.

Dispense in tight, light resistant container as defined in USP/NF.

Store between 2°C and 30°C (36°F and 86°F).

Watson Laboratories, Inc.
Corona, CA 91720

N 3 52544-605-10 5

Lot No.:

Exp:

NDC 52544-606-01

LABETALOL HYDROCHLORIDE TABLETS, USP

200 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

Each Tablet Contains:
Labetalol Hydrochloride, USP ..... 200 mg

Usual Dosage: See package insert for full prescribing information.

Dispense in tight, light resistant container as defined in USP/NF.

Store between 2°C and 30°C (36°F and 86°F).

Watson Laboratories, Inc.
Corona, CA 91720

N 3 52544-606-01 0

Lot No.:

Exp:

NDC 52544-606-05

LABETALOL HYDROCHLORIDE TABLETS, USP

200 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

Each Tablet Contains:
Labetalol Hydrochloride, USP ..... 200 mg

Usual Dosage: See package insert for full prescribing information.

Dispense in tight, light resistant container as defined in USP/NF.

Store between 2°C and 30°C (36°F and 86°F).

Watson Laboratories, Inc.
Corona, CA 91720

N 3 52544-606-05 8

Lot No.:

Exp:

NDC 52544-607-10

LABETALOL HYDROCHLORIDE TABLETS, USP

300 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

Each Tablet Contains:
Labetalol Hydrochloride, USP ..... 300 mg

Usual Dosage: See package insert for full prescribing information.

Dispense in tight, light resistant container as defined in USP/NF.

Store between 2°C and 30°C (36°F and 86°F).

Watson Laboratories, Inc.
Corona, CA 91720

N 3 52544-607-10 9

Lot No.:

Exp:

NDC 52544-607-01

LABETALOL HYDROCHLORIDE TABLETS, USP

300 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

Each Tablet Contains:
Labetalol Hydrochloride, USP .....300 mg

Usual Dosage: See package insert for full prescribing information.

Dispense in tight, light resistant container as defined in USP/NF.

Store between 2°C and 30°C (36°F and 86°F).

Watson Laboratories, Inc.
Corona, CA 91720

N 3 52544-607-01 7

Lot No.:

Exp:

NDC 52544-607-05

LABETALOL HYDROCHLORIDE TABLETS, USP

300 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

Each Tablet Contains:
Labetalol Hydrochloride, USP .....300 mg

Usual Dosage: See package insert for full prescribing information.

Dispense in tight, light resistant container as defined in USP/NF.

Store between 2°C and 30°C (36°F and 86°F).

Watson Laboratories, Inc.
Corona, CA 91720

N 3 52544-607-05 5

Lot No.:

Exp:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75133

CHEMISTRY REVIEW(S)

DIVISION REVIEW SUMMARY

ANDA: 75-133

DRUG PRODUCT: Labetalol Hydrochloride Tablets
FIRM: Watson Laboratories, Inc.
DOSAGE FORM: Tablets
STRENGTHS: 100, 200 and 300 mg
CONTAINER: 100 mg--50 cc/100's & 300 cc/1000's
200 mg--100 cc/100's & 625 cc/1000's
300 mg--120 cc/100's & 950 cc/1000's

CGMP STATEMENT/EIR UPDATE STATUS:
Pending

BIO INFORMATION:
Satisfactory dated 1/20/97

VALIDATION
N/A

STABILITY
Accelerated and room temperature stability studies were conducted using the largest and smallest container closure systems. The company has been granted a 24 month expiry based on the satisfactory results from the accelerated studies.

The container/closure systems are described in the container section of the application.

LABELING
Satisfactory. See review dated 1/5/98.

STERILIZATION VALIDATION
N/A

SIZE OF BIO/STABILITY BATCHES
Labetalol Hydrochloride is manufactured by DMF Number This DMF was found acceptable on September 30, 1997. No relevant revisions since last review.

The stability batches are the same as the bio batches.

PROPOSED PRODUCTION BATCH
Blank batch records for Labetalol Tablets USP, 100 mg for

and units; 200 mg for units; and 300 mg for units are provided.

RECOMMENDATION:
Recommend approval of generic drug product Labetalol Hydrochloride Tablets, 100 mg, 200 mg and 300 mg.

SIGNATURE: DATE: April 2, 1998

cc: 75-133

Endorsements:
HFD-645/TRogers/4/2/98 /S/ 5/28/98
HFD-645/BTArnwine/5/18/98 5/29/98

F/T by pah/5/20/98 /S/
x:\new\firmsnz\watson\ltrs&rev\75133.taf

APPROVAL - Tentative

1. CHEMIST'S REVIEW **NO.3**

2. ANDA **#75-133**

3. NAME AND ADDRESS OF APPLICANT
Watson Laboratories, Inc.
311 Bonnie Circle
Corona, CA 91720

4. LEGAL BASIS FOR ANDA SUBMISSION
The submission is based on equivalence to the reference listed drug, Normodyne.

5. SUPPLEMENT(S)
N/A

6. PROPRIETARY NAME
Normodyne®

7. NONPROPRIETARY NAME
Labetalol Hydrochloride Tablets,USP

9. AMENDMENTS AND OTHER DATES:
Original Submission 5/7/97
FAX Amendment 12/15/97
FAX Amendment 3/24/98
Telephone Amendment 5/13/98

10. PHARMACOLOGICAL CATEGORY
Antihypertensive

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF #

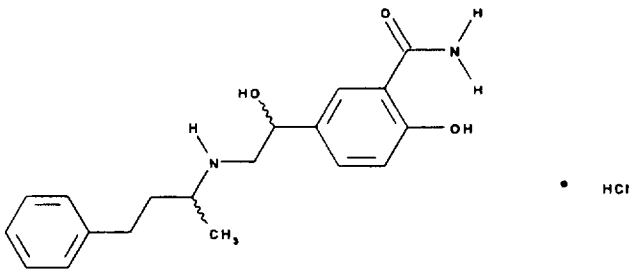
13. DOSAGE FORM
Tablets

14. POTENCY
100, 200, 300 mg

15. CHEMICAL NAME AND STRUCTURE

Labetalol Hydrochloride USP

$C_{19}H_{24}N_2O_3.HCl$; M.W. = 364.87



5-[1-Hydroxy-2-[(methyl-3-phenylpropyl)amino]-ethyl]-salicylamide monohydrochloride. CAS [32780-64-6]

16. RECORDS AND REPORTS

N/A

17. COMMENTS

See review.

18. CONCLUSIONS AND RECOMMENDATIONS

APPROVABLE.

