CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 70-704

Name: Propranolol Hydrochloride and Hydrochlorothiazide Tablets, 40 mg/25 mg

Sponsor: Barr Laboratories, Inc.

Approval Date: October 1, 1986

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 70-704

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 70-704

APPROVAL LETTER

OCT 1 1986

ANDA 70-704

Barr Laboratories, Inc.
Attention: Marilyn A. Wenger
265 Livingston Street
Northvale, NJ 07647

Dear Ms. Wenger:

Reference is made to your abbreviated new drug application, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Propranolol Hydrochloride and Hydrochlorothiazide Tablets, 40 mg/25 mg.

Reference is also made to your communication dated September 17, 1986.

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.

Any significant change in the conditions outlined in this abbreviated application requires an approved supplemental application before the change may be made, except for changes made in conformance with other provisions of Section 314.70 of the New Drug Regulations.

Postmarketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80 and 314.81 of the Regulations.

This Administration should be advised of any change in the marketing status of this drug.

For Initial Campaigns: We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your immediate 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 Advertising and Labeling (HFN-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

For Subsequent Campaigns: We call your attention to Section 314.81(b)(3) of the Regulations which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Advertising and Labeling (HFN-240) with a completed Form FD-2253.

Sincerely yours,

Marvin Seife 10/1/86

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc:
HFN-237
HFN-83
MChang/CChang/DBrancato/tr/9/29/86
Approval

Attachment

Attachment

At the time of the next printing highlight 'Use in Pregnancy' under "WARNINGS" as a subsection heading (i.e. in different type style than your section heading).

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 70-704

APPROVED LABELING

PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS

WARNING

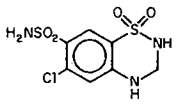
This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

DESCRIPTION: Propranolol Hydrochloride and Hydrochlorothiazide tablets combine two antihypertensive agents: propranolol hydrochloride, a beta-adrenergic blocking agent, and hydrochlorothiazide, a thiazide diuretic-antihypertensive.

Propranolol hydrochloride is a stable, white to off-white, crystalline powder with a melting point of about 164° C. It is odorless and has a bitter taste. It is readily soluble in water and ethanol, and insoluble in non-polar solvents. Its chemical name is 1-(Isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride.

Hydrochlorothiazide is a white, or practically white, practically odorless, crystalline powder. It is slightly soluble in water, freely soluble in sodium hydroxide solution, sparingly soluble in methanol; insoluble in ether, chloroform, benzene, and dilute mineral acids. Its chemical name is 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. The structural formulas are:

Propranolol HCl



Hydrochlorothiazide

CLINICAL PHARMACOLOGY: Propranolol hydrochloride: Propranolol hydrochloride is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta-receptor sites. When access to beta-receptor sites is blocked by propranolol, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. Propranolol is not significantly dialyzable. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

The mechanism of the antihypertensive effects of propranolol has not been established. Among the factors that may be involved are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain.

Propranolol hydrochloride decreases heart rate, cardiac output, and blood pressure. Although total peripheral vascular resistance may increase initially, it readjusts to the pretreatment level or lower with chronic usage. Earlier studies indicate that plasma volume remains unchanged or may decrease. However, there are certain more recent studies suggesting that in the absence of sodium restriction, plasma volume may increase.

Beta-receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate, and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta-blockade therapy is to decrease adverse sympathetic stimulation, but not to the degree that may impair necessary sympathetic support.

Hydrochlorothiazide: Hydrochlorothiazide is a benzothiadiazine (thiazide) diuretic closely related to chlorothiazide. The mechanism of the antihypertensive effect of the thiazides is unknown. Thiazides do not affect normal blood pressure.

Thiazides affect the renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage, all thiazides are approximately equal in their diuretic potency.

Thiazides increase excretion of sodium and chloride in approximately equivalent amounts. Natriuresis causes a secondary loss of potassium and bicarbonate.

Onset of diuretic action of thiazides occurs in two hours, and the peak effect in about four hours. Its action persists for approximately six to 12 hours. Thiazides are eliminated rapidly by the kidney.

INDICATION: Propranolol Hydrochloride and Hydrochlorothiazide Tablets are indicated in the management of hypertension. (See boxed warning.)

CONTRAINDICATIONS: Propranolol hydrochloride: Propranolol hydrochloride is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

Hydrochlorothiazide: Hydrochlorothiazide is contraindicated in patients with anuria or hypersensitivity to this or other sulfonamide-derived drugs.

WARNINGS: Propranolol hydrochloride: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. Propranolol acts selectively without abolishing the inotropic action of digitalis on the heart muscle. (i.e. that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by propranolol's negative inotropic effect. The effects of propranolol and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during propranolol therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following **abrupt** discontinuation of propranolol therapy. Therefore, when discontinuance of propranolol is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long-term use have not been

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IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during propranolol therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following **abrupt** discontinuation of propranolol therapy. Therefore, when discontinuance of propranolol is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long-term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since propranolol is a competitive inhibitor of beta-receptor agonists, its effects can be reversed by administration of such agents, e.g. isoproterenol or norepinephrine. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (e.g., CHRONIC BRONCHITIS, EMPHYSEMA), propranolol should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. In patients with impaired renal function, cumulative effects of the drug may develop.

Thiazides should also be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Thiazides may add to or potentiate the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

USE IN PREGNANCY: Propranolol hydrochloride: The safe use of propranolol in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers: Thiazides appear in breast milk. If the use of the drug is deemed essential, the patient should stop nursing.

PRECAUTIONS: Propranolol hydrochloride: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if propranolol is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of propranolol may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause are: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

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

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

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

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

Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Diabetes mellitus which has been latent may become manifest during thiazide administration.

Thiazide drugs may increase the responsiveness to tubocurarine.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

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

ADVERSE REACTIONS: Propranolol hydrochloride: Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by diorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Hydrochlorothiazide: Gastrointestinal: anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis.

Central Nervous System: dizziness, vertigo, paresthesias, headache, xanthopsia.

Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.

Cardiovascular: orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity: purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions.

Other: hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

DOSAGE AND ADMINISTRATION: The dosage must be determined by individual titration (see boxed warning).

Hydrochlorothiazide is usually given at a dose of 50 to 100 mg per day. The initial dose of propranolol is 40 mg twice daily and it may be increased gradually until optimum blood pressure control is achieved. The usual effective dose is 160 to 480 mg per day.

One to two Propranolol Hydrochloride and Hydrochlorothiazide tablets twice daily can be used to administer up to 320 mg of propranolol and 100 mg of hydrochlorothiazide. For doses of propranolol greater than 320 mg, the combination products are not appropriate because their use would lead to an excessive dose of the thiazide component.

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

OVERDOSAGE OR EXAGGERATED RESPONSE: The propranolol hydrochloride component may cause bradycardia, cardiac failure, hypotension, or bronchospasm.

The hydrochlorothiazide component can be expected to cause diuresis. Lethargy of varying degree may appear and may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function, and in the absence of significant serum electrolyte changes or dehydration. The mechanism of central nervous system depression with thiazide overdosage is unknown. Gastrointestinal irritation and hypermotility can occur; temporary elevation of BUN has been reported, and serum electrolyte changes could occur, especially in patients with impairment of renal function.

TREATMENT

The following measures should be employed:

GENERAL: If ingestion is or may have been recent

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

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Central Nervous System: dizziness, vertigo, paresthesias, headache, xanthopsia.

Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.

Cardiovascular: orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity: purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions.

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TREATMENT

The following measures should be employed:

GENERAL - If ingestion is, or may have been, recent, evacuate gastric contents taking care to prevent pulmonary aspiration.

BRADYCARDIA - Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

CARDIAC FAILURE - Digitalization and diuretics.

HYPOTENSION - Vasopressors, e.g., norepinephrine or epinephrine.

BRONCHOSPASM - Administer isoproterenol and aminophylline.

STUPOR OR COMA - Administer supportive therapy as clinically warranted.

GASTROINTESTINAL EFFECTS - Though usually of short duration, these may require symptomatic treatment.

ABNORMALITIES IN BUN AND/OR SERUM ELECTROLYTES - Monitor serum electrolyte levels and renal function; institute supportive measures as required individually to maintain hydration, electrolyte balance, respiration and cardiovascular-renal function.

HOW SUPPLIED: Propranolol Hydrochloride and Hydrochlorothiazide tablets are available in doses of:

40mg Propranolol Hydrochloride and 25mg Hydrochlorothiazide, white round scored tablets, identified with 555/427 on one side of the tablet and barr on the other side. NDC 0555-0427 in bottles of 100 and 1000.

80mg Propranolol Hydrochloride and 25mg Hydrochlorothiazide, white round scored tablets, identified with 555/428 on one side of the tablet and barr on the other side. NDC 0555-0428 in bottles of 100 and 1000.

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

Manufactured By
BARR LABORATORIES, INC.
NORTHVALE, NEW JERSEY 07647

BR-427,428

Revised November 1985

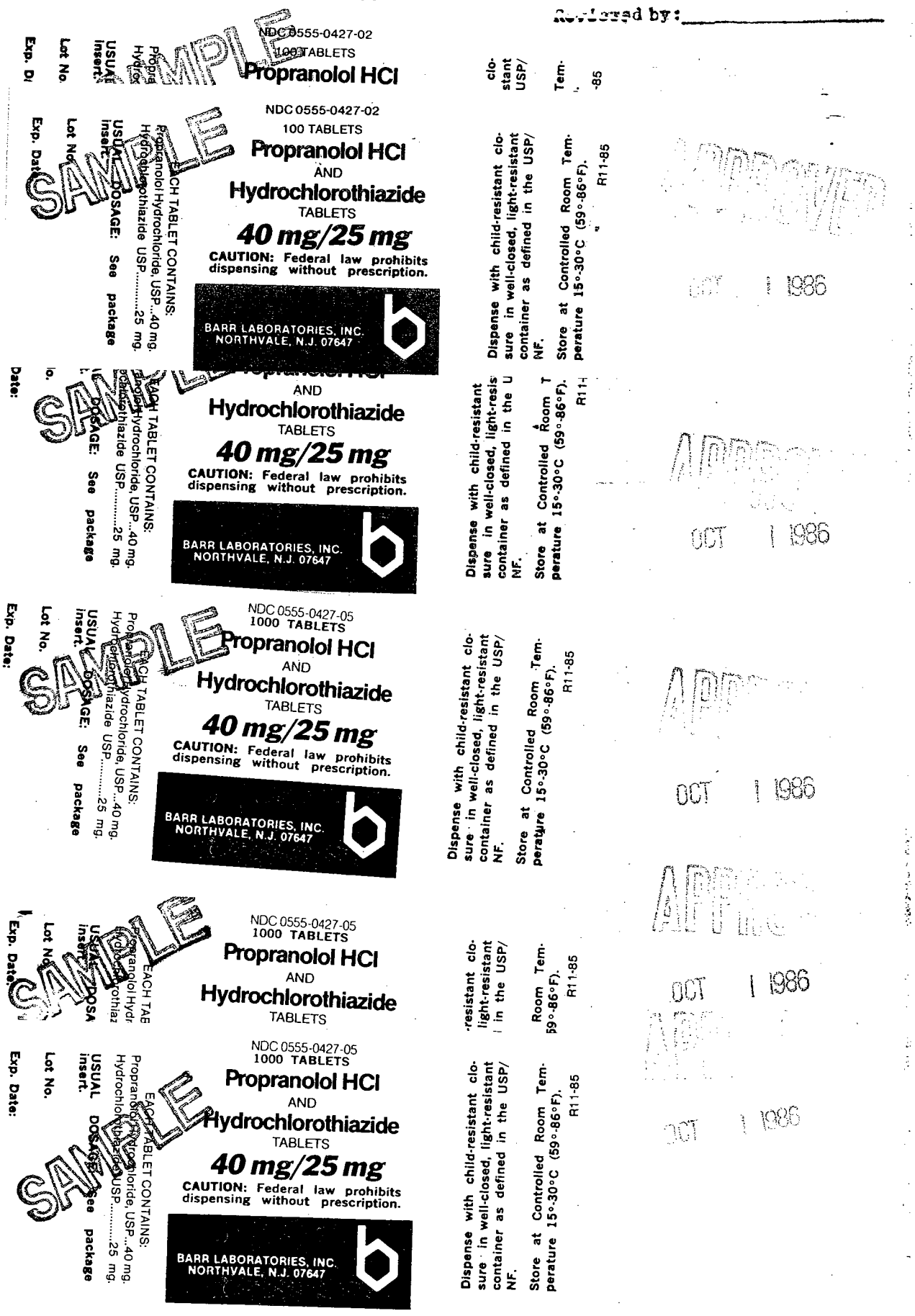
SUPPLEMENTAL PAGE S-856

Labeling: Draft

NDA No: 70-704 Rec'd. 11/29/85

Reviewed by:

NDA 70-704



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 70-704

LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING

ANDA - FPL

DATE OF REVIEW: 10/3/85

ANDA/NDA #: 70-704 (40 mg/25 mg)
70-705 (80 mg/25 mg)

NAME OF FIRM: Barr

NAME OF DRUG: Generic: Propranolol Hydrochloride and Hydrochlorothiazide Tablets.