19. REVIEWER

Tracey Rogers, PhD

DATE COMPLETED

March 26, 1998

Revised May 14, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75133

BIOEQUIVALENCY REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-133 APPLICANT: Watson Laboratories

DRUG PRODUCT: Labetalol Hydrochloride 100 mg, 200 mg and 300 mg tablet

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

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 provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Labetalol Hydrochloride
100 mg, 200 mg, & 300 mg tablet
AND 75-133
Reviewer: Nhan L. Tran
WP File: 75133SDW.597

Watson Laboratories, Inc.
Corona, California
Submission date:
May 7, 1997

REVIEW OF TWO BIO-STUDIES, DISSOLUTION DATA AND WAIVER REQUESTS

I. BACKGROUND INFORMATION

Labetalol is a beta-blocker with some alpha adrenergic blocking activity. Labetalol oral bioavailability is about 18% (high first pass). Protein binding is about 50% and half-life is about 5 hours after an oral dose.

At the present time, there are two labetalol products on the market, each with separate NDA: Normodyne^{R} by Schering (NDA 18-687) and Trandate^{R} by Glaxo (NDA 18-716). In the "ORANGE BOOK", Schering's Normodyne 300 mg tablet is listed as RLD.

II. CURRENT SUBMISSION

The current submission contains fasting and fed studies for the highest strength of Watson's labetalol 300 mg tablet, dissolution data for 100 mg, 200 mg and 300 mg tablets, and waiver request for 100 mg and 200 mg strengths.

III. REVIEW OF THE FASTING STUDY

Objective: The objective of the study is to compare the bioavailability after administration of the test and reference formulation under fasting conditions.

Study Design: This was a randomized, single dose, two treatment, two period crossover study in 30 male volunteers. Subjects were divided in two groups with subject 1 to 20 in Group I, and 21 to 30 in Group II. Washout period was one week between treatments.

Group I, period I started on July 26, 1996 and ended on July 28,1996, and period II started on August 2 , 1996 and ended on August 4, 1996. For Group II, period I started on August 2, 1996 and ended on August 4, 1996 and period II started on August 9, 1996 and ended on August 11, 1996.

Study Site/Principal Investigator:

Drug Used in the Study:

Test Formulation: Labetalol tablets, 300 mg by Watson Laboratories
Lot #: R71096, Lot size: tablets, expiry date: 7/98.
Content uniformity: %, potency: %
Reference: Normodyne^{R} 300 mg by Schering
Lot #: 96669, expiration date: Jan 1999
Content uniformity: %, potency: %.
Dosing schedule is given in the Appendix at the end of the review.

Drug administration: Drug was given to the subjects with 240 ml water after an overnight fast. Subjects were fasted for 10 hours prior to dosing and 5 hours after drug administration. Water was allowed ad lib except within one (1) hour of drug administration. Subjects were required to remain seated for 4 hours post dose.

Subject Selection: Subjects were selected according to the following criteria: male, healthy betweren 18 to 50 years of age, weight betweren % from ideal weight for height, acceptable medical histories, physical exams and laboratory results. No alcoholics or drug abusers were accepted for the study.

Blood sample collection: Ten (10) ml of blood were collected in Vacutainers at 0, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 14, 18, and 24 hours post dose. Samples were centrifuged, separated, and transferred to prelabeled tubes and frozen at -20°C until assay.

Analytical Summary:

Statistical Analysis: Statistical analyses were performed using SAS and PROC GLM for the analysis of variance. All parameters were analyzed by analysis of variance and the F-test to determine statistically significant differences betweren the drug formulations. The 90% confidence intervals for important parameters were calculated.

RESULTS

Analytical Methodology:

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confidential

commercial

information

Pharmacokinetic and Statistical Analyses:

Thirty (30) subjects enrolled and all completed the study. Eight subjects experienced 19 mild adverse events during the study. Details of those events are listed in the Adverse Events Section of this review.
From the plasma concentration - time data submitted, no first non zero concentration being the maximum concentration was seen in any of the subjects. Subjects seemed to tolerate well 300 mg dose.
Mean plasma concentration-time profiles for all subjects under test and reference treatments are shown below.

Mean Plasma Concentrations of Labetalol After 300 mg Dose

Time (hr)	Test (ng/ml) (%CV, N=30)	Reference (ng/ml) (%CV, N=30)	Ratio Test/Ref.
0	0	0	---
0.25	32.54 (129.86)	21.39 (201.80)	1.52
0.5	174.53(73.02)	128.54 (93.48)	1.36
0.75	214.34(65.83)	172.38 (66.35)	1.24
1	164.44 (66.23)	153.90 (81.36)	1.07
1.33	119.96 (67.54)	130.66 (64.60)	0.92
1.67	100.05 (63.11)	123.30 (69.05)	0.81
2	94.47 (63.37)	98.83 (64.24)	0.96
2.5	75.12 (63.57)	89.37 (80.83)	0.84
3	64.14 (64.52)	73.33 (77.25)	0.87
4	53.27 (81.94)	52.00 (65.83)	1.02
6	39.12 (62.47)	40.78 (75.19)	0.96
8	29.38 (70.82)	29.96 (71.61)	0.98
10	21.39 (64.04)	21.25 (57.21)	1.01
14	12.79 (78.98)	13.20 (91.03)	0.97
18	7.57 (92.93)	8.28 (80.07)	0.91
24	5.33 (142.94)	4.47 (134.67)	1.19

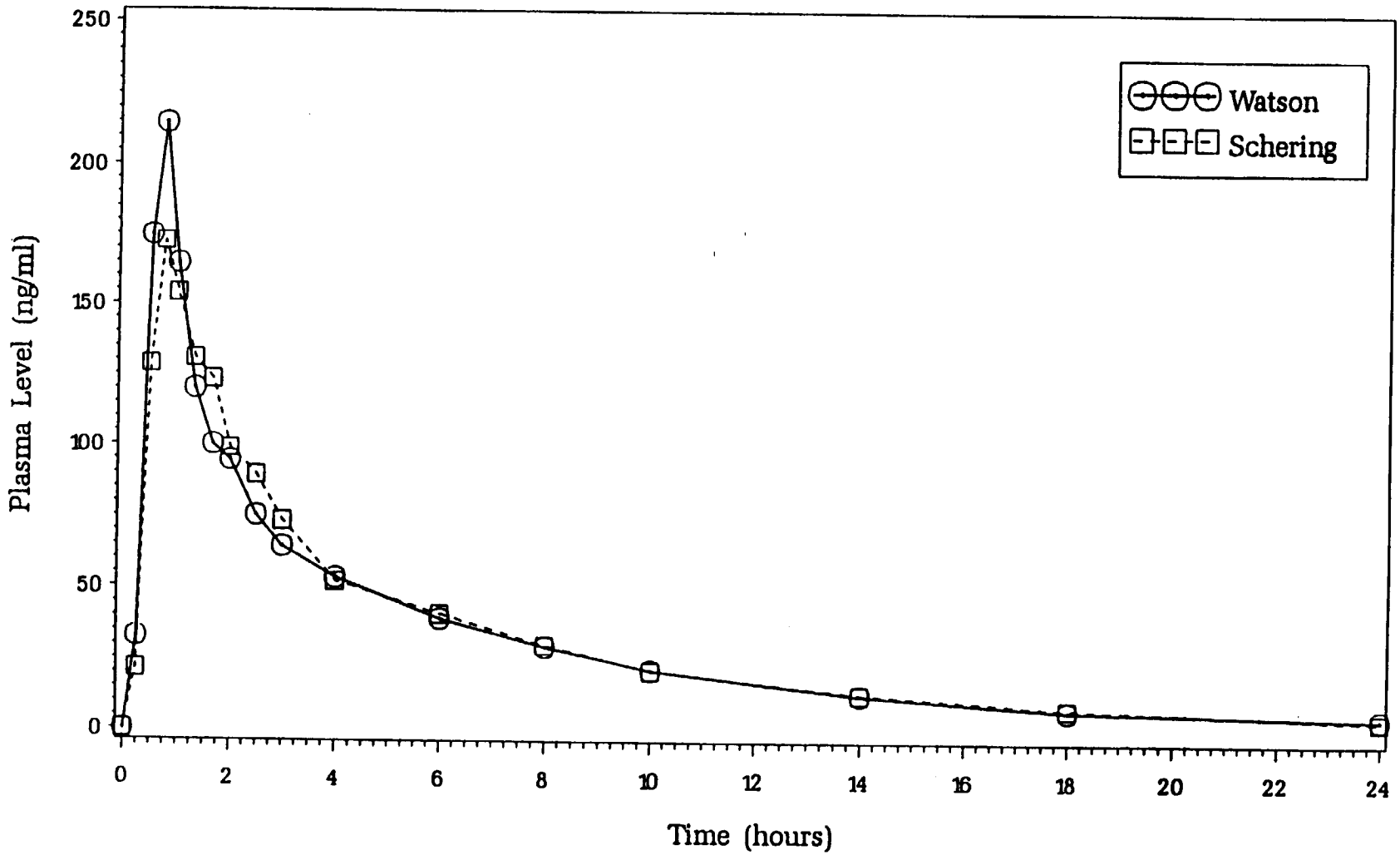
Following are pharmacokinetic parameters reported by the firm:

Parameter	Test (%CV, N=30)	Reference (%CV, N=30)	Ratio Test/Reference
AUC_{0-t}(ng*hr/ml)	729.51 (64.76)	731.37 (60.36)	1.0
$AUC_{0-\infty}$(ng*hr/ml)	745.28 (56.33)	806.77 (60.11)	0.92
Cmax(ng/ml)	244.16 (50.71)	243.65 (52.30)	1.0
Tmax (hr)	0.86 (78.47)	0.95 (55.08)	0.91
$T_{1/2}$ (hr)	6.36 (23.29)	6.31 (21.59)	1.01
$LAUC_{0-t}$	6.42	6.43	0.99
$LAUC_{0-\infty}$	6.48	6.54	0.94
LCmax	5.36	5.36	1.0

Figure 1: Mean Labetalol Plasma Levels

#148-09-11123

N = 30



Using raw data provided by the firm, the reported values were spot-checked by the reviewer. The reported parameters and the ones calculated by the reviewer are comparable.

Statistical Analysis

All parameters were analyzed by analysis of variance (ANOVA). In order to test for group effect (there were two separate groups of subjects in this study), the firm used an ANOVA model which took GROUP effect into consideration. The ANOVA model was:

RESPONSE = GRP SEQ GRP*SEQ SUB(GRP*SEQ) PER(GRP) TREAT GRP*TREAT

Results of the analysis of variance with test of group interaction effects indicate no statistically significant group effect, treatment effect or sequence effect for any analysis of AUCt, AUCinf and Cmax.

Since the effect of group was not statistically significant, the following model was used:

RESPONSE = GRP SEQ SUB(GRP*SEQ) PER(GRP) TREAT

No statistically significant treatment effect or sequence effect for any analysis of AUCt, AUCinf and Cmax. 90% confidence intervals were estimated for AUC and Cmax and results are shown in the following table.

Parameter	90% C.I.
$LAUC_{0-t}$	%
$LAUC_{0-\infty}$	%
LCmax	%

The results were confirmed by the reviewer and no discrepancies were found.

Adverse Reactions:

Of 30 subjects participated in this study, adverse reactions occurred in 8 subjects as shown in table below. The firm stated that no treatment was required for any of those adverse events.

Sub #	Events	Severity	Relat. to drug	Treatment
1	Lightheaded	Mild	none	Pre-dose
1	Lightheaded	Mild	definite	Test formulation
5	Headache	Mild	possible	Ref. formulation
9	Headache	Mild	probable	Test formulation
9	Sore throat, fever	Mild	none	Test formulation
12	Hypotension	Mild	probable	Test formulation
15	Lightheaded,	Mild	definite	Ref. formulation
15	Headache,syncope, diaphoretic	Mild	definite	Ref. formulation
20	Syncope,diaphoresis, abrasion,headache	Mild	definite	Test formulation
20	Lightheaded	Mild	definite	Ref. formulation
21	Diarrhea	Mild	possible	Ref. formulation
29	Headache, intermittent	Mild	possible	Ref. formulation
29	Headache, left frontal	mild	probable	Test formulation

Pharmacodynamic effects:

It should be noted that, in this study, sitting blood pressure and heart rate were measured before dosing and 12 times after each dose: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12 and 24 hours. These measurements were designed to monitor the safety of the subjects and were not designed to provide data for the estimation of pharmacological effect of the drug.
A summary of the pharmacodynamic data submitted by the firm is given below:

1. Systolic blood pressure: 30 subjects completed the study. Based on arithmetic mean, one can observe that systolic blood pressure was decreased from 0.5 to 4 hours and at 8 hours after the test and from 1 to 4 hours and at 8 hours after the reference formulation. Maximum effect was a decrease of 9.9 mmHg at 1 hour after the test and a decrease of 10.3 mmHg at 3 hours after the reference product.

2. Diastolic blood pressure: The mean diastolic blood pressure was decreased from 0.5 through 12 hours after the test and from 1 to 12 hours after the reference formulationn. The maximum effect was a decrease of 12.2 mmHg at 2 hours after the test and a decrease of 9.4 mmHg at 6 hours after the reference product.

3. Change in heart rate: The mean change in heart rate did not show any significant decreases at any time after dosing, but was increased at 1, 3.5, 6, 8, and 12 hours after the test and at 6, 8, and 12 hours after the reference formulation.

IV. REVIEW OF THE NON-FASTING STUDY

Objective: The objective of the study is to compare the bioavailability after administration of the test and reference formulation under fasting and non-fasting conditions.

Study Design: This was a randomized, single dose, three treatment, three period crossover study in 18 male volunteers. Subjects were divided in two groups with subject 1 to 13 (minus #10) in Group I, and #14 to #19 in Group II. Washout period was one werek betweren treatments.

Group I:
Period I: Sept 25 - 27, 1996
Period II: October 2 - 4, 1996
Period III: October 9 - 11, 1996.