DATE OF SUBMISSION: 9/5/85

COMMENTS:

Container: Not Satisfactory (100s & 1000s)

1. Dispensing recommendation (1000s)

This statement should be either in singular or plural form.

2. The quantity of each active ingredient must be ~~labeled~~ included. We suggest that you use the following:

Each Tablet contains:

Propranolol Hydrochloride, USP.....xx mg
Hydrochlorothiazide USP.....xx mg

Insert: Not Satisfactory

1. Not Satisfactory

i. DESCRIPTION

A. Please include the following as the first paragraph:

Propranolol Hydrochloride and hydrochlorothiazide tablets combines two antihypertensive agents: propranolol hydrochloride, a beta-adrenergic blocking agent, and hydrochlorothiazide, a thiazide diuretic-antihypertensive.

2. WARNINGS

A. IN PATIENTS WITH ANGINA PECTORIS

This entire section should be boxed off.

B. IN PATIENTS UNDERGOING MAJOR SURGERY, 8th line

-----Isoproterenol or Norepinephrine-----
(replace ———— with Norepinephrine)

3. OVERDOSAGE OR EXAGGERATED RESPONSE

A. HYPOTENSION - Vasopressors, e.g. Norepinephrine----
(replace ———————— with norepinephrine)

RECOMMENDATIONS:

1. Inform the firm of above comments.

2. Request that the firm revise their container labels and package insert labeling and prepare and submit FPL.

Marina Chang

cc:
DUP
MChang/gp/10/7/85
0248g

Additional labeling review comments are handwritten on the correspondence from Barr dated 11/27/1985 and 6/12/1986.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 70-704

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW NDA 70-704

3. NAME AND ADDRESS OF APPLICANT

Barr Laboratories, Inc.
Northvale, NJ. 07647

6. NAME OF DRUG

Propranolol hydrochloride and hydrochlorothiazide

11. HOW DISPENSED

Rx

12. RELATED IND/NDA/DMF(s)

70-704
70-705

13. DOSAGE FORM(s)

Tablet

14. POTENCY

40 mg/25 mg

15. CHEMICAL NAME AND STRUCTURE

See USP

17. COMMENTS

See letter

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable

19. REVIEWER:

PDLeinbach

DATE COMPLETED:

11/13/85

20. COMPONENTS AND COMPOSITION

Propranolol HCl
Hydrochlorothiazide
Lactose

Croscarmellose Sodium
Mg Stearate
Colloidal Silicon Dioxide

21. FACILITIES AND PERSONNEL

OK

22. SYNTHESIS

23. RAW MATERIAL CONTROLS

A. NEW DRUG SUBSTANCE

Not Satisfactory

B. OTHER INGREDIENTS

Not Satisfactory

24. OTHER FIRM(s)

---

26. CONTAINER

Bottles of 100 and 1000 white, HDPE bottle, s/c with innerseal.
Not satisfactory.

29. STABILITY

Not Satisfactory

31. SAMPLES AND RESULTS

HPLC to be validated.

32. LABELING

Not Satisfactory

PDLeinbach
0377S

APPEARS THIS WAY
ON ORIGINAL

CHEMIST'S REVIEW ANDA 70-704

3. NAME AND ADDRESS OF APPLICANT

Barr Laboratories
Northvale, NJ. 07647

6. NAME OF DRUG

Propranolol Hydrochloride and Hydrochlorothiazide

10. PHARMACOLOGICAL CATEGORY

Antihypertensive; anti hypertensive

11. HOW DISPENSED

Rx

12. RELATED IND/NDA/DMF(s)

70-704
70-705

13. DOSAGE FORM(s)

Tablet

14. POTENCY

40/25 mg

17. COMMENTS

1. HCT to be updated to USP XXI Supplement 3.
2. HPLC procedure for finished product.
3. Container information not satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable

19. REVIEWER:

PLeinbach

DATE COMPLETED:

5/1/86

20. COMPONENTS AND COMPOSITION

Propranolol Hydrochloride
Hydrochlorothiazide
Lactose
Croscarmellose Sodium
Magnesium Stearate
Colloidal Silicon Dioxide

21. FACILITIES AND PERSONNEL

OK

22. SYNTHESIS

24. OTHER FIRM(s)

26. CONTAINER

Bottle of 100 and 1000, white, HDPE bottle with S/C and innerseal. only.

29. STABILITY

OK

32. LABELING

Not Satisfactory

PLeinbach
0733S

CHEMIST'S REVIEW ANDA 70-704

3. NAME AND ADDRESS OF APPLICANT

Barr Laboratories
Northvale, NJ. 07647

6. NAME OF DRUG

Propranolol Hydrochloride and Hydrochlorothiazide

10. PHARMACOLOGICAL CATEGORY

Antihypertensive; anti hypertensive

11. HOW DISPENSED

Rx

12. RELATED IND/NDA/DMF(s)

70-704
70-705

13. DOSAGE FORM(s)

Tablet

14. POTENCY

40/25 mg

17. COMMENTS

1. HCT to be updated to USP XXI Supplement 3.
2. HPLC procedure for finished product.
3. Container information not satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable

19. REVIEWER:

David J Brancato

DATE COMPLETED:

5-23-86

20. COMPONENTS AND COMPOSITION

Propranolol Hydrochloride
Hydrochlorothiazide
Lactose
Croscarmellose Sodium
Magnesium Stearate
Colloidal Silicon Dioxide

21. FACILITIES AND PERSONNEL

OK

22. SYNTHESIS

24. OTHER FIRM(s)

---

26. CONTAINER

Bottle of 100 and 1000, white, HDPE bottle with S/C and innerseal.
---- only.

29. STABILITY

OK

32. LABELING

Not Satisfactory

Pleinbach
0733S

APPEARS THIS WAY
ON ORIGINAL

CHEMIST'S REVIEW ANDA 70-704

3. NAME AND ADDRESS OF APPLICANT

Barr Laboratories
Northvale, NJ. 07647

6. NAME OF DRUG

Propranolol Hydrochloride and Hydrochlorothiazide

10. PHARMACOLOGICAL CATEGORY

Antihypertensive; anti hypertensive

11. HOW DISPENSED

Rx

12. RELATED IND/NDA/DMF(s)

70-704
70-705

13. DOSAGE FORM(s)

Tablet

14. POTENCY

40/25 mg

17. COMMENTS

1. HCT to be updated to USP XXI Supplement 3.
2. HPLC procedure for finished product.
3. Container information not satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable

19. REVIEWER: David J Broncato

DATE COMPLETED: 6/9/86

20. COMPONENTS AND COMPOSITION

Propranolol Hydrochloride
Hydrochlorothiazide
Lactose
Croscarmellose Sodium
Magnesium Stearate
Colloidal Silicon Dioxide

21. FACILITIES AND PERSONNEL

OK

22. SYNTHESIS

24. OTHER FIRM(s)

26. CONTAINER

Bottle of 100 and 1000, white, HDPE bottle with S/C and innerseal. only.

29. STABILITY

OK

32. LABELING

Not Satisfactory

0733S

APPEARS THIS WAY
ON ORIGINAL

CHEMIST'S REVIEW ANDA 70-704

3. NAME AND ADDRESS OF APPLICANT

Barr Laboratories
Northvale, NJ. 07647

6. NAME OF DRUG

Propranolol Hydrochloride and Hydrochlorothiazide

10. PHARMACOLOGICAL CATEGORY

Antihypertensive; anti hypertensive

11. HOW DISPENSED

Rx

12. RELATED IND/NDA/DMF(s)

70-704
70-705

13. DOSAGE FORM(s)

Tablet

14. POTENCY

40/25 mg

17. COMMENTS

1. HCT to be updated to USP XXI Supplement 3.
2. HPLC procedure for finished product.
3. Container information not satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable

19. REVIEWER:

DJ Francetto

DATE COMPLETED:

7/7/86

20. COMPONENTS AND COMPOSITION

Propranolol Hydrochloride
Hydrochlorothiazide
Lactose
Croscarmellose Sodium
Magnesium Stearate
Colloidal Silicon Dioxide

21. FACILITIES AND PERSONNEL

OK

22. SYNTHESIS

24. OTHER FIRM(s)

26. CONTAINER

Bottle of 100 and 1000, white, HDPE bottle with S/C and innerseal. only.

29. STABILITY

OK

32. LABELING

Not Satisfactory

0733S

APPEARS THIS WAY
ON ORIGINAL

CHEMIST'S REVIEW ANDA 70-704

3. NAME AND ADDRESS OF APPLICANT

Barr Laboratories
Northvale, NJ. 07647

6. NAME OF DRUG

Propranolol Hydrochloride and Hydrochlorothiazide

10. PHARMACOLOGICAL CATEGORY

Antihypertensive; anti hypertensive

11. HOW DISPENSED

Rx

12. RELATED IND/NDA/DMF(s)

70-704
70-705

13. DOSAGE FORM(s)

Tablet

14. POTENCY

40/25 mg

17. COMMENTS

1. HCT to be updated to USP XXI Supplement 3.
2. HPLC procedure for finished product.
3. Container information not satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

Approvable

19. REVIEWER:

MJ Brancato

DATE COMPLETED:

8/18/86

20. COMPONENTS AND COMPOSITION

Propranolol Hydrochloride
Hydrochlorothiazide
Lactose
Croscarmellose Sodium
Magnesium Stearate
Colloidal Silicon Dioxide

21. FACILITIES AND PERSONNEL

OK

22. SYNTHESIS

1. OTHER FIRM(s)

6. CONTAINER

Bottle of 100 and 1000, white, HDPE bottle with S/C and innerseal. only.

9. STABILITY

OK

12. LABELING

Satisfactory

0733S

APPEARS THIS WAY
ON ORIGINAL

THE COMPOSITION OF THE DRUG

INGREDIENTS	MG/TABLET
Propranolol Hydrochloride, USP	40.00
Hydrochlorothiazide, USP	25.00
Lactose, ——— NF	———
——— (Microcrystalline Cellulose, NF)	———
——— (Croscarmellose Sodium, ——— NF)	———
Magnesium Stearate, NF	———
——— (Colloidal Silicon Dioxide, NF)	———
	210.00

Manufacturers and Suppliers of the Raw Materials:

———————————

Manufacturer:

Distributor:

———————————

Manufacturer:

Distributor:

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 70-704

BIOEQUIVALENCE REVIEW(S)

OCT 9 1985

Propranolol HCl and Hydrochlorothiazide
80 mg/25 mg tablet
ANDA # 70-704
Reviewer: A. Jackson
Wang # 6241e

Barr Laboratories
Northvale, N.J.
Submission Date:
September 4, 1985

Review Of Bioequivalence Protocol

Objective:
To compare the plasma levels of propranolol, 4-hydroxypropranolol and the hydrochlorothiazide urinary excretion after single dose administration of the test product with those produced after administration of a reference tablet.

Methods:

The study will be done at ——————————— under the clinical direction of ——————, MD.

Clinical:

Subjects-

Subjects for the study will be 21-35 yrs of age. A total of 50 will be used in the study. The subjects will be housed in the ——————— live-in facility from 10 hours before until 24 hours after drug administration. They will be instructed to be free of all other medications including aspirin and OTC preparations from one week before the drug administration until after the study. Subjects who have ingested substances which compromise the validity of their measured levels of the drug will be excluded.

Subjects shall fast for 10 hours prior to and 5 hours after the drug is administered. Three standard meals will be served each day. Only the food served will be allowed until after each phase.

The criteria for subject eligibility will include:

No more than plus or minus 10% from ideal weight for his height as defined by Metropolitan life Insurance Company statistical bulletin 40:1, 1979. Without a history of serious hepatic, renal or gastrointestinal disease, alcohol or drug abuse, as evidenced by a medical history and physical examination within 30 days prior to the start of the study.