Group II:
Period I: October 2 - 4, 1996
Period II: October 9 - 11, 1996
Period III: October 16 - 18, 1996.

The dosing schedule can be found in the Appendix at the end of the review.

Study Site/Principal Investigator:

Drug Used in the Study:

Test Formulation:	Labetalol tablets, 300 mg by Watson Laboratories Lot #: R71096, Lot size: 150,000 tablets Content uniformity: 102%, potency: 101%
Reference:	Normodyne® 300 mg by Schering Lot #: 96669, expiration date: Jan 1999 Content uniformity: 103.4%, potency: 101.4%.

Drug administration: Drug was given to the subjects with 240 ml water after a standard breakfast (treatment A and B) and after an overnight fast (treatment C). Subjects were fasted for 10 hours prior to dosing and 5 hours after drug administration. Water was allowed ad lib except within one (1) hour of drug administration. Subjects were required to remain seated for 4 hours post dose.

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, 240 ml of whole milk. Breakfast was served 35 minutes prior to dosing, and subjects ate the entire meal within 30 minutes.

Subject Selection: Subjects were selected according to the following criteria: male, healthy betweren 18 to 50 years of age, weight betweren 15% from ideal weight for height, acceptable medical histories, physical exams and laboratory results. No alcoholics or drug abusers were accepted for the study.

Blood sample collection: Ten (10) ml of blood were collected in Vacutainers at 0, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 14, 18, and 24 hours post dose. Samples were centrifuged, separated, and transferred to prelabeled tubes and frozen at -20°C until assay.

Analytical Summary:

Statistical Analysis: Statistical analyses were performed using SAS and PROC GLM for the analysis of variance. All parameters were analyzed by analysis of variance and the F-test to determine statistically significant differences betweren the drug formulations. The least squares mean ratio of the test/reference, under different treatments for important parameters were calculated.

RESULTS

Analytical Methodology:

Pharmacokinetic and Statistical Analyses:

Eighteen (18) subjects enrolled in the study and 16 completed. Subject 3 failed to return for period III dosing, subject #16 was withdrawn shortly after period I dosing due to his poor social behavior. Ten subjects experienced 27 mild adverse events during the study. Details of those events are listed in the Adverse Events Section of this review. Tingling of the head (9 events, 5 subjects) headache (6 events, 4 subjects) were the most frequently reported.

From the plasma concentration - time data submitted, no first non zero concentration being the maximum concentration was seen in any of the subjects. Subjects seemed to tolerate well 300 mg dose.

Mean plasma concentration-time profiles for all subjects under test and reference treatments are shown below.

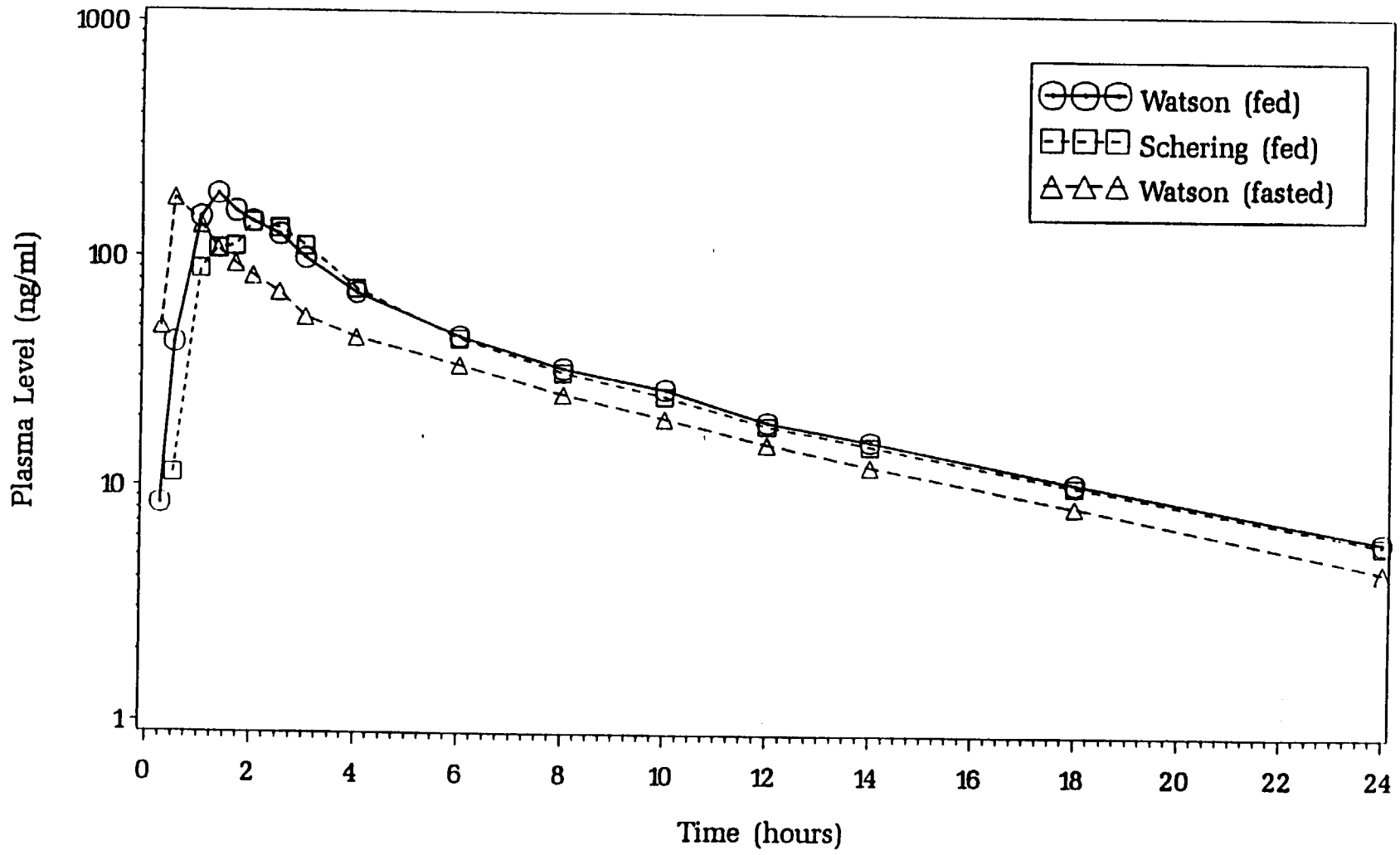
Mean Concentrations of Labetalol After 300 mg Dose Under Fed/Fasting Conditions