Blood chemistry (alkaline phosphatase, SGOT, BUN, bilirubin), hematology (hemoglobin, hematocrit, white blood count, differential count) and urine analysis (routine and microscopic) values within the normal ranges. This may be waived in part by the investigator, if, in his opinion, the protection of the subjects is not compromised. The above tests will be performed within 30 days prior to the start of the study.

Normal EKG.

Non-smoker.

Normal thyroid function.

Free of acute viral of bacterial infections for two weeks prior to the study.

The products to be studied will be test propranolol HCl (80 mg) and hydrochlorothiazide (25 mg) tablets versus Inderide 80/25 mg manufactured by Ayerst.

Drug will be administered with 180 ml of water at 0 hour. The subjects will be required to remain seated for 2 hours after dosing except for urine samples.

Blood samples will be collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 18 and 24 hours post dose, immediately centrifuged and frozen.

Pulse and blood pressure will be monitored prior to dosing and after each blood sample until 2 hours after dosing.

There will be a seven day washout period between studies.

Collection Of Urine Samples

All of the urine voided will be collected in the following intervals: -2 to 0, 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, and 12-24 hours. The pH will be measured and a 20 ml aliquot save and frozen for assay. Subjects will be administered 180 ml at the end of each collection interval throughout 12 hours.

Comments:

1. A complete assay validation for propranolol, 4-hydroxypropranolol in plasma and for hydrochlorothiazide in urine should be included in the final submission.

2. Urinary samples should be collected to 36 hours instead of 24 with the intervals being -2 to 0, 0-2, 2-4, 4-6, 6-8, 8-12, 12-24 and 24-36. Since only cumulative urine is of interest, the shorter collection periods are not required.

3. The statistical analysis of the data should include a statement for LS Means and a comparison of treatment means in the SAS analysis.

4. If the submitted dissolution data is to be used for approval of the Barr product, then the bioavailability study should be done on the same lot.

5. The firm should include lot numbers for all drugs used in the study.

6. Fifty subjects maybe excessive, it is possible that the study could probably be completed with 40 participants.

7. The dissolution data submitted is acceptable but should be resubmitted with the in-vivo data.

8. The composition of all formulations for other strengths and any request for waiver at other strengths should be submitted with the in-vivo data.

Recommendation

The protocol for a proposed bioavailability study comparing the test product with Ayerst's Inderide 80/25 mg tablet is acceptable to the Division of Bioequivalence provided the firm incorporates comments 1-8 in the final protocol. The firm should be informed of the comments 1-8.

The in-vitro dissolution data is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of 0.1N HCl at 37°C using USP XXI method 1 at 100 rpm. The test should meet the following specification:

> Not less than —% of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

Andre Jackson, Ph. D. Andre Jackson
Division of Bioequivalence
Review Branch 1

RD INITIALED CIse
FT INITIALED CIse C. M Ise

AJackson/sg/10/4/85/Wang # 6241e

cc: ANDA # 70-704 original, HFN-230,(2) HFN-200 (Hare), HFN-223 (Shah - 2), HFN-252 (Ise, Jackson), Drug File

Generic Name: Propranolol HCl and Hydrochlorothiazide

Trade Name: _____

Dosage: 80 mg | 25 mg

ANDA #: 70-704

Reviewer: _____

Firm Name: Barr Laboratories

Firm Location: Northvale, NJ

Submission Date: September 4, 1985

Wang # 6241e

REVIEW OF DISSOLUTION DATA

Objective of Submission: To compare the propranolol, 4-hydroxypropranol plasma levels and the hydrochlorothiazide urinary excretion after administration of the test product with those produced after administration of the reference drug.

Condition for Dissolution Testing

USP XX Apparatus Paddle _____ Basket ✓ RPM 100

Medium: 0.1N HCl Volume 900 ml

Number of Tab/Capsules Tested: 12

Reference Drug: Inderide

Assay Methodology

Propranolol

Results

Time	Test Product Lot # 4L42732 Mean % Dissolved	Range	(CV)	Reference Product Lot # 1JT9 Mean % Dissolved	Range	(CV)
___	___	___	( )	~~97.4~~	___	( )
5	94.2		(4)	97.4		(4)
10	101.1		(1)	101.9		(2)
20	102.2		(2)	102.6		(2)
30	101.9		(1)	102.6		(2)
45	102.1		(2)	102.7		(2)
60	102.5		(2)	102.7		(2)
___	___	___	( )	___	___	( )
___	___	___	( )	___	___	( )

Hydrochlorothiazide

	Lot # 4L42732			Lot # 1JT9		
___	___	___	( )	___	___	( )
5	79.5		(4)	75		(7)
10	93.1		(2)	89		(3)
20	97.2		(2)	95		(2)
30	97.7		(2)	96		(2)
45	98.1		(2)	97		(2)
60	98.4		(2)	97		(2)
___	___	___	( )	___	___	( )
___	___	___	( )	___	___	( )

MAR 12 1986

Propranolol HCl/Hydrochlorothiazide
ANDA 70-704: 40 mg/25 mg Tablets
70-705: 80 mg/25 mg Tablets
Reviewer: J.F. Kinsel
Wang 6996e

Barr Laboratiories
Northvale, NJ
Submission Dates:
December 31, 1985
February 19, 1986

Review of an in vivo Bioequivalence Study, in vitro Dissolution Data and Request for Waiver

Objective

This submission provides the report on a two treatment single dose crossover study comparing the test product, Propranolol HCl/Hydrochlorothiazide (80 mg/25 mg) Tablet, with the reference product, Inderide 80/25 tablet, manufactured by Ayerst Labs. A request for waiver of the bioavailability requirements is made for Propranolol HCl/Hydrochlorothiazide (40 mg/25 mg) Tablet based on formulation proportionality and dissolution data.

Study Design

The study was conducted by ——————————— under the supervision of ————, M.D. and ————, Ph.D. The study employed 34 healthy, non-smoking, male volunteers between 19 and 35 years of age. Their weights did not deviate by more than ± 10% of ideal weight for height and body frame (Metropolitan Life Insurance Company). Subjects with obvious symptoms of ill health or with a history of serious cardiovascular, hepatic, renal or gastrointestinal disease, alcohol or drug abuse were not included in the study.

Good health was ascertained from medical history, physical examination and routine laboratory tests. Subjects were instructed to abstain from taking any medications for 2 weeks prior to the start of the study and from consuming alcoholic beverages, xanthines and caffeine-containing substances for 48 hours before the study. Subjects were admitted the evening before dosing and fasted for 10 hours prior to dosing. Each tablet was administered orally with 240 ml of water. Subjects remained fasted until 5 hours post-dose. There was a one week washout interval between dosings.

The products employed in this study were as follows:

a) Test: Propranolol HCl/Hydrochlorothiazide (80 mg/25 mg) Tablet, Barr Laboratories, Lot # 4L42836

b) Reference: Inderide 80/25 Tablet, Ayerst Laboratories, lot # 1063, exp date 8/87

Blood (15 ml) was collected at 0, 0.5, 1, 1.5, 2, 2.5. 3, 4, 6, 8, 10, 12, 16 and 24 hours after dosing. The plasma was harvested at 4°C and stored at -15°C until the samples could be analyzed for total and free propranolol and 4-hydroxypropranolol.

Urine was collected pre-dose and over the following intervals after drug administration: 0-1, 1-2, 2-4, 4-8, 8-12 and 12-24 hours. Urine volumes and pH were recorded and two 15 ml aliquots were frozen for assay of hydrochlorothiazide and a possible future assay of propranolol. The subjects were administered 240 ml of water at the end of each collection interval through 12 hours.

Plasma Analysis

The plasma samples were assayed for free and total propranolol and its metabolite, 4-hydroxypropranolol, by a high performance liquid chromatography method. Protriptyline HCl was used as the internal standard.

A. Free Propranolol

1. Sensitivity: 2.0 ng/ml
2. Linearity : 2.0-300 ng/ml
3. Specificity: no interfering chromatographic peaks
4. Precision :

	Actual ng/ml	Found ng/ml	CV %	Acuracy %
Intraday	2	1.9	12.8	97.0
	10	9.5	8.1	95.0
	100	99.1	7.1	99.1
	300	297.0	3.8	99.0
Interday	2	2.1	6.2	97.3
	10	9.6	7.0	95.5
	100	101.6	4.7	98.4
	300	296.5	3.1	98.8

5. Standard curve summary for $y = a + b\ (\ln x) + c\ (\ln x)^2$ (% CV):

a:	4.117 (7.0)
b:	0.9729 (5.8)
c:	0.0142
correlation coefficient:	0.998 (0.1)

B. Free 4-Hydroxypropranolol

1. Sensitivity: 0.8 ng/ml
2. Linearity : 0.8-120 ng/ml
3. Specificity: no interfering peaks
4. Precision :

	Actual ng/ml	Found ng/ml	CV %	Accuracy %
Intraday	0.8	0.76	12.2	94.7
	10	10.5	11.4	95.0
	120	116.4	1.8	97.0

Interday	0.8	0.82	5.5	97.5
	10	10.1	5.6	99.0
	120	117.2	4.3	99.7

5. Standard curve summary for $y = a + b\ (\ln x) + c\ (\ln x)^2$ (% CV):

a:	2.867 (9.5)
b:	1.019 (5.7)
c:	-0.0264
correlation coefficient:	0.998 (0.1)

Urine Analysis

The urine samples were assayed for hydrochlorothiazide (HCT) by a high performance liquid chromatography method. Hydroflumethiazide was used as the internal standard.

HCT

1. Sensitivity: 1.0 mcg/ml
2. Linearity : 1.0-50.0 mcg/ml
3. Specificity: no interfering chromatographic peaks
4. Precision :

	Actual mcg/ml	Found mcg/ml	CV %	Accuracy %
Intraday	1.0	0.92	4.5	92.1
	5.0	4.86	3.1	97.2
	50.0	49.5	0.7	99.0
Interday	1.0	0.99	1.3	99.1
	5.0	5.04	4.6	99.2
	50.0	49.8	1.7	99.6

5. Standard curve summary for $y = a + b\ (\ln x) + c\ (\ln x)^2$ (% CV):

a:	2.535 (5.1)
b:	1.003 (2.9)
c:	-0.0030
correlation coefficient:	0.999 (0.1)

Data Analysis

Analytical data for 34 subjects were evaluated by ANOVA to determine if there were statistically significant differences (p 0.05) between dosing groups. Evalutions of bioequivalence were based upon plasma concentrations of propranolol and 4-hydroxypropranolol and the urinary excretion of HCT for both test and reference products. The study report includes an SAS statistical summary.

Results

The results of the single dose study comparing Propranolol HCl/ Hydrochlorothiazide, 80 mg/25 mg, tablets from Barr Labs (test) and Ayerst Labs (Inderide; reference) are given in Tables 1-5 (plasma) and 6 a + b (urine).

Table 1. Mean Plasma Levels of Free Propranolol, ng/ml (% CV)

Time hrs	Barr (test)	Ayerst (reference)
0.5	12.89 (148)	9.27 (139)
1	47.24 (93)	48.33 (80)
1.5	69.27 (68)	76.89 (76)
2	80.82 (65)	82.63 (61)
2.5	82.60 (63)	82.62 (56)
3	75.97 (59)	77.89 (56)
4	66.39 (57)	66.84 (57)
6	41.88 (57)	42.88 (61)
8	26.23 (55)	28.25 (69)
10	15.82 (61)	17.91 (78)
12	10.27 (76)	11.14 (84)
16	4.72 (91)	5.57 (114)
24	1.36 (161)	1.87 (152)

Table 2. Mean Plasma Levels of Free 4-Hydroxypropranolol, ng/ml (% CV)

Time hrs	Barr (test)	Ayerst (reference)
0.5	5.69 (99)	4.64 (98)
1	9.57 (73)	9.05 (66)
1.5	7.75 (62)	8.11 (62)
2	5.27 (66)	5.65 (64)
2.5	4.30 (69)	4.56 (61)
3	3.10 (71)	3.28 (62)
4	1.95 (80)	1.98 (54)
6	1.06 (98)	1.70 (169)
8	0.47 (160)	0.60 (128)
10	0.26 (187)	0.43 (167)
12	0.13 (278)	0.27 (246)
16	0.05 (401)	0.14 (381)
24	0	0

Table 3. Individual AUC (0-24) and AUC I(0-inf) values for test and Reference products:

Free Propranolol (ng-hr/ml)

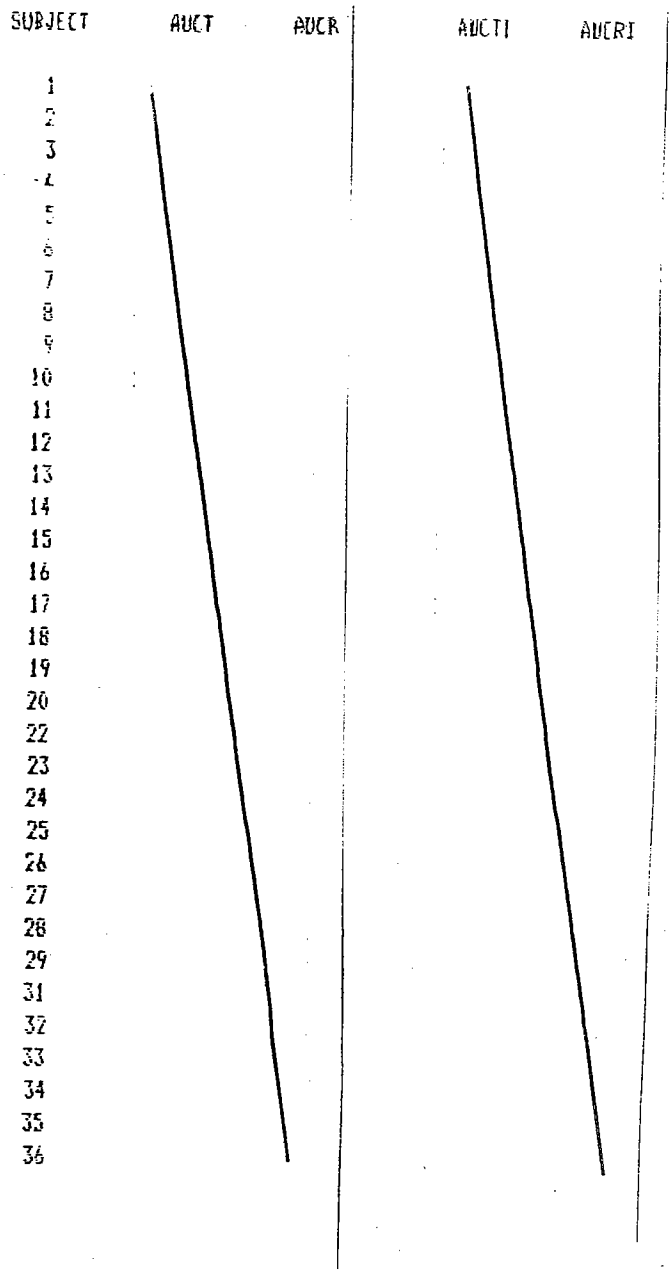
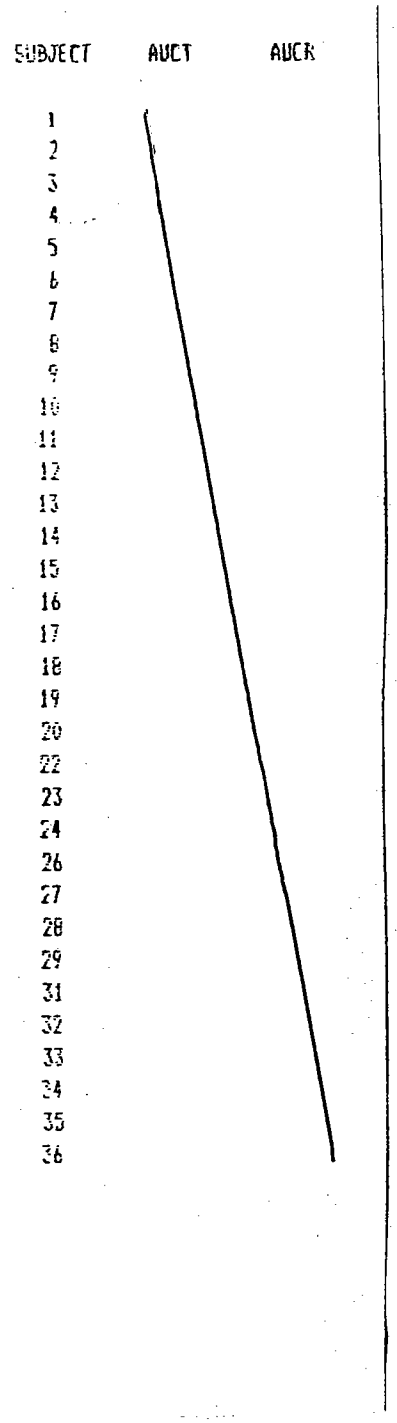


Table 4. Individual AUC (0-24) value for Test and Reference products:

Free 4-Hydroxypropranolol (ng-hr/ml)



SUBJECT	AUCT	AUCR
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
22		
23		
24		
26		
27		
28		
29		
31		
32		
33		
34		
35		
36		

Table 5. Derived Pharmacokinetic Parameters (% CV)

	Barr (test)	Ayerst (reference)
Free Propranolol		
AUC (0-24 hr) ng hr/ml	535.42 (60)	560.91 (64)
AUC (0-inf), ng hr/ml	551.46 (60)	586.69 (63)
Cmax, ng/ml	86.79 (61)	90.36 (61)
Tmax, hr	2.44 (24)	2.15 (23)
Kel, hr^{-1}	0.196 (29)	0.190 (33)
T 1/2, hr	3.84 (30)	4.28 (51)
Free 4-Hydroxypropranolol		
AUC (0-24 hr), ng hr/ml	25.83 (72)	28.54 (60)
Cmax, ng/ml	10.12 (66)	9.98 (60)
Tmax, hr	1.14 (28)	1.35 (67)

Table 6a. Mean Urinary Excretion (mg), Excretion Rate (mg/hr) and Pharmacokinetic Parameters (% CV) for HCT

	Time hrs	Barr (test)	Ayerst (reference)
Cumulative			
	0-1	0.35 (71)	0.28 (120)
	0-2	2.54 (41)	2.60 (68)
	0-4	6.60 (26)	6.73 (39)
	0-8	9.95 (25)	10.16 (32)
	0-12	11.34 (25)	11.63 (30)
	0-24	12.94 (27)	13.07 (31)
Rate			
	0-1	0.35 (71)	0.28 (120)
	1-2	2.19 (44)	2.31 (66)
	2-4	2.03 (37)	2.07 (42)
	4-8	0.84 (39)	0.86 (41)
	8-12	0.35 (43)	0.39 (45)
	12-24	0.13 (70)	0.12 (63)
Rmax, mg/hr		2.60 (28)	2.81 (45)
Tmax, hr		2.07 (36)	2.12 (35)

Table 6[b] Individual cumulative HCT excretion values for Test and Reference products (mg).

SUBJECT	CUMT	CUMR
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
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20		
22		
23		
24		
25		
26		
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28		
29		
31		
32		
33		
34		
35		
36		

There were no significant differences in any of the pharmacokinetic parameters tested for free propranolol between the test and reference products. The power of the study at alpha= 0.05 to detect a 20% difference from the reference mean was greater than 80% for AUC (0-24), AUC (0-inf) and Cmax. For the metabolite, free 4-hydroxypropranolol, no significant differences were found in AUC (0-24) and Cmax with a statistical power of greater than 80% at alpha= 0.05 to detect a 20% difference from the reference means.

The 90% confidence intervals of the estimate for the difference of the two means were calculated. It was found that the parameters for free propranolol and 4-hydroxypropranolol were within the acceptable range (Table 7).

Table 7. Confidence Intervals (90%) of the Derived Pharmacokinetic Parameters

Free Propranolol

AUC (0-24)	(86.2, 104.7)
AUC (0-inf)	(84.8, 103.2)
Cmax	(86.2, 105.9)

Free 4-hydroxypropranolol

AUC (0-24)	(77.8, 103.2)
Cmax	(91.8, 111.0)

There was not a significant difference in any of the pharmacokinetic parameters between the two products for HCT. The power to detect a 20% difference as statistically significant at alpha= 0.05 was > 99% for cumulative HCT excretion and 91% for peak excretion rate (Rmax).

Dissolution Test Results

Dissolution testing was conducted in 900 ml of 0.1N HCl at 37°C using USP XXI apparatus I (basket) at 100 rpm. Samples were monitored at 5, 10, 15, 30, 45 and 60 minutes. Results are appended in Tables 8a and 8b. Both strengths of the test and reference products exhibited similar dissolution profiles, with not less than —% of each drug dissolved at 60 minutes.

Formulation

Comparative formulation information for Barr's Propranolol HCl/Hydrochlorothiazide tablets, 80 mg/25 mg and 40 mg/25 mg, is shown in Table 9. The 40 mg/25 mg strength tablets are proportionally similar in formula to the 80 mg/25 mg strength tablets, which are the subject of the acceptable in vivo bioequivalence study.

Comments

1. The in vivo bioequivalency study and in vitro dissolution test results are acceptable. They support the contention of bioequivalence between the test (Propranolol HCl/Hydrochlorothiazide 80 mg/25 mg tablet; Barr) and reference (Inderide 80/25 tablet; Ayerst) products. The firm should be advised accordingly.

2. The firm has fulfilled the requirements for waiver of in vivo bioequivalence evidence under CFR 320.22 (d)(2) for Propranolol HCl/Hydrochlorothiazide 40 mg/25 mg tablet:

i) The bioequivalence of the test 80 mg/25 mg tablet to the reference product, Inderide 80/25 tablet, has been demonstrated.

ii) Both drug products meet the in vitro dissolution standards.

iii) The 40 mg/25 mg and 80 mg/25 mg strengths are proportionally similar in their active and inactive ingredients.

3.It is requested that you mail 200 tablets/capsules of the same product lot used in your in vivo bioavailability/bioequivalence study to:

Dr. V. K. Prasad
Chief, Biopharmaceutics Laboratory Branch
Center for Drugs and Biologics
200 C Street, S.W. (HFN-224)
Washington, D.C. 20204

Please assure that the ANDA Number, Ingredient and Strength, Lot No., and Expiration Date are included in the label information.

Recommendations

1. The bioequivalence study conducted by Barr Laboratories on its Propranolol HCl/Hydrochlorothiazide (80 mg/25 mg) tablet, lot # 4L42836, comparing it to Ayerst's Inderide (Propranolol HCl/Hydrochlorothiazide 80 mg/25 mg) tablet, has been found acceptable to the Division of Bioequivalence. The study demonstrates that the test product, Barr's Propranolol HCl/Hydrochlorothiazide (80 mg/25 mg) is bioequivalent to the reference product, Ayerst's Inderide 80/25 tablet.

2. The in vitro dissolution testing is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of 0.1N HCl at 37°C using USP XXI apparatus I (basket) at 100 rpm. The test product should meet the following specification:

> Not less than —% of the labeled amount of drug in the capsule is dissolved in 60 minutes.

3. The dissolution testing conducted by Barr on its Propranolol HCl/Hydrochlorothiazide 40 mg/25 mg tablet, lot #4L42732, is acceptable. The formulation for the 40 mg/25 mg strength is proportionally similar to the 80 mg/25 mg strength of the test product which underwent the bioequivalence study. The waiver of in vivo bioequivalence study requirements for the 40 mg/25 mg strength of the test product is granted. Barr's Propranolol HCl/Hydrochlorothiazide 40 mg/25 mg tablet is therefore deemed bioequivalent to Inderide (Propranolol HCl/Hydrochlorothiazide 40 mg/25 mg) tablet manufactured by Ayerst.

4. From the bioequivalence point of view the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing and both applications, NDA 70-704 (40 mg/25 mg) and 70-705 (80 mg/25 mg), are acceptable.

The firm should be informed of the above comments and recommendations.