Time (hrs)	Test,fed (ng/ml) (%CV, N=16)	Ref., Fed (ng/ml) (%CV, N=16)	Test, Fast (ng/ml) (%CV, N=16)	Ratio Test/Ref. (Fed/Fed)	Ratio Test/Test (Fed/Fast)
0	0	0	0	------	------
0.25	8.37 (324.16)	0	49.79 (122.02)	------	0.17
0.5	42.54 (253.07)	11.32 (211.68)	176.59 (79.33)	3.76	0.24
1	146.38 (122.45)	88.67 (112.02)	135.97 (41.87)	1.65	1.08
1.33	184.26 (131.99)	108.43 (83.56)	107.50 (49.58)	1.70	1.71
1.67	155.57 (81.13)	110.66 (66.10)	93.24 (46.89)	1.41	1.67
2	140.36 (49.19)	139.64 (74.99)	83.03 (52.07)	1.01	1.69
2.5	124.51 (46.25)	132.12 (64.38)	70.57 (55.08)	0.94	1.76
3	98.97 (41.19)	111.47 (53.44)	55.36 (49.34)	0.89	1.79
4	70.60 (41.90)	73.40 (44.48)	45.05 (49.56)	0.96	1.57
6	45.82 (48.23)	44.64 (35.56)	34.35 (49.01)	1.03	1.33
8	33.42 (43.03)	32.03 (37.08)	25.72 (46.95)	1.04	1.30
10	27.26 (47.58)	25.37 (39.81)	20.24 (48.72)	1.07	1.35
12	19.67 (44.92)	18.91 (41.0)	15.65 (54.30)	1.04	1.26
14	16.17 (46.96)	15.41 (39.75)	12.54 (51.41)	1.05	1.29
18	10.73 (45.39)	10.38 (42.75)	8.46 (57.79)	1.03	1.27
24	6.03 (95.28)	5.85 (86.82)	4.51 (110.08)	1.03	1.34

Figure 2: Mean Labetalol Plasma Levels (Semi–log Scale)

#148–10–11124

N = 16



Following are pharmacokinetic parameters reported by the firm:

Parameter	Test, Fed (%CV)	Reference, Fed (%CV)	Test, Fast (%CV)	Ratio T/Ref (Fed/Fed)
AUC_{0-t}(ng*hr/ml)	858.63 (51.28)	783.03 (39.34)	658.9 (49.2)	1.09
$AUC_{0-\infty}$(ng*hr/ml)	958.56 (52.13)	877.07 (39.82)	743.6 (49.7)	1.09
Cmax(ng/ml)	268.5 (82.14)	218.0 (42.16)	197.43 (66.3)	1.23
Tmax (hr)	1.68 (40.37)	2.06 (42.07)	0.81 (42.51)	0.81
$T_{1/2}$ (hr)	7.68 (25.29)	7.72 (22.69)	7.75 (24.53)	0.99

Least squares means of the Log transformed parameters from ANOVA, and the ratio of the test (fed)/reference (fed) defined as $e^{(LSM_{test,fed} - LSM_{reference,fed})}$ are shown in table below:

Parameter	Test, Fed	Ref., Fed	Test, Fast	Ratio Test,fed/Ref,fed
$LAUC_{0-t}$	6.69	6.61	6.51	1.08
$LAUC_{0-\infty}$	6.79	6.72	6.63	1.08
LCmax	5.48	5.34	5.27	1.16

Using raw data provided by the firm, the reported values were spot-checked by this reviewer. The reported parameters and the ones calculated by the reviewer are comparable.

Adverse Reactions:

27 adverse reactions occurred in 10 subjects as shown in table below. The firm stated that no treatment was required for any of those adverse events.

Sub #	Events	Severity	Relat. to drug	Treatment
2	Tingling top of head	Mild	possible	Test, fed
3	Headache	Mild	possible	Reference, fed
5	Headache	Mild	possible	Test, fed
5	Abdominal cramp	Mild	none	Reference, fed
6	Headache	Mild	possible	Reference, fed
6	Headache	Mild	possible	Test, fast
6	Headache	Mild	possible	Test, fed
7	Tingling top of head	Mild	possible	Test, fed
7	Headache	Mild	possible	Reference, fed
7	Drowsy	Mild	possible	Reference, fed
9	Tingling top of head	Mild	possible	Test, fed
11	Tingling top of head	Mild	possible	Test, fed
11	Tingling top of head	Mild	possible	Test, fast
11	Tingling top of head	Mild	possible	Reference, fed
15	Decrease dias. pressure	Mild	Possible	Test, fast
18	Tingling top of head	Mild	possible	Reference, fed
18	Tingling top of head	Mild	possible	Test, fed
18	Tingling top of head	Mild	possible	Test, fast
18	Upset stomach	Mild	possible	Test, fed
18	Abdominal cramp	Mild	possible	Reference, fed

18	Fatigue	Mild	possible	Test, fast
19	Sleepy	Mild	none	Test, fed
19	Sleepy	Mild	none	Test, fast
19	Decrease dias. pressure	Mild	Possible	Test, fed

According to firm, all adverse events were mild in intensity and no treatment was required. No subjects were withdrawn from this study due to any of those adverse events.

Pharmacodynamic effects:

It should be noted that, in this study, sitting blood pressure and heart rate were measured before dosing and 12 times after each dose: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12 and 24 hours. These measurements were designed to monitor the safety of the subjects and were not designed to provide data for the estimation of pharmacological effect of the drug.

A summary of the pharmacodynamic data submitted by the firm is given below:

1. Systolic blood pressure: 16 subjects completed the study. Based on arithmetic mean, one can observe that systolic blood pressure was decreased from 1 to 4 hours and at 8 hours after the test (fed) and from 1.5 to 8 hours after the reference formulation (fed), and from 1 to 8 hours after the test formulation (fasting). Maximum effect was a decrease of 16.9 mmHg at 3 hour after the test (fed) and a decrease of 15.5 mmHg at 3.5 hours after the reference product (fed) and a decrease of 14.6 mmHg at 1.5 hours after the test (fasting).

2. Diastolic blood pressure: The mean diastolic blood pressure was decreased from 0.5 through 12 hours after the test (fed) and from 1 through 12 hours after the reference (fed) and from 0.5 to 12 hours after the test (fasting). The maximum effect was a decrease of 13.7 mmHg at 3 hours after the test (fed) and a decrease of 14.4 mmHg at 4 hours after the reference product (fed), and a decrease of 12.7 mmHg at 6 hours after the test (fast).

3. Change in heart rate: The mean change in heart rate was increased from 0.5 to 2.5 hours and from 8 to 12 hours after the test (fed) dose, and from 0.5 to 1.5 hours and from 8 to 12 hours after the reference dose (fed). There was a decrease in heart rate at 2, 2.5, 3.5, and 4 hours after the test (fast).

V. IN-VITRO TESTING

Dissolution test was conducted using USP method for labetalol tablet. Conditions for dissolution testing and dissolution data for 100 mg, 200 mg, and 300 mg tablets are summarized in the following tables.

The dissolution testing indicated that at 5min. and 10min. time points, the reference products (all strengths) appeared to dissolve slower than the test tablets. A large variation was observed at those time points. However, after 10 minutes, both test and reference tablets showed similar percent dissolution. Both test and reference tablets meet the USP dissolution specifications of NLT (Q) % in 45 minutes.