Jane F. Kinsel 3/7/86

Jane F. Kinsel, Ph.D.
Division of Bioequivalence
Review Branch 1

RD INITIALED CIse
FT INITIALED CIse Agnes T. Ilo 3/7/86

JKinsel/sg/2/12/86/Wang # 6996e

cc: ANDA # 70-704, 70-705 original, HFN-230,(4) HFN-200 (Hare), HFN-223 (Shah - 2), HFN-252 (Ise, Kinsel), HFN-340 (Turner) Drug File

TABLE 8a. DISSOLUTION DATA FOR PROPRANOLOL HCl / HYDROCHLOROTHIAZIDE (80MG/25MG) TABLETS

Results

A. Propranolol HCl

Time	Test Product (Barr) Lot # 4L42836 Mean % Dissolved	Range	(CV)	Reference Product (Inderide; Ayerst) Lot # 1Q63 Mean % Dissolved	Range	(CV)
5	99.5		(2)	69.0		(42)
10	102.7		(1)	100.5		(9)
15	102.9		(1)	104.0		(3)
30	103.1		(1)	105.0		(2)
45	103.0		(1)	105.2		(1)
60	103.3		(1)	105.3		(1)
			( )			( )
			( )			( )
			( )			( )

B. HCT

Time	Test Product Lot #	Range	(CV)	Reference Product Lot #	Range	(CV)
5	83.4		(4)	39.6		(52)
10	95.3		(3)	78.3		(14)
15	98.6		(2)	90.6		(6)
30	100.8		(2)	97.9		(3)
45	101.1		(2)	98.9		(3)
60	101.4		(2)	99.2		(3)
			( )			( )
			( )			( )
			( )			( )

TABLE 8b. DISSOLUTION DATA FOR PROPRANOLOL HCl / HYDROCHLOROTHIAZIDE (40MG/25MG) TABLETS

Results A. Propranolol HCl

Time, min.	Test Product (Barr) Lot # 4L 42732 Mean % Dissolved	Range	(CV)	Reference Product (Inderide; Ayerst) Lot # 1JT9 Mean % Dissolved	Range	(CV)
5	94.2		(5)	97.4		(4)
10	101.1		(1)	101.9		(2)
20	102.2		(2)	102.6		(2)
30	101.9		(1)	102.6		(2)
45	102.1		(2)	102.7		(2)
60	102.5		(2)	102.7		(2)
			( )			( )
			( )			( )
			( )			( )

B. HCT

Time, min.	Test Product Lot # Mean % Dissolved	Range	(CV)	Reference Product Lot # Mean % Dissolved	Range	(CV)
5	79.5		(4)	75.0		(7)
10	93.1		(2)	89.1		(3)
20	97.2		(2)	95.2		(2)
30	97.7		(2)	96.7		(2)
45	98.1		(2)	97.4		(2)
60	98.4		(2)	97.6		(2)
			( )			( )
			( )			( )
			( )			( )

Table 9. Formulas of Propranolol HCl/Hydrochlorothiazide Tablets (Barr)

	40 mg/25 mg		80 mg/25 mg	
	mg	% w/w	mg	% w/w
Propranolol HCl, USP	40.0	19.05	80.0	25.00
Hydrochlorothiazide, USP	25.0	11.91	25.0	7.81
Lactose, NF	———	———	———	———
———	———	———	———	———
———	———	———	———	———
Magnesium Stearate, NF	———	———	———	———
———	———	———	———	———
	210.0	100.01	320.0	100.01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 70-704

ADMINISTRATIVE DOCUMENTS

ANDA ADMINISTRATIVE CONTROL RECORD

Applicant Barr Laboratories, Inc ANDA # 70-704

Date Recd.

Trade Name RX ✓ OTC

Generic Name/Dosage Form/Strength: Propranolol Hcl and Hydrochlorothiazide tablets 40mg/25mg

DESI Drug

Similar or Related

Applicant Manufacturer: Yes ✓ No

If No: Name of Manufacturer

ANDA # Approved: Pending Same Formulation

Application Complete YES NO ✓
Application Acceptable: YES ✓ NO
needs certification of GMP Has information on the listed drug

Letter to Firm: Acknowledgement: ✓ Not-acceptable Date 9-16-85 DAR
needs to address Bio on 40/25mg Tablet

CSO/CST: Margo Bennett Date 9-10-85

BIO Review Required: YES X NO IN VITRO X IN VIVO X

Medical Officer M. CHANG

Chemist P Duncan

Inspection Request to HFD 320 (Date): 9-10-85

NWK-Do

7899e/mlb

TS

9/1

DEPARTMENT OF HEALTH & HUMAN SERVICES

M

Durham

TO :Manufacturing Review Branch (HFN-322) DATE: 9-10-85
Division of Drug Quality Compliance

FROM :Division of Generic Drugs
Requester's Name David Rosen PHONE: 443-4080

SUBJECT: ESTABLISHMENT EVALUATION REQUEST

NDA, ANDA, AND SUPPLEMENT NUMBER: 70-704 (40 mg/25 mg) 70-705 (80 mg/25 mg)

DRUG TRADE MARK (if any)

DRUG NONPROPRIETARY NAME: Propranolol HCl and Hydrochlorothiazide Tablets

DOSAGE FORM AND STRENGTH(S): TCM

DRUG CLASSIFICATION: PROFILE CLASS CODE:
(Priority) A or B 1C Other

APPLICANT'S NAME: Barr Laboratories, Inc.
ADDRESS: 265 Livingston St., Northvale, NJ 07647

FACILITIES TO BE EVALUATED: (Name, Full Address, DMF# (if any), and Responsibility)

1. applicant above and 248 Pegasus Ave., Northvale, NJ 07647 (Bergen County)

New Brunswick, NJ 08903

Comments: ( ) See Attached.
( ) Actual on-site inspection requested.

Reason:

****

FOR HFN-322 USE ONLY:

Request Rec'd: Inspection Requested: (if applicable)

Firm(s) are in Compliance With GMPs: Approvable
Basis for Decision:
Reviewing CSO: Thomas J Schultz 9/17/85 Concurrance:

cc: HFN-
HFN-
HFN-322

FORM FDA 3274 (1/83)

cc: DDarrow 12-18 HFC-131

ANDA Approval Summary

70-704 — ANDA Number
Barr Laboratories, Inc. — Applicant Name
50cc & 300cc 33mm 53mm HDPE

Propranolol Hydrochloride & Hydrochlorothiazide — Established Name of Drug
Tablets — Dosage Form
40mg/25mg — Strength
bottles, 100s, 1000s — Container size(s)

	Date Found Satisfactory	Comment
Labeling	6/23/86 & 12/2/85	Use in Pregnancy under Warnings needs highlighting at next printing
Chemistry, Manufacturing, and Controls	9/25/86	
MP's		
Manufacturer - Finished Dosage Form	9/17/85	
Outside Facilities	9/17/85	
Manufacturer(s) - Active Ingredient(s)	9/17/85	

David J. Brancato — Chemist Reviewer — 9/25/86 — Date
[signature] — Branch Chief — 9-26-86 — Date

Petition Required	✓ No ___ Yes	
Listed Drug Information 505(j)(2)(A)	yes	From letter dated 9/4/85
Patent Certification 505(j)(2)(A)	yes	From letter dated 9/4/85
Date Patent/Exclusivity Expires (if applicable)	N/A	

Bioequivalence Section

Dissolution Required? ___ No ✓ Yes : ✓ DB ___ DGD	yes	FDA letter dated 3/20/86
In vivo study(s) required? ✓* No ___ Yes		*Study performed on 80mg/25mg tablet strength.
Study(s) Found Acceptable	N/A	
Waiver Request Granted	yes	FDA letter of 3/20/86
Total Bioequivalence-Requirement Met	yes	3/20/86

DW
A J Sturm — Administrative Reviewer — 9/25/86 — Date

Approved ✓
Disapproved ___

Warren Lufe MD — Director, Division of Generic Drugs — 9/29/86 — Date

Comments:

ANG #0479A (Rev-5/85)

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 70-704

DATE APPROVAL LETTER ISSUED: OCT 1 1986

TO: Press Relations Staff (HFI-40)

FROM:
- [x] Bureau of Drugs
- [ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION
- [ ] ORIGINAL NDA
- [ ] SUPPLEMENT TO NDA
- [x] ABBREVIATED ORIGINAL NDA
- [ ] SUPPLEMENT TO ANDA

CATEGORY
- [x] HUMAN
- [ ] VETERINARY

TRADE NAME *(or other designated name)* AND ESTABLISHED OR NONPROPRIETARY NAME *(if any)* OF DRUG

Propranolol Hydrochloride and Hydrochlorothiazide

DOSAGE FORM

Tablets 40 mg/25 mg

HOW DISPENSED
- [x] RX
- [ ] OTC

ACTIVE INGREDIENT(S) *(as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)*

Propranolol Hydrochloride, USP
Hydrochlorothiazide, USP

NAME OF APPLICANT *(Include City and State)*

Barr Laboratories, Inc.
265 Livingston Street
Northvale, NJ 07647

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Antihypertensive

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME: David J. Brancato DJ Brancato — DATE: 9/25/86

FORM APPROVED BY

NAME: Charles Chang — DATE: 9/25/86

FORM FD 1642 (2/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 70-704

CORRESPONDENCE

Barr Laboratories, Inc. 265 Livingston St, Northvale, N.J. 07647 Telephone (201) 767-1900

September 4, 1985

505 j 2A
information
is
satisfactory
except for
B10.
DWR
9-10-85

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
HFN-230, ROOM 16-70
Food and Drug Administration
Center For Drugs And Biologics
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Seife:

We are submitting herewith, in triplicate, an Abbreviated New Drug Application pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS, 40MG/25MG.

Included in this Application is the Protocol #7188 prepared by Ayerst Laboratories for Bioavailability of Propranolol Hydrochloride and Hydrochlorothiazide Tablets.

In accordance with "Patent Certification" requirement guidelines issued by the Agency on October 11, 1984, please refer to section "Patent Certification" directly following the "Table of Contents" section, where you will find a fully signed Certification Statement.

Samples will be submitted when Barr Laboratories receives the Agency's request.

Your earliest reply to this submission would be very much appreciated.

RECEIVED
SEP 5 1985
GENERIC DRUGS

Sincerely,

BARR LABORATORIES, INC.

Edwin A. Cohen
President

EAC:tm
Enclosures

NDA 70-704

SEP 16 1985

Barr Laboratories, Inc.
Attention: Edwin A. Cohen
265 Livingston Street
Northvale, NJ 07647

Gentlemen:

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

NAME OF DRUG: Propranolol Hydrochloride and Hydrochlorothiazide Tablets, 40 mg/25 mg

DATE OF APPLICATION: Not dated

DATE OF COVER LETTER: September 4, 1985

DATE OF RECEIPT: September 5, 1985

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

Please submit Certification that the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and holding of the drug are in conformity with current good manufacturing practice in accord with 21 CFR 210 and 211.

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

Sincerely yours,

9-16-85

Kent C. Johnson for 9-16-85

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

NWK-DO DUP HFN-230
CChang/mlb/9-10-85
Ack
(1471A)

NDA 70-704

OCT 17 1985

Barr Laboratories, Inc.
Attention: Edwin A. Cohen
265 Livingston Street
Northvale, NJ 07647

Gentlemen:

Reference is made to the dissolution data and protocol you submitted for bioavailability studies on September 4, 1985 for Propranolol Hydrochloride and Hydrochlorothiazide Tablets, 40 mg/25 mg.

The protocol has been reviewed by our Division of Bioequivalence and they have the following comments:

1. A complete assay validation for propranolol, 4-hydroxypropranolol in plasma and for hydrochlorothiazide in urine should be included in the final submission.

2. Urinary samples should be collected to 36 hours instead of 24 with the intervals being -2 to 0, 0-2, 2-4, 4-6, 6-8, 8-12, 12-24 and 24-36. Since only cumulative urine is of interest, the shorter collection periods are not required.

3. The statistical analysis of the data should include a statement for LS Means and a comparison of treatment means in the SAS analysis.

4. If the submitted dissolution data is to be used for approval of the Barr product, then the bioavailability study should be done on the same lot.

5. The firm should include lot numbers for all drugs used in the study.

6. Fifty subjects maybe excessive, it is possible that the study could probably be completed with 40 participants.

7. The dissolution data submitted is acceptable but should be resubmitted with the in-vivo data.

8. The composition of all formulations for other strengths and any request for waiver at other strengths should be submitted with the in-vivo data.

Recommendation

The protocol for a proposed bioavailability study comparing the test product with Ayerst's Inderide 80/25 mg tablet is acceptable to the Division of Bioequivalence provided the firm incorporates comments 1-8 in the final protocol.

The in-vitro dissolution data is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of 0.1N HCl at 37°C using USP XXI method 1 at 100 rpm. The test should meet the following specification:

Not less than — % of the labeled amount of the drug in the dosage form is dissolved in 60 minutes."

Sincerely yours,

Marvin Seife 10/17/85

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc: NWK-DO
HFN-230
PDLeinbach
MSeife/MSeife/jt/10-11-85
BIO 1170A

NDA 70-704

NOV 15 1985

Barr Laboratories, Inc.
Attention: Edwin A. Cohen
265 Livingston Street
Northvale, NJ. 07647

Dear Mr. Cohen:

Please refer to your abbreviated new drug application submitted pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act for Propranolol Hydrochloride and Hydrochlorothiazide Tablets, 40 mg/25 mg.

The application is deficient and therefore not approvable under Section 505 of the Act for the following reasons:

1. It fails to contain satisfactory labeling. In that regard:

   A. Container: Not Satisfactory (100's and 1000's)

      1. Dispensing recommendation (1000's)

         This statement should be either in singular or plural form.

      2. The quantity of each active ingredient must be included. We suggest that you use the following:

         Each Tablet contains:

         Propranolol Hydrochloride, USP. . . . . .xx mg
         Hydrochlorothiazide USP. . . . . xx mg

   B. Insert: Not Satisfactory

      1. DESCRIPTION

         Please include the following as the first paragraph:

         Propranolol Hydrochloride and hydrochlorothiazide tablets combine two antihypertensive agents: propranolol hydrochloride, a beta-adrenergic blocking agent, and hydrochlorothiazide, a thiazide diuretic-antihypertensive.

      2. WARNINGS

         A. INPATIENTS WITH ANGINA PECTORIS

            This entire section should be boxed.

B. IN PATIENTS UNDERGOING MAJOR SURGERY, 8th line

——Isoproterenol or Norepinephrine——
(rather than. . . Isoproterenol or ————————. . . .)

3. OVERDOSAGE OR EXAGGERATED RESPONSE

A. HYPOTENSION-Vasopressors, e.g. Norepinephrine
(rather than, ————————)

C. Revise container labels and package insert labeling. Prepare and submit 12 copies of final printed labeling of each.

2. It fails to assure that the drug dosage form and components will comply with the specifications and tests described in an official compendium, if such article is recognized therein, or if not listed, or if the article differs from the compendium drug, that the specifications and tests applied to the drug and its components are adequate to assure their identity, strength, quality and purity. In this regard:

Bulk active ingredients

A.

B.

C.

D.

E.

F.

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

FDA LETTER 11/15/1985

The file is now closed. You are required to take one of the actions described at 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Kent T. Johnson for 11-15-85

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc:
NWK-DO
HFN-230
MChang/CChang/PDLeinbach/tr/11/4/85
0377S
Not Approved

mailed 11/14/85

WPf 11/13/85

cy 11-14-85

Orig

Barr Laboratories, Inc. 265 Livingston St, Northvale, N.J. 07647 Telephone (201) 767-1900

1. FPL Container labels (100s & 1000s) Satisfactory
2. Firm did not submit FPL, we believe that they submitted is not their usual FPL quality
3. Also request the firm to include - "scored or unscored and debossing (if applicable) in describing their tablets in Item 120 Section

NDA ORIG AMENDMENT

mcb 12/10/85

FPL

November 27, 1985

Marvin Seife, M.D.
Director
Division of Generic Drugs
HFN-230, ROOM 16-70
FOOD AND DRUG ADMINISTRATION
5600 Fishers Lane
Rockville, Maryland 20857

REFERENCE: NDA 70-704
PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG

Dear Dr. Seife:

Please refer to our Abbreviated New Drug Application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG.

Reference is also made to your letter of November 15, 1985, in which the following is stated:

THE APPLICATION IS DEFICIENT AND THEREFORE NOT APPROVABLE UNDER SECTION 505 OF THE ACT FOR THE FOLLOWING REASONS:

COMMENT #1

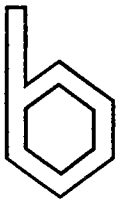
1. IT FAILS TO CONTAIN SATISFACTORY LABELING. IN THAT REGARD:

A. CONTAINER: NOT SATISFACTORY (100's AND 1000's)

1. DISPENSING RECOMMENDATION (1000's)

THIS STATEMENT SHOULD BE EITHER IN SINGULAR OR PLURAL FORM.

2. THE QUANTITY OF EACH ACTIVE INGREDIENT MUST BE INCLUDED. WE SUGGEST THAT YOU USE THE FOLLOWING:



REFERENCE: NDA 70-704
PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS,
40 MG/25 MG

EACH TABLET CONTAINS:

PROPRANOLOL HYDROCHLORIDE, USP .....XX MG
HYDRCHLOROTHIAZIDE USP .....XX MG

B. INSERT: NOT SATISFACTORY

1. DESCRIPTION

PLEASE INCLUDE THE FOLLOWING AS THE FIRST PARAGRAPH:

PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS COMBINE TWO ANTIHYPERTENSIVE AGENTS: PROPRANOLOL HYDROCHLORIDE, A BETA-ADRENERGIC BLOCKING AGENT, AND HYDROCHLOROTHIAZIDE, A THIAZIDE DIURETIC-ANTIHYPERTENSIVE.

2. WARNINGS

A. INPATIENTS WITH ANGINA PECTORIS

THIS ENTIRE SECTION SHOULD BE BOXED.

B. IN PATIENTS UNDERGOING MAJOR SURGERY, 8th LINE

----ISOPROTERENOL OR NOREPINEPHRINE----
(RATHER THAN:.....ISOPROTERENOL OR
————— .....)

3. OVERDOSAGE OR EXAGGERATED RESPONSE

A. HYPOTENSION-VASOPRESSORS, e.g. NOREPINEPHRINE
(RATHER THAN, —————)

REFERENCE: NDA 70-704
PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS,
40 MG/25 MG

C. REVISE CONTAINER LABELS AND PACKAGE INSERT LABELING. PREPARE AND SUBMIT 12 COPIES OF FINAL PRINTED LABELING OF EACH.

RESPONSE

Attached as Supplemental Pages S-256 through S-257 please find final printed container labels and package insert labeling, revised according to the above Agency requirements.

COMMENT

2. IT FAILS TO ASSURE THAT THE DRUG DOSAGE FORM AND COMPONENTS WILL COMPLY WITH THE SPECIFICATIONS AND TESTS DESCRIBED IN AN OFFICIAL COMPENDIUM, IF SUCH ARTICLE IS RECOGNIZED THEREIN, OR IF NOT LISTED, OR IF THE ARTICLE DIFFERS FROM THE COMPENDIUM DRUG, THAT THE SPECIFICATIONS AND TESTS APPLIED TO THE DRUG AND ITS COMPONENTS ARE ADEQUATE TO ASSURE THEIR IDENTITY, STRENGTH, QUALITY AND PURITY. IN THIS REGARD:

BULK ACTIVE INGREDIENTS

A. [redacted]

RESPONSE

Attached as Supplemental Page S-258 please find a revised Certificate [redacted] including the [redacted].

COMMENT

B. SUBMIT COMPLETED CERTIFICATES OF ANALYSIS FROM BARR.

Redacted 10 page(s)

of trade secret and/or

confidential commercial

information from

11/27/1985 BARR LETTER

Marvin Seife, M.D.
Food and Drug Administration

REFERENCE: NDA 70-704
PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS,
40 MG/25 MG

This completes our present Amendment to our Application and response to your letter of November 15, 1985.

Sincerely,

BARR LABORATORIES, INC.

Thomas Bellaagh m.a. wenger

Thomas Bellaagh, Ph.D.
Vice President of Technical Affairs

TB:lva
Enclosure

This Submission is comprised of Supplemental Pages S-256 through S-309.

Dup to Bio OPS

Barr Laboratories, Inc. 265 Livingston St, Northvale, N.J. 07647 Telephone (201) 767-1900

December 31, 1985

Marvin Seife, M.D.
Director
Division of Generic Drugs
HFN-230, Room 16-70
Food and Drug Administration
Center For Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857

NDA 70-704 Amendment 4/22/86

ORIG NEW CORRES

BIOAVAILABILITY MATERIAL

REFERENCE: **NDA 70-704**
PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG

Dear Dr. Seife:

Reference is made to our Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Propranolol Hydrochloride and Hydrochlorothiazide Tablets, 40 Mg/25 Mg.

In accordance with Agency requirements, under separate cover, as a Supplement to our Abbreviated New Drug Application, **NDA 70-705, Propranolol Hydrochloride and Hydrochlorothiazide Tablets, 80 Mg/ 25 Mg**, we have submitted a Randomized, Two-Way Crossover Bioavailability Study (fasting conditions), #43-44-08-5. This Study was performed on BARR's behalf by _____.

The products compared in this Study were BARR's Propranolol Hydrochloride and Hydrochlorothiazide Tablets, 80 Mg/25 Mg, (Lot 4L42836) and Ayerst Laboratories' Inderide® Tablets, 80 Mg/25 Mg (Lot 1063).

This Study was submitted to the Agency in support of BARR's **TWO** Abbreviated New Drug Applications for Propranolol Hydrochloride and Hydrochlorothiazide Tablets **40 Mg/25 Mg (NDA 70-704)** and **80 Mg/ 25 Mg (NDA 70-705).**

At this time we respectfully request a **"waiver"** from the Bioavailability/ Bioequivalence requirements of this Application based on our above described In Vivo Study. This request for "waiver" is further based on the fact that BARR's both formulations (40 Mg/25 Mg and 80 Mg/25 Mg) use exactly the **same ingredients with identical manufacturing, quality control, analytical procedures and package styles.**

... continued

FORMULATIONS

Ingredient	NDA 70-704 40 Mg/25 Mg	NDA 70-705 80 Mg/25 Mg
Propranolol HCl, USP	40.00	80.00
Hydrochlorothiazide, USP	25.00	25.00
Lactose, ———, NF	———	———
(Microcrystalline Cellulose, NF)	———	———
(Croscarmellose Sodium, ———, NF)	———	———
Magnesium Stearate, NF	———	———
(Colloidal Silicon Dioxide, NF)	———	———
MG/TAB	210.00	320.00

In further support of our "Requiest for Bioavailability Waiver", we offer the following evidence as required by 21 CFR 320.22(d)(2) which states:

> AS DEMONSTRATED ABOVE THE DRUG PRODUCT IS IN THE SAME DOSAGE FORM, BUT IN A DIFFERENT STRENGTH, AND IS SIMILAR IN ITS ACTIVE AND INACTIVE INGREDIENTS TO ANOTHER DRUG PRODUCT MADE BY BARR LABORATORIES AND THE FOLLOWING CONDITIONS ARE MET:
>
> (i) THE BIOAVAILABILITY OF THIS OTHER DRUG PRODUCT HAS BEEN DEMONSTRATED.
>
> (ii) BOTH DRUG PRODUCTS MET AN APPROPRIATE IN VITRO TEST.
>
> (iii) AS DEMONSTRATED BY THE ABOVE MASTER FORMULATIONS THE APPLICANT HAS SUBMITTED EVIDENCE SHOWING THAT BOTH DRUG PRODUCTS ARE SIMILAR IN THEIR ACTIVE AND INACTIVE INGREDIENTS.

In accordance with the above cited Regulations and based on documentation outlined in this letter, it is our firm belief that BARR LABORATORIES clearly meets the criteria to be granted the requested WAIVER.

This completes the present Amendment to our Application.

Cordially,

BARR LABORATORIES, INC.

Marilyn A. Wenger
Administrative Director

/bmy

NDA 70-704
70-705

MAR 20 1986

Barr Laboratories
Attention: Thomas Bellaagh, Ph.D.
265 Livingston Street
Northvale, NJ 07647

Dear Sir:

Reference is made to your bioequivalence related submissions of December 31, 1985 and February 19, 1986 for Propranolol Hydrochloride and Hydrochlorothiazide Tablets, 40 mg/25 mg and 80 mg/25 mg.

Your submissions have been reviewed by our Division of Bioequivalence and they have the following comments:

"1. The bioequivalence study conducted by Barr-Laboratories on its Propranolol HCl/Hydrochlorothiazide (80 mg/25 mg) tablet, lot # 4L42836, comparing it to Ayerst's Inderide (Propranolol HCl/Hydrochlorothiazide 80 mg/25 mg) tablet, has been found acceptable to the Division of Bioequivalence. The study demonstrates that the test product, Barr's Propranolol HCl/Hydrochlorothiazide (80 mg/25 mg) is bioequivalent to the reference product, Ayerst's Inderide 80/25 tablet.