SUMMARY OF DISSOLUTION TESTING

Drug: Labetalol | Dose Strengths: 100, 200, 300 mg Tablets | ANDA No.: 75-133
Firm: Watson | Submission Date: May 7, 1997 | File Name: 75133SDW.597

I. Conditions for Dissolution Testing:

USP XXIII Apparatus 2 (Paddle), 50 RPM | No. Units Tested: 12 | Medium: Water | Volume: 900 ml
Specifications: NLT % (Q) in minutes | Reference Drug: NORMODYNE®, by Schering
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # R75896 Strength(mg) : 100 mg			Reference Product Lot # 95308 Strength(mg): 100 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
5	22		27.68	6.5		47.65
10	67.7		8.68	60.2		32.88
15	93.2		1.38	97.5		3.66
30	100.3		2.06	101.7		0.91
45	100.7		2.06	101.9		0.97

Sampling Times (Minutes)	Test Product Lot # R75996 Strength(mg) : 200 mg			Reference Product Lot # 96939 Strength(mg): 200 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
5	15.9		22.38	3.0		39.24
10	53.6		11.50	26.3		43.64
15	85.4		6.31	82.0		14.07
30	99.8		5.78	99.1		0.98
45	100.4		5.82	99.4		0.89

Sampling Times (Minutes)	Test Product Lot # R71096 Strength(mg): 300 mg			Reference Product Lot # 96669 Strength(mg): 300 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
5	32.9		41.42	2.6		47.74
10	95.7		6.90	65.7		18.35
15	101.8		1.67	100.6		1.19
30	102.8		1.59	102.0		0.88
45	103.0		1.51	102.0		0.89

VI. FORMULATION

Comparative formulations of different tablet strengths for the test products are shown in the table below:

Tablet strength	100 mg Tablet		200 mg Tablet		300 mg Tablet	
CORE TABLETS						
Ingredients	mg/Tab	%	mg/Tab	%	mg/Tab	%
Labetalol HCl						
Pregela. Starch (Starch 1500)						
Anhydrous Lactose						
Crospovidone (Polyplasdone XL)						
Microcrystalline Cell. (Avicel PH 102)						
Coll. Silicon Dioxide						
Magnesium Stearate						
Purified Water	NMT %	NMT %	NMT %	NMT %	NMT %	NMT %
TABLET CORE WEIGHT	ng	%	mg	%	mg	%
FILM-COATED TABLETS						
Opadry Butterscotch YS-1-7302-A						
Opadry White YS-1-7003						
Opadry Light Blue YS-1-4228						
Purified Water	NMT %	NMT %	NMT %	NMT %	NMT %	NMT %
FILM-COATED TABLET WEIGHT						
TOTAL COATED TABLET WEIGHT	img	%	mg	%	.5mg	%

Comments:

1. For this drug, there are some concerns on the safety of the subjects due to adverse effects associated with high dose, i.e., 300 mg tablet. However, there were no serious adverse events occurring in any of the subjects during the fasting and non-fasting. All seemed to tolerate well 300 mg dose.

2. There were no first non zero concentration being Cmax for both studies.

3. No statistical significance for sequence or group effect was observed. ANOVA model used by the firm is appropriate for this study. No group effect was detected.

4. For the estimation of Kel (hence AUC inf), there were several subjects for whom the AUCinf could not be accurately estimated. The reviewer re-ran the ANOVA without those subjects and re-calculated 90% C.I. The results of 90% C.I. limits were comparable to the ones reported by the firm. In addition, the ratios of the AUCt/AUCinf in all treatments were more than 80% indicating that sampling times were quite adequate to capture the majority of the areas. Thus, data provided for the fasting and non fasting studies, as well as in-vitro dissolution data are found acceptable. All parameters meet the criteria requirements for acceptance of bioequivalence studies.

VII. WAIVER REQUEST

Based on the results of the in-vivo bioequivalence studies (fasting and non-fasting), on 300 mg tablet strength, comparative in-vitro dissolution data of the test and reference tablets, and the similarity of the formulations of different test tablet strengths, the firm requests waiver of in-vivo bioequivalence testing for 100 mg and 200 mg tablets according to 21CFR 320.22.(d)(2).
Since the in-vivo bioequivalence studies and dissolution data are acceptable, the request for waiver for 100 mg and 200 mg tablet is granted from bioequivalence standpoint.

VIII. RECOMMENDATION:

1. The bioequivalence fasting and non-fasting studies conducted by Watson on its labetalol tablets, 300 mg, lot #R71096, comparing it to Normodyne® Tablet, 300 mg, lot # 96669, manufactured by Schering has been found acceptable by the Division of Bioequivalence. The study demonstrates that Watson's labetalol tablets, 300 mg is bioequivalent to Normodyne® tablets, 300 mg, manufactured by Schering.

2. The dissolution testing conducted by Watson on labetalol tablets, 300 mg, lot #R71096, 200 mg, lot # R75996 and 100 mg, lot # R75896, comparing to Normodyne® tablets, 300 mg, lot # 96669, 200 mg, lot # 96939, and 100 mg, lot # 95308, manufactured by Schering is acceptable. The firm has conducted an acceptable in-vivo bioequivalence study on 300 mg tablet, and the formulations for the 200 mg and 100 mg strengths 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 200 mg and 100 mg tablets of the test product is granted. The 200 mg and 100 mg tablets of the test product are therefore deemed bioequivalent to the 200 mg and 100 mg Normodyne™ tablets manufactured by Schering.

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

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

3. From the bioequivalence point of view, the firm has met the requirements of in-vivo bioequivalence and in-vivo dissolution testing and the application is acceptable.

/S/ Dec 18, 97

Nhan L. Tran, Ph.D.
Review Branch II

RD INITIALED BY SNERURKAR
FT INITIALED BY SNERURKAR

/S/

Concur: /S/ 1/26/98 Date: 1/20/1998

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

CC: ANDA #75-133 (Original), HFD 655 (Nerurkar, Tran), Division File, Drug File.

DOSING SCHEDULE FOR FASTING STUDY
LABETALOL HYDROCHLORIDE TABLETS

GROUP I
PERIOD I **Administered 07/27/96**
PERIOD II Administered 08/03/96

SUBJECT NO.	PERIOD I	PERIOD II	DOSING TIME
1	A	B	0800
2	B	A	0802
3	A	B	0804
4	B	A	0806
5	B	A	0808
6	A	B	0810
7	B	A	0812
8	A	B	0814
9	A	B	0816
10	B	A	0818
11	B	A	0820
12	A	B	0822
13	A	B	0824
14	B	A	0826
15	A	B	0828
16	B	A	0830
17	B	A	0832
'8	A	B	0834
.9	B	A	0836
20	A	B	0838

GROUP 2
PERIOD I **Administered 08/03/96**
PERIOD II Administered 08/10/96

SUBJECT NO.	PERIOD I	PERIOD II	DOSING TIME
21	B	A	0840
22	A	B	0842
23	B	A	0844
24	A	B	0846
25	A	B	0848
26	B	A	0850
27	B	A	0852
28	A	B	0854
29	A	B	0856
30	B	A	0858

Treatment A = Labetalol Tablets, 300mg, Watson, Dose= 1 Tablet
Treatment B = Labetalol Tablets, 300mg, Schering Dose= 1 Tablet
All doses administered with 240 mL of water

DOSING SCHEDULE FOR NON-FASTING STUDY

LABETALOL IIYDROCHLORIDE TABLETS

GROUP 1

PERIOD I Administered 09/26/96
PERIOD II Administered 10/03/96
PERIOD 111 Administered 10/10/96

SUBJECT	PERIOD I	PERIOD II	PERIOD III	DOSING TIME
1	B	A	C	0800
2	A	B	C	0802
3	B	C	-	0804
4	C	A	B	0806
5	A	C	B	0808
6	C	B	A	0810
7	A	C	B	0812
8	C	A	B	0814
9	B	A	C	0816
11	C	B	A	0820
12	A	B	C	0822
* 13	B	C	A	0824

.'reatment A & C = Labetalol Hydrochloride USP Tablets, 300 mg Supplied by: Watson Laboratories, luc. Dose= 1 Tablet

Treatment B = Labetalol Hydrochloride USP Tablets, 300 mg Mfg: Schering Corporation Dose= 1 Tablet

All doses administered with 240 mL of water

*Subject #13 received the doses that were assigned for subject #10 in the original randomization schedule

DOSING SCHEDULE

LABETALOL HYDROCHLORIDE TABLETS

GROUP 2

PERIOD I Administered 10/03/96
PERIOD II Administered 10/10/96
PERIOD III Administered 10/17/96

SUBJECT NO.	PERIOD I	PERIOD II	PERIOD III	DOSING TIME
14	A	C	B	0826
15	A	B	C	0828
16	A	--	--	0830
17	C	A	B	0832
18	B	A	C	0834
* 19	C	B	A	0836

Treatment A & C = Labetalol Hydrochloride USP Tablets, 300 mg Supplied by: Watson Laboratories, Inc. Dose= 1 Tablet

Treatment B = Labetalol Hydrochloride USP Tablets, 300 mg Mfg: Schering Corporation Dose= 1 Tablet

All doses administered with 240 mL of water

Subject #19 received the doses that were assigned to subject #13 in the original randomization schedule.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75133

ADMINISTRATIVE DOCUMENTS

NOV 17 1997

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

ANDA Number: 75-133 Date of Submission: **May 7, 1997**

Applicant's Name: **Watson Laboratories, Inc.**

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

Labeling Deficiencies:

1. CONTAINER 100s, 500s, 1000s (100 mg, 200 mg and 300 mg)

   a. We acknowledge your comment that different colors will be used to differentiate the different strengths of this product.

   b. "package insert" rather than .

   c. "36°F and 86°F" rather than

   d. Dispense in a tight, light resistant container as defined in USP/NF.

2. INSERT

   a. GENERAL COMMENT

      Please note that corrections needed are noted on the enclosed "mocked-up" copy of your insert labeling.

   b. HOW SUPPLIED

      i. We encourage the inclusion of the following statements in this section:

         A). CAUTION: Federal law prohibits dispensing without prescription.

         B). Dispense in a tight, light resistant container as defined in USP/NF.

      ii. We note that the HOW SUPPLIED section mentions that your proposed 300 mg tablet is

scored. The 300 mg tablet for the reference listed drug for this drug product is unscored. Please note that the scoring configuration for your drug product must be the same as that of the reference listed drug.

Revise your container labels and package insert labeling as described above, then prepare and submit final printed (or printers proof) package insert labeling and final printed container labels. Please note that final printed insert labeling is not required for tentative approval of an application if it is granted with more than 90 days remaining from the date when full approval can be considered. We will accept final "printers proof" for the insert only.

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

Enclosure: "Mocked-up" insert labeling.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75133

CORRESPONDENCE

ANDA 75-133

Watson Laboratories, Inc.
Attention: David C. Hsia, Ph.D.
311 Bonnie Circle
Corona, CA 91720

JUL 7 1997

Dear Sir:

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: May 7, 1997

DATE OF RECEIPT: May 9, 1997

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) 827-5849

Sincerely yours,

/S/

Jerry Phillips 7/2/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

May 7, 1997

505(j)(2)(A)(ok)
Anne-marie H. Weibel
Anne
6/9/97

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: **Abbreviated New Drug Application**
Labetalol Hydrochloride Tablets USP, 100 mg, 200 mg, and 300 mg

Dear Mr. Sporn:

Pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.92, Watson Laboratories Inc. submits herein an original Abbreviated New Drug Application for Labetalol Hydrochloride Tablets USP, 100 mg, 200 mg and 300 mg.

The drug product described above is the same as Normodyne®, from Schering Corporation. We have submitted comparative information to indicate that our product is the same as the reference listed drug product. This information is presented in tabular form, comparing active ingredient, conditions of use, route of administration, dosage form, strength, bioequivalence, and labeling for the products as supplied by Watson Laboratories, Inc. and by Schering Corporation.

We have enclosed one (1) archival, one (1) review, and in accordance with 21 CFR § 314.94(5), one (1) field copy of the application will be forwarded to the LA District Office.

Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application.

As required, three (3) additional separately bound copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient and finished dosage form) are included as one of the volumes of the archival copy of this ANDA.

RECEIVED
MAY 09 1997
GENERIC DRUGS

Cont'd/....2

311 Bonnie Circle, Corona, California 91720 • Tel: 909/270-1400 • Fax: 909/270-1096

The number of volumes in the archival, review, and field copies of the ANDA are as follows:

Blue Archival Copy	- 9 volumes
Orange Review Copy	- 7 volumes
Red Review Copy	- 2 volumes
Burgundy Field Copy	- 2 volumes

In addition, for the Bioequivalence Section, we have also enclosed computer diskettes with the analytical data and bioavailability parameters in the format prescribed by the FDA. These diskettes are located at the front of Section VI of the Orange Review Copy of this application.

We trust the information submitted is sufficient for this Abbreviated New Drug Application to be evaluated. Please contact me by phone at (909) 270-1400 or by fax at (909) 270-1428 if you have any questions or if I can assist you with the review of this application.

Sincerely,

David C. Hsia, Ph.D.
Senior V.P., Scientific Affairs
WATSON LABORATORIES, INC.