2. The in vitro dissolution testing is also acceptable. The dissolution testing should be incorporated into your manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of 0.1N HCl at 37°C using USP XXI apparatus I (basket) at 100 rpm. The test product should meet the following specification:

   Not less than —% of the labeled amount of drug in the capsule is dissolved in 60 minutes.

3. The dissolution testing conducted by Barr on its Propranolol HCl/Hydrochlorothiazide 40 mg/25 mg tablet, lot #4L42732, is acceptable. The formulation for the 40 mg/25 mg strength is proportionally similar to the 80 mg/25 mg strength of the test product which underwent the bioequivalence study. The waiver of in vivo bioequivalence study requirements for the 40 mg/25 mg strength of the test product is granted. Barr's Propranolol HCl/Hydrochlorothiazide 40 mg/25 mg tablet is therefore deemed bioequivalent to Inderide (Propranolol HCl/Hydrochlorothiazide 40 mg/25 mg) tablet manufactured by Ayerst.

4. From the bioequivalence point of view the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing and both applications, NDA 70-704 (40 mg/25 mg) and 70-705 (80 mg/25 mg), are acceptable.

5. It is requested that you mail 200 tablets of the same product lot used in your in vivo bioavailability/bioequivalence study to:

Dr. V. K. Prasad
Chief, Biopharmaceutics Laboratory Branch
Center for Drugs and Biologics
200 C Street, S.W. (HFN-224)
Washington, D.C. 20204

Please assure that the ANDA Number, Ingredient and Strength, Lot No., and Expiration Date are included in the label information.

Sincerely yours,

3/20/86

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc: NWK-DO
HFN-230
Poux
Leinbach
MSeife/JSturm/jt/3-19-86
BIO 1733A

Drug

Barr Laboratories, Inc. 265 Livingston St, Northvale, N.J. 07647 Telephone (201) 767-1900

March 24, 1986

NAI
per 5/16/86

Dr. V. K. Prasad
Chief
Biopharmaceutics Laboratory Branch
Center for Drugs and Biologics
HFN-224
200 C Street, S.W.
Washington, D.C. 20204

ORIG NEW CORRES

REFERENCE: NDA 70-704 PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG
NDA 70-705 PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS, 80 MG/25 MG

Dear Dr. Prasad:

Reference is made to our Abbreviated New Drug Application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG and 80 MG/25 MG.

Reference is also made to Dr. Seife's comment letter dated March 20, 1986 requesting Barr mail 200 tablets of the same product lot used in our vivo bioavailability/bioequivalence study to your attention.

Enclosed find:

1 x 200 TABLETS OF
PROPRANOLOL HYDROCHLORIDE and
HYDROCHLOROTHIAZIDE, 80 MG/25 MG
BATCH NO. 4L42836

This completes the present Supplement to our Application.

Sincerely,

BARR LABORATORIES, INC.

Marilyn A. Wenger

Marilyn A. Wenger
Administrative Director

RECEIVED
MAR 26 1986
GENERIC DRUGS

MAW:mtw
Enclosure
cc: M.Seife,M.D.

ANDA 70-704

Barr Laboratories
Attention: Thomas Bellaagh, Ph.D.
265 Livingston Street
Northvale, NJ. 07647

MAY 5 1986

Dear Dr. Bellaagh:

Please refer to your abbreviated new drug application submitted pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act for Propranolol Hydrochloride and Hydrochlorothiazide Tablets, 40 mg/25 mg.

Reference is made to your November 27, 1985, submission.

The application is deficient and therefore not approvable under Section 505 of the Act for the following reasons:

1. It fails to contain satisfactory labeling. In that regard:

   A. Revise insert labeling to include "scored" or "unscored" and debossing (if applicable) in describing tablets in "How Supplied" section of the insert labeling.

   B. Submit 12 copies of final printed insert labeling. The insert labeling submitted is not your usual final printed labeling quality.

2. It fails to assure that the drug dosage form and components will comply with the specifications and tests described in an official compendium, if such article is recognized therein, or if not listed, or if the article differs from the compendium drug, that the specifications and tests applied to the drug and its components are adequate to assure their identity, strength, quality and purity. In this regard:

   A.

   B.

   C.

   D.

   E.

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

5/5/1986 FDA LETTER

The file is now closed. You are required to take one of the actions described at 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Ken Johnson for 5-5-86

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc:
NWK-DO
HFN-237 DDZ 5/1/86
MChang/CChang/PLeinbach/tr/4/28/86
0733S
Not Approvable

CChang 5-2-86

Orig

Barr Laboratories, Inc. 265 Livingston St, Northvale, N.J. 07647 Telephone (201) 784-0400

May 9, 1986

Mr. Donald Page
FOOD AND DRUG ADMINISTRATION
Division of Drug Analysis
Room 1002
1114 Market Street
St. Louis, Missouri 63101

ORIG NEW CORRES

REFERENCE: NDA 70-704 - PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG
NDA 70-705 - PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS, 80 MG/25 MG

Dear Mr. Page:

Pursuant to a recent telephone conversation with Mr. David Broncotto, Food and Drug Administration, Rockville, Maryland, requesting Barr Laboratories to forward to your attention the following raw material samples:

PROPRANOLOL HYDROCHLORIDE USP RAW MATERIAL - 50 GRAMS

[redacted]

Certificate of Analysis - Batch No. 5864
Methodology

HYDROCHLOROTHIAZIDE USP RAW MATERIAL - 50 GRAMS

[redacted]

Certificate of Analysis - Batch No. 582224
Methodology

If you require any additional information and/or samples, please do not hesitate to contact me.

Sincerely,

BARR LABORATORIES, INC.

Marilyn A. Wenger
Marilyn A. Wenger
Administrative Director

MAW:mtw
Enclosure

RECEIVED
MAY 12 1986
GENERIC DRUGS

cc: Marvin Selfe,M.D.
Mr. David Broncotto
Food and Drug Administration
Rockville, Maryland

ANDA 70-704

Barr Laboratories
Attention: Marilyn A. Wenger
265 Livingston Street
Northvale, NJ 07647

MAY 27 1986

Dear Madam:

Please refer to your abbreviated new drug application dated September 4, 1986 submitted pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act for Propranolol Hydrochloride and Hydrochlorothiazide Tablets, 40 mg/25 mg.

Reference is also made to your communication dated May 9, 1986 relating to shipment of raw materials to the FDA Laboratory in St. Louis.

The application is deficient and therefore not approvable under Section 505 of the Act for the following reasons:

1. We acknowledge the shipment of the raw material to the St. Louis facility. Please await our call regarding shipment of the finished dosage form for methods validation.

2. It fails to address the deficiencies itemed in our correspondence to Barr Laboratories, dated May 5, 1986.

The file is now closed. You are required to take one of the actions described at 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Kent C. Johnson /for 5-27-86

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc:
HFN-237
CChang/DBrancato/gp/5/22/86
0537 NOT APPROVABLE

D. Brancato 5-23-86

cmp 5-23-86

Orig

Barr Laboratories, Inc. 265 Livingston St, Northvale, N.J. 07647 Telephone (201) 784-0400

May 29, 1986

Mr. John Redd
Dept. of Health & Human Services
FOOD AND DRUG ADMINISTRATION
1521 W. Pico Blvd.
Los Angeles, California 90015-2486

ORIG NEW CORRES

REFERENCE: ANDA 70-704 - PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG
ANDA 70-705 - PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS, 80 MG/25 MG

Dear Mr. Redd:

Pursuant to a telephone conversation with Mr. Dave Brancato, Food and Drug Administration, Rockville, Maryland, enclosed are the following:

2 x 100 - PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG
BATCH NO. 4L42732

USP REFERENCE STANDARD PROPRANOLOL HYDROCHLORIDE 200 MG
1-(α naphthohydroxy)-3-chloro, 2-Propanol
1-(α naphthohydroxy)2,3 epoxypropane
3-chloro,1-(α naphthohydroxy) 2-Propanol

ACCEPTANCE TESTS FOR IN-PROCESS AND FINISHED PRODUCTS
METHOD TM-197B

If you require any additional information and/or samples, please do not hesitate to contact me.

Sincerely,

BARR LABORATORIES, INC.

Marilyn A. Wenger
Marilyn A. Wenger
Administrative Director

RECEIVED
JUN 2 1986
GENERIC DRUGS

MAW:mtw
Enclosures

cc: Marvin Seife, M.D.
Mr. D. Brancato
Rockville, Maryland

ANDA 70-704

Barr Laboratories
Attention: Marilyn A. Wenger
265 Livingston Street
Northvale, NJ 07647

JUN 10 1986

Dear Madam:

Please refer to your abbreviated new drug application dated September 4, 1986 submitted pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act for Propranolol Hydrochloride and Hydrochlorothiazide Tablets, 40 mg/25 mg.

Reference is also made to your communication dated May 29, 1986 relating to shipment of the finished dosage form to the FDA Laboratory in Los Angeles.

The application is deficient and therefore not approvable under Section 505 of the Act for the following reasons:

1. We acknowledge the shipment of the finished dosage form to the Los Angeles facility. You will be informed, after the analysis is completed, whether the method is suitable for regulatory purposes.

2. It fails to address the deficiencies itemed in our correspondence to Barr Laboratories, dated May 5, 1986.

The file is now closed. You are required to take one of the actions described at 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Robert C. Johnson /FOR 6-10-86

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc:
HFN-237
CChang/DBrancato/gp/5/22/86
0537 NOT APPROVABLE

D Brancato 6/9/86

cy 6-9-86

Orig

Barr Laboratories, Inc. 265 Livingston St, Northvale, N.J. 07647 Telephone (201) 767-1900

FPL package insert labeling is satisfactory. However at the time of next printing highlight Use in Pregnancy under WARNINGS as a subsection heading (i.e. different type style than section heading)
6/23

Dave Daniel was told that she didn't sign this for her but he said please

June 12, 1986

NDA ORIG AMENDMENT FPL

Marvin Seife, M.D., Director
Division of Generic Drugs
Attention: Document Control Room
HFN-230, ROOM 17B-20
FOOD AND DRUG ADMINISTRATION
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857

REFERENCE: ANDA 70-704
PROPRANOLOL HYDROCHLORIDE AND
HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG

Dear Dr. Seife:

Reference is made to our Abbreviated New Drug Application submitted under Section 505 (j) of the Federal Food, Drug and Cosmetic Act for PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG.

Reference is also made to your letters of May 5, 1986 and May 27, 1986 in which the following was stated:

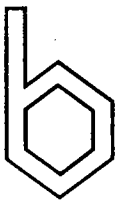
MAY 5, 1986 COMMUNICATION:

THE APPLICATION IS DEFICIENT AND THEREFORE NOT APPROVABLE UNDER SECTION 505 OF THE ACT FOR THE FOLLOWING REASONS:

COMMENT #1

IT FAILS TO CONTAIN SATISFACTORY LABELING. IN THAT REGARD:

....Continued



REFERENCE: ANDA 70-704
PROPRANOLOL HYDROCHLORIDE AND
HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG

A) REVISE INSERT LABELING TO INCLUDE "SCORED" OR "UNSCORED" AND DEBOSSING (IF AVAILABLE) IN DESCRIBING TABLETS IN "HOW SUPPLIED" SECTION OF THE INSERT LABELING.

B) SUBMIT 12 COPIES OF FINAL PRINTED INSERT LABELING. THE INSERT LABELING SUBMITTED IS NOT YOUR USUAL FINAL PRINTED LABELING QUALITY.

RESPONSE

Enclosed as Supplemental Page S-310, find 12 copies of our final printed labeling (Package Insert), which was revised to incorporate the Agency's above cited recommendation.

COMMENT #2

IT FAILS TO ASSURE THAT THE DRUG DOSAGE FORM AND COMPONENTS WILL COMPLY WITH THE SPECIFICATIONS AND TESTS DESCRIBED IN AN OFFICIAL COMPENDIUM, IF SUCH ARTICLE IS RECOGNIZED THEREIN, OR IF NOT LISTED, OR IF THE ARTICLE DIFFERS FROM THE COMPENDIUM DRUG, THAT THE SPECIFICATIONS AND TESTS APPLIED TO THE DRUG AND ITS COMPONENTS ARE ADEQUATE TO ASSURE THEIR IDENTITY, STRENGTH, QUALITY AND PURITY. IN THIS REGARD:

A)

B)

....Continued

Redacted 9 page(s)

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confidential commercial

information from

6/12/1986 BARR LETTER

REFERENCE: ANDA 70-704
PROPRANOLOL HYDROCHLORIDE AND
HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG

This completes our present Amendment and response to the Agency's letters of May 5, 1986 and May 27, 1986.

Sincerely,

BARR LABORATORIES, INC.

Marilyn A. Wenger
Administrative Director

MAW:va
Enclosure

cc: Dave Brancato, FDA (Desk Copy)

This Amendment is comprised of Supplemental Pages S-310 through S-369, Exhibit A, B and C.

Orig

Barr Laboratories, Inc. 265 Livingston St, Northvale, N.J. 07647 Telephone (201) 767-1900

June 19, 1986

Marvin Seife, M.D., Director
Division of Generic Drugs
Attention: Document Control Room
HFN-230, ROOM 17B-20
FOOD AND DRUG ADMINISTRATION
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857

AMENDMENT

REFERENCE: NDA 70-704
PROPRANOLOL HYDROCHLORIDE AND
HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG

Dear Dr. Seife:

Reference is made to our Abbreviated New Drug Application submitted under Section 505 (j) of the Federal Food, Drug and Cosmetic Act for PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG.

Reference is also made to your letter of June 10, 1986, in which you state the following:

> THE APPLICATION IS DEFICIENT AND THEREFORE NOT APPROVABLE UNDER SECTION 505 OF THE ACT FOR THE FOLLOWING REASONS:

COMMENT #1

> WE ACKNOWLEDGE THE SHIPMENT OF THE FINISHED DOSAGE FORM TO THE LOS ANGELES FACILITY. YOU WILL BE INFORMED, AFTER THE ANALYSIS IS COMPLETED, WHETHER THE METHOD IS SUITABLE FOR REGULATORY PURPOSES.

....Continued

REFERENCE: NDA 70-704
PROPRANOLOL HYDROCHLORIDE AND
HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG

RESPONSE

We thank the Agency for rapid acknowledgement of the finished dosage form which was mailed to FDA's Los Ageles facility on May 29, 1986.

COMMENT #2

IT FAILS TO ADDRESS THE DEFICIENCIES ITEMED IN OUR CORRESPONDENCE TO BARR LABORATORIES, DATED MAY 5, 1986.

RESPONSE

The Agency's letter dated May 5, 1986, was addressed in full by BARR LABORATORIES on June 12, 1986 and mailed via Federal Express on the same day.

This completes our response to the Agency's letter of June 10, 1986.

Sincerely,

BARR LABORATORIES, INC.

Marilyn A. Wenger

Marilyn A. Wenger
Administrative Director

MAW:va

ANDA 70-704

Barr Laboratories
Attention: Marilyn A. Wenger
265 Livingston Street
Northvale, NJ 07647

JUL 8 1986

Dear Ms. Wenger:

Please refer to your abbreviated new drug application dated September 4, 1985, submitted pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act for Propranolol Hydrochloride and Hydrochlorothiazide Tablets, 40 mg/25 mg.

Reference is also made to your communication dated June 12 and 19, 1986 relating to labeling and manufacturing revisions.

The application is deficient and therefore not approvable under Section 505 of the Act for the following reasons:

1. Final printed package insert labeling is satisfactory. However at the time of the next printing please highlight "Use in Pregnancy" under "WARNINGS" as a subsection heading (i.e. in different type style then your section heading).

2. The in-process methods validation for the finished dosage form is not suitable for regulatory purposes. Please await our comments as to its deficiencies which will be given once our chemist has a chance to review the comments from the L.A. District.

3. [redacted]

4. [redacted]

The file is now closed. You are required to take one of the actions described at 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Kent C. Johnson (for) 1-8-86

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards

cc:
HFN-237
MChang/CChang/DBrancato/tr/7/2/86
0871S
Not Approvable

D Brancato 7/7/86

1-7-86

Orig

Barr Laboratories, Inc. 265 Livingston St, Northvale, N.J. 07647 Telephone (201) 784-0400

August 12, 1986

Marvin Seife, M.D., Director
Division of Generic Drugs
Attention: Document Control Room
HFN-230, ROOM 17B-20
FOOD AND DRUG ADMINISTRATION
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857

NDA ORIG AMENDMENT

REFERENCE: ANDA 70-704 - PROPRANOLOL HYDROCHLORIDE and HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG

Dear Dr. Seife:

Reference is made to our Abbreviated New Drug Application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for PROPRANOLOL HYDROCHLORIDE and HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG.

Reference is also made to your letter of July 8, 1986, in which the following was stated.

> THE APPLICATION IS DEFICIENT AND THEREFORE NOT APPROVABLE UNDER SECTION 505 FOR THE FOLLOWING REASONS:

COMMENT #1

> FINAL PRINTED PACKAGE INSERT LABELING IS SATISFACTORY. HOWEVER AT THE TIME OF THE NEXT PRINTING PLEASE HIGH LIGHT "USE IN PREGNANCY" UNDER "WARNINGS" AS A SUBSECTION HEADING (i.e. IN DIFFERENT TYPE STYLE THEN YOUR SECTION HEADING).

RESPONSE

> Since the Agency's recommendations are considered editorial format minor changes in labeling, and in accordance with CFR 314.70(d)(3) of the NDA Rewrite, the package insert will be revised to reflect the Agency's concerns. The revised package insert will be submitted in BARR's first periodic report.

. . . Continued

REFERENCE: ANDA 70-704 - PROPRANOLOL HYDROCHLORIDE and HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG

COMMENT #2

THE IN-PROCESS METHODS VALIDATION FOR THE FINISHED DOSAGE FORM IS NOT SUITABLE FOR REGULATORY PURPOSES. PLEASE AWAIT OUR COMMENTS AS TO ITS DEFICIENCIES WHICH WILL BE GIVEN ONCE OUR CHEMIST HAS A CHANCE TO REVIEW THE COMMENTS FROM THE L.A. DISTRICT.

RESPONSE

Enclosed as Supplemental Pages S-370 through S-391, find Analytical Testing Method for Finished Product (Method TM-197C). Supplemental Pages S-392 through S-421 are the corresponding Analytical Validation for Method TM-197C.

This data is revised to incorporate appropriate testing as cited by the Agency and will satisfy all concerns and deficiencies as noted by the LA. District.

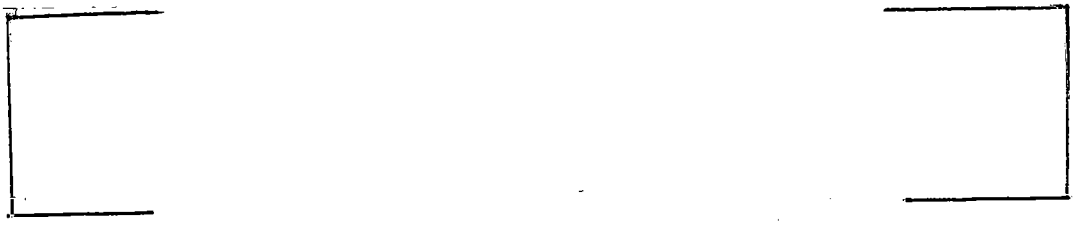
COMMENT #3

RESPONSE

. . . Continued

REFERENCE: ANDA 70-704 - PROPRANOLOL HYDROCHLORIDE and HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG

COMMENT #4



RESPONSE

A.

B.

Supplemental Pages S-433 through S-444 is a copy of the actual Batch Records for Lot 6G42785

We firmly believe that the enclosed documentation should fully satisfy all of the Agency's concerns.

Since we have met the Division of Bioequivalence requirements, i.e., requested Bio Waiver "granted" and In-Vitro Dissolution Testing "accepted" by the Agency on March 20, 1986, we respectfully request that this Application be approved without further delay.

. . . Continued

REFERENCE: ANDA 70-704 - PROPRANOLOL HYDROCHLORIDE and HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG

Should anything further be required, please call me direct at (201) 784-0400.

This completes our response to the Agency's letter of July 8, 1986 and the present Amendment.

Sincerely,

BARR LABORATORIES, INC.

Marilyn A. Wenger
Administrative Director

MAW:mtw
Enclosures

Desk Copy:
Mr. Charles Chang
FOOD & DRUG ADMINISTRATION
Rockville, Maryland

This Submission consists of Supplemental Pages S-370 through S-444.

ANDA 70-704

AUG 18 1986

Barr Laboratories
Attention: Marilyn A. Wenger
265 Livingston Street
Northvale, NJ 07647

Dear Ms. Wenger:

Please refer to your abbreviated new drug application dated September 4, 1985, submitted pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act for Propranolol Hydrochloride and Hydrochlorothiazide Tablets, 40 mg/25 mg.

Reference is also made to your communication dated August 12, 1986.

The application is deficient and therefore not approvable under Section 505 of the Act for the following reasons:

> The in-process methods validation for the finished dosage form was not suitable for regulatory purposes. It has been shown that the methodology was changed per recommendation by our LA District. Initially the method was not properly researched. Therefore, it is our procedure to request analyses by our LA District according to the revised method. Please await our comments as to its acceptability for regulatory purposes.

The file is now closed. You are required to take one of the actions described at 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Ron T Johnson /for 8-18-86

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc:
HFN-237
CChang/DBrancato/tr/8/15/86
0977S
Not Approvable

ANDA 70-704

Barr Laboratories
Attention: Marilyn A. Wenger
265 Livingston Street
Northvale, NJ 07647

SEP 8 1986

Dear Ms. Wenger:

Please refer to your abbreviated new drug application dated September 4, 1985, submitted pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act for Propranolol Hydrochloride and Hydrochlorothiazide Tablets, 40 mg/25 mg.

The application is deficient and therefore not approvable under Section 505 of the Act for the following reasons:

The Los Angeles District has reviewed the new analytical procedures submitted by Barr and performed analytical work where it seemed relevant. The methodology changes, and our response to these changes, are as follows:

1.

2.

3.

4.

The file is now closed. You are required to take one of the actions described at 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

9/8/86

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc:
HFN-237 DBrancato 9/8/86
CChang/DBrancato/tr/9/4/86
1013S
Not Approvable
cc 9-8-86

Orig

Barr Laboratories, Inc. 265 Livingston St, Northvale, N.J. 07647 Telephone (201) 767-1900

Analytical Satisfactory
D Branata
9/25/86

September 17, 1986

Marvin Seife, M.D., Director
Division of Generic Drugs
Attention: Document Control Room
HFN-230, ROOM 17B-20
FOOD AND DRUG ADMINISTRATION
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857

NDA ORIG AMENDMENT

REFERENCE: ANDA 70-704
PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG

Dear Dr. Seife:

Reference is made to our Abbreviated New Drug Application submitted under Section 505 (j) of the Federal Food, Drug and Cosmetic Act for **PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS, 40 MG/25 MG.**

Reference is also made to your letter of September 8, 1986, in which the following was stated:

> THE APPLICATION IS DEFICIENT AND THEREFORE NOT APPROVABLE UNDER SECTION 505 OF THE ACT FOR THE FOLLOWING REASONS:
>
> THE LOS ANGELES DISTRICT HAS REVIEWED THE NEW ANALYTICAL PROCEDURES SUBMITTED BY BARR AND PERFORMED ANALYTICAL WORK WHERE IT SEEMED RELEVANT. THE METHODOLOGY CHANGES, AND OUR RESPONSE TO THESE CHANGES, ARE AS FOLLOWS:

COMMENT #1:

[redacted]

....Continued

REFERENCE: ANDA 70-704
PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE
TABLETS, 40 MG/25 MG

RESPONSE:

Acknowledged.

COMMENT #2:

RESPONSE:

Acknowledged.

COMMENT #3:

....Continued

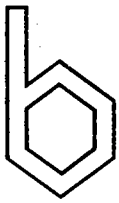
REFERENCE: ANDA 70-704
PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE
TABLETS, 40 MG/25 MG

RESPONSE:

Supplemental Pages S-467 through S-470 are copies of —— which were obtained by BARR.

COMMENT #4:

....Continued



REFERENCE: ANDA 70-704
PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE
TABLETS, 40 MG/25 MG

RESPONSE:

This completes our response to the Agency's letter of September 8, 1986 and the present Amendment to our Application.

Sincerely,

BARR LABORATORIES, INC.

Marilyn A. Wenger
Administrative Director

MAW:va

This Submission is comprised of Supplemental Pages S-445 through S-470.

cc: Desk Copies: Mr. Charles Chang
Food and Drug Administration
Rockville, Maryland

Mr. David J. Brancato
Food and Drug Administation
Rockville, Maryland