A
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WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

December 15, 1997

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place Room 150
Rockville, MD 20855-2773

Minor Amendment

Re: ANDA 75-133
LABETALOL HYDROCHLORIDE TABLETS, USP
100 mg, 200 mg and 300 mg

INCLUDE FINAL PRINTED LABELING

Dear Mr. Sporn:

Pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.96, Watson Laboratories is submitting this minor amendment to provide a complete response to the comments included in the FDA letter dated November 17, 1997 (copy attached) pertaining to the referenced ANDA. Our responses are given in the order in which the comments appear in the letter. This amendment also includes final printed labeling.

We have enclosed one (1) archival, one (1) review copy, and in accordance with 21 CFR §314.96(b), one (1) field copy of the application will be forwarded to the FDA Los Angeles District Office.

Watson Laboratories, Inc. certifies that the Field copy is a true copy of the technical section contained in this amendment.

We trust this information is sufficient for this amendment to be evaluated. If I can assist with the review of this application, please contact me by phone at (909) 270-1400 or by fax at (909) 270-1428.

Sincerely,

RECEIVED
DEC 16 1997
GENERIC DRUG

Ron Lapré
Senior Director
Regulatory Affairs

311 Bonnie Circle, PO Box 1900 Corona, California 91718-1900 • Tel: 909/270-1400 • Fax: 909/270-1096

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

December 15, 1997

Ms. Elaine C. Messa
District Director
Food & Drug Administration
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

Minor Amendment

RE: **Field Copy**
ANDA 75-133
LABETALOL HYDROCHLORIDE TABLETS, USP
100 mg, 200 mg AND 300 mg

Dear Ms. Messa:

Pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.96, Watson Laboratories has submitted an amendment to the referenced ANDA to the Office of Generic Drugs. In accordance with 21 CFR §314.96(b), Watson is providing the enclosed Field Copy (1 volume) of the amendment to the LA District Office.

Watson Laboratories certifies that this Field copy is a true copy of the technical section of the Labetalol Hydrochloride Tablets, USP 100 mg, 200 mg and 300 mg Minor Amendment submitted to the Office of Generic Drugs on December 15, 1997.

Please call me at (909) 270-1400 if you have any questions regarding this submission.

Sincerely,

Ron Lapré
Senior Director
Regulatory Affairs

ARCHIVAL COPY

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

May 13, 1998

ORIG AMENDMENT

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT
CMC

Re: ANDA 75-133
LABETALOL HYDROCHLORIDE TABLETS, USP
100 mg, 200 mg and 300 mg

Dear Mr. Sporn:

Pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.96, Watson Laboratories is submitting this facsimile amendment to provide a complete response to telephone comments from Ms. Tracy Rogers, Division of Chemistry, OGD on May 12, 1998. Specifically Ms. Rogers requested that in-process weight check be instituted for the film-coated tablets of the referenced ANDA.

A review of the proposed film-coating instructions of the batch records for the 100 mg, 200 mg and 300 mg drug product strengths intended for post-approval commercial production, indicates that a film-coated tablet weight check requirement has already been included. We have included copy of the applicable pages from the proposed production batch records for all three product strengths that were previously submitted in a Minor Amendment on December 15, 1997 for your ease of reference. Film-coated tablets samples are obtained from each coating pan for this weight check to ensure the appropriate amount of coating solids has been applied. Please noted the film coating for this product is only for cosmetic purposes as stated in the batch records

We have enclosed one (1) archival, one (1) review copy, and in accordance with 21 CFR § 314.96(b), one (1) field copy of the amendment will be forwarded to the FDA Los Angeles District Office.

RECEIVED

Watson Laboratories, Inc. certifies that the Field copy is a true copy of the technical section contained in this amendment.

MAY 14 1998

GENERIC DRUGS

311 Bonnie Circle, PO Box 1900 Corona, California 91718-1900 • Tel: 909/270-1400 • Fax: 909/270-1096

We trust this information is sufficient for this amendment to be evaluated. If I can assist with the review of this application, please contact me by phone at (909) 270-1400 or by fax at (909) 270-1428.

Sincerely,

Ron Lapré
Senior Director
Regulatory Affairs
Watson Laboratories, Inc.

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

May 13, 1998

Ms. Elaine C. Messa
District Director
Food & Drug Administration
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

FACSIMILE AMENDMENT

RE: **Field Copy**
ANDA 75-133
LABETALOL HYDROCHLORIDE TABLETS, USP
100 mg, 200 mg and 300 mg

Dear Ms. Messa:

Pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.96, Watson Laboratories has submitted an amendment to the referenced ANDA to the Office of Generic Drugs. In accordance with 21 CFR § 314.96(b), Watson is providing the enclosed Field Copy of the amendment to the LA District Office.

Watson Laboratories certifies that this Field copy is a true copy of the technical section of the Labetalol Hydrochloride Tablets, USP 100 mg, 200 mg and 300 mg Facsimile Amendment submitted to the Office of Generic Drugs on May 13, 1998.

Please call me at (909) 270-1400 if you have any questions regarding this submission.

Sincerely,

Ron Lapré
Senior Director
Regulatory Affairs

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

March 24, 1998

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT

Re: ANDA 75-133
LABETALOL HYDROCHLORIDE TABLETS, USP
100 mg, 200 mg and 300 mg

Dear Mr. Sporn:

Pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.96, Watson Laboratories is submitting this facsimile amendment to provide a complete response to the comments included in the FDA letter dated March 6, 1998 (copy attached) pertaining to the referenced ANDA. Our responses are given in the order in which the comments appear in the letter.

We have enclosed one (1) archival, one (1) review copy, and in accordance with 21 CFR § 314.96(b), one (1) field copy of the amendment will be forwarded to the FDA Los Angeles District Office.

Watson Laboratories, Inc. certifies that the Field copy is a true copy of the technical section contained in this amendment.

We trust this information is sufficient for this amendment to be evaluated. If I can assist with the review of this application, please contact me by phone at (909) 270-1400 or by fax at (909) 270-1428.

Sincerely,

Ron Lapré
Senior Director
Regulatory Affairs

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

March 24, 1998

Ms. Elaine C. Messa
District Director
Food & Drug Administration
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

FACSIMILE AMENDMENT

RE: **Field Copy**
ANDA 75-133
LABETALOL HYDROCHLORIDE TABLETS, USP
100 mg, 200 mg and 300 mg

Dear Ms. Messa:

Pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.96, Watson Laboratories has submitted an amendment to the referenced ANDA to the Office of Generic Drugs. In accordance with 21 CFR § 314.96(b), Watson is providing the enclosed Field Copy (1 volume) of the amendment to the LA District Office.

Watson Laboratories certifies that this Field copy is a true copy of the technical section of the Labetalol Hydrochloride Tablets, USP 100 mg, 200 mg and 300 mg Facsimile Amendment submitted to the Office of Generic Drugs on March 16, 1998.

Please call me at (909) 270-1400 if you have any questions regarding this submission.

Sincerely,

Ron Lapré
Senior Director
Regulatory Affairs

311 Bonnie Circle. PO Box 1900 Corona, California 91718-1900 • Tel: 909/270-1400 • Fax: 909/270-1